Effective Pain Reduction for Multiple Immunization Injections in Young Infants

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Background: Infants experience undue pain with multiple immunization injections.

Objective: To assess the effectiveness, feasibility, and parental acceptance of a simple combination pain reduction intervention for infants receiving multiple immunization injections.

Design: Randomized, controlled, clinical trial.

Setting: Academic hospital-based primary care center.

Participants: Infants receiving their 2-month immunizations, consisting of 4 injections (diphtheria and tetanus toxoids and acellular pertussis vaccine, inactivated poliovirus vaccine, *Haemophilus influenzae* b conjugate and hepatitis B vaccine [Comvax], and heptavalent pneumococcal conjugate vaccine [Prevnar]).

Interventions: Subjects were randomly assigned to the intervention or control group for administration of 4 injections. The intervention group received sucrose and oral tactile stimulation (with a pacifier or a bottle) and were held by their parents during immunization. The control group did not receive these interventions (standard practice).

Main Outcome Measures: Blinded assessment of audiotaped crying, heart rate, parent preference for future use of the injection technique, and nurse-rated ease of vaccine administration.

Results: One hundred sixteen infants (mean ± SD age, 9.5 ± 2.0 weeks) participated. The median (25th-75th percentile range) first cry duration was 19.0 (5.8-62.8) seconds for the intervention group compared with 57.5 (31.0-81.5) seconds for the control group (P = 0.002). Parents of the intervention group reported a stronger preference for future use of the injection procedure. For intervention vs control, the median (25th-75th percentile) parent preference visual analog scale score was 97.0 (82.0-100.0) vs 44.0 (5.0-77.2) (P < 0.001) (100 indicates definitely prefer). Nurse-rated ease of vaccine administration was equivalent for both treatment groups.

Conclusions: Combining sucrose, oral tactile stimulation, and parental holding was associated with significantly reduced crying in infants receiving multiple immunization injections. Parents stated a strong preference for future use of this method, and nurses found the intervention injection technique easy to apply.

as heel lancing. Swaddling, holding, and providing the oral tactile stimulation of sucking on a pacifier are effective nonpharmacologic approaches.6-10 Oral sucrose is an effective pharmacologic analgesic that acts via endogenous opioid pathways.11-17 In neonates, oral sucrose is enhanced when combined with holding6 or with nonnutritive sucking.15 However, the analgesic effect of oral sucrose alone16 or combined only with parent holding19 has been reported to be limited in infants beyond the newborn period.

Many successful pain management approaches use pharmacologic and nonpharmacologic strategies. We previously demonstrated the efficacy of combining topical vapocoolant spray and distraction for older children receiving immunization injections.20 We, subsequently, demonstrated that combining sucrose, oral tactile stimulation, and parental holding is an effective and convenient method for reducing pain in 6-month-old infants receiving one injection.21 The generalizability of this study’s findings was limited by the administration of a single injection. The efficacy of our approach needs to be investigated in the setting of multiple injections, which young infants typically receive at most vaccination visits.

In the present study, we conducted a randomized controlled trial to assess the effectiveness, feasibility, and parental acceptance of combining sucrose, oral tactile stimulation, and parental holding to reduce the pain associated with multiple immunization injections in young infants. To enhance the generalizability of our findings, we conducted the trial in a natural clinical setting of a busy primary care pediatric practice.

METHODS

This randomized controlled trial of immunization pain reduction interventions was approved by the Human Rights Committee, the Institutional Review Board of the Children’s Hospital of Pittsburgh.

PARTICIPANTS

Infants were eligible for study inclusion if they were aged 6 to 16 weeks and were presenting to the Children’s Hospital of Pittsburgh Primary Care Center for their 2-month immunizations, consisting of 4 injections: diphtheria and tetanus toxoids and acellular pertussis vaccine (Connaught; Swiftwater, Pa), inactivated poliovirus vaccine (Connaught), Haemophilus influenzae b conjugate and hepatitis B vaccine (Comvax; Merck & Co, Inc, West Point, Pa), and heptavalent pneumococcal conjugate vaccine (Prevnar; Wyeth-Lederle, Philadelphia, Pa). Infants who were not accompanied by a parent were excluded.

INFORMED CONSENT

Parents of eligible infants were approached in the examination room before immunization. The benefits and risks of the study were explained to parents, and their questions were answered. Interested parents read and signed 2 copies of the consent form, 1 of which they kept. Documentation of the informed consent process was completed and stored separately from study data.

RANDOMIZATION

Assignment to treatment groups was randomized using a computer-generated blocked randomization scheme generated by one of us (R.H.). Treatment group assignment was written on slips of paper that were folded and placed in consecutively numbered opaque envelopes and sealed. Envelopes were not opened until after parents signed the consent forms. Under the direct supervision of one of us (E.C.R.), 2 others (E.K.R. and J.L.S.) enrolled participants and assigned them to treatment groups.

BLINDING

Because parents and nurses participated in providing the intervention, they could not be blinded to treatment group assignment. Investigators were blinded only during assessment of the audiotaped cry data, as described in the “Outcome Measurements” subsection of this section.

PAIN REDUCTION INTERVENTIONS

Participants were randomly assigned to 1 of the 2 treatment groups: (1) intervention group, consisting of oral sucrose, oral tactile stimulation (sucking), and parental holding; or (2) control group, consisting of standard immunization practice (ie, no pain reduction).

Intervention Group

Oral Sucrose and Oral Tactile Stimulation. Infants were given a bottle with 10 mL of 25% sucrose to suck 2 minutes before the injection. Two minutes has been demonstrated to be the interval associated with greatest analgesic effect.22 The 25% sucrose solution was prepared by mixing one standard packet of table sugar with 10 mL of tap water immediately before use, as has been described for use in busy clinical settings.23 After drinking the sucrose solution, infants continued to suck during the injection and postinjection periods, using either a pacifier or a formula bottle. Given our aim to enhance the generalizability of our findings, use of a pacifier or a bottle was based on parents’ preference and the infant supplies that they had brought, as would be feasible in practice. Breastfeeding mothers would have been encouraged to put their infants to breast after the sucrose ingestion; no mothers in our study chose to do so.

Parental Holding. Parents were instructed to hold their infants across their laps in a cross-craddle position throughout the injection procedure, hugging their infants’ upper bodies close to their chests. This position allowed the children’s anterior thighs to be accessible for immunization. Parents were instructed to keep their infants on their laps until the 6-minute observation period was completed.

Two minutes after the infant ingested the sucrose solution, the injection site was cleaned with alcohol and the injection was performed as described in the “Injection Procedure” subsection of this section.

Control Group

Following standard practice in the Primary Care Center, infants were placed on the examination table during the procedure and no specific comfort measures were provided. The injection site was cleaned with alcohol, and the injection was performed as described in the “Injection Procedure” subsection of this section. During the postinjection period, parents were instructed to engage their infants in any activity they deemed appropriate, including picking up their infants whenever they desired after the injection.

INJECTION PROCEDURE

The immunization injection was performed according to the standard Primary Care Center nursing protocol. A dose (0.5 mL) of...
each of the 4 vaccines (diphtheria and tetanus toxoids andacellular pertussis vaccine, inactivated poliovirus vaccine, Haemophilus influenzae b conjugate and hepatitis B vaccine, and heptavalent pneumococcal conjugate vaccine) was drawn into a 1-mL syringe under aseptic technique and administered intramuscularly to the anterior thigh at a 90° angle to the skin with a 26-gauge 1.59-cm needle. Before initiation of the study, the Primary Care Center nursing staff participated in an in-service workshop to ensure a standardized injection procedure.

SUBJECT CHARACTERISTICS

The following information was obtained for each subject before immunization: age, weight, sex, race or ethnicity, previous painful procedures (heel stick, circumcision, intravenous cannulation, hepatitis B vaccine at birth, venipuncture, lumbar puncture, and surgery), and baseline heart rate (HR).

OUTCOME MEASUREMENTS

Primary Outcomes

Because the dissimilar positioning of the infants (parent's lap vs examination table) precluded the blinded assessment of a videotaped recording, auditory and physiologic pain measures served as the primary measures of infant pain response.

Cry Duration. All infants were audiотaped during immunization and postinjection recovery, for a total 6-minute observation period beginning with the first needle puncture of the skin. Cry duration (in seconds) was timed with an electronic timer by one of us (J.L.S.), who was blinded to treatment group assignment while reviewing the audiотapes. Before beginning the study, 2 of us (E.C.R. and J.L.S.) trained in assessment of audiотaped cry duration until a high rate of interrater reliability was reached. Success of the blinding was confirmed by one of us (E.C.R.), who independently reviewed 24 (20.7%) of the audiотapes to ensure that treatment group assignment was not identified.

First cry duration was defined as the interval from the initiation of cry (the first audible distress vocalization after the first needle puncture of the skin) to the first pause in crying (absence of audible distress vocalization >3 seconds). Total cry duration was defined as the total time that the subject was producing audible distress vocalizations during the 6-minute observation.

HR Elevation. Heart rate was measured using a cardiac monitor (Neo-Trak 502; Corometrics Medical Systems, Wallingford, Conn). Baseline HR was manually recorded every 10 seconds for 60-second intervals before the injection procedure while infants were resting on their parent's lap. The control group was then transferred to the examination table for vaccination. Following the first injection, HR was recorded every 10 seconds for the first 120 seconds, then every 15 seconds for 60 seconds beginning 2 and 5 minutes after the first injection. The maximum HR recorded during the period following the first needle puncture was noted. Maximum HR elevation was calculated as the difference between the maximum HR and the mean baseline HR.

Vaccination Time. The duration of the vaccination procedure, from the first injection to the placement of the fourth adhesive bandage, was measured from prompts on the audiотaped recordings.

Secondary Outcomes

In addition to these investigator-assessed outcomes, the following parent and nurse assessments were conducted. These nonblinded measures were included to assess the feasibility and parental acceptance of the interventions in clinical practice.

Preference for Future Use Visual Analog Scale (VAS). Parents answered the question, “Would you prefer to have your child get his/her shots the same way next time?” by completing a 100-mm linear VAS, representing the range from 0 (absolutely not) to 100 (definitely prefer).

Ease of Administration VAS. Nurses answered the question, “How easy/difficult was it for you to administer the shots to this infant?” by completing a 100-mm linear VAS, representing the range from 0 (very easy) to 100 (very difficult).

STATISTICAL ANALYSIS

Summary data were obtained for each treatment group by calculating proportions for categorical data and either mean±SD or median and the 25th and 75th percentiles for continuous data. To compare proportions between treatment groups, we used the Pearson χ² test or the Fisher exact test when cell sizes were small. Because infant age, weight, and HR data were approximately normally distributed, the t test was used to assess between-group differences in these variables. The remaining outcome variables (cry duration, vaccination time, and parent and nurse assessments) exhibited substantially skewed non-normal distributions. For these variables, a nonparametric test (Mann-Whitney) was used to test for group differences, and distribution-free confidence intervals based on this test were calculated.

RESULTS

From June 1, 2000, to April 10, 2001, we randomized 120 infants to either the intervention or the control group. Four infants were disenrolled (2 intervention group infants’ parents could not stay for the postinjection observation, 1 intervention group infant received only 2 injections, and 1 control group infant’s mother wanted to hold her during immunization). All remaining 116 infants (56 in the intervention group and 60 in the control group) completed the study and were analyzed according to intention-to-treat analysis. Comparison of demographic characteristics and prior painful procedures showed no significant differences between these 2 groups (Table 1). No adverse events or effects of the study intervention were observed.

Meaningful differences were found between the intervention and control groups for cry duration and parent-reported preference for future use (Table 2). The intervention group had significantly shorter median first cry and total cry durations than the control group. There was strong evidence that distributions of first cry durations differed significantly between the intervention and control groups (P=.002, Mann-Whitney test) (Figure 1). Because the 95% confidence interval for this treatment effect was from −11 to −42 seconds, we have high confidence that the treatment effect of the intervention was to decrease the duration of first cry by more than 10 seconds. The intervention group’s median total cry duration was also shorter than that of the control group.
Parents of infants in the intervention group reported a significantly greater preference to use the same method for future injections. The median preference VAS score for parents of infants in the intervention group, more than double that of the median VAS score for parents in the control group, 44.0 (P < .001) (100 indicates definitely prefer) (Figure 2). Heart rate elevation did not differ between treatment groups. The nurses rated the ease of vaccine administration as equivalent and relatively easy for both treatment groups. For intervention vs control, median ease of administration of VAS scores were 15.5 vs 15.0 (t = .7, P = .49) (0 indicates very easy). This demonstrates that while median vaccination time was statistically significantly longer for the intervention group (65.0 vs 60.0 seconds; P = .01), this 5-second difference did not adversely affect nurses’ perceptions.

We found that combining sucrose, oral tactile stimulation, and parental holding was associated with significantly reduced initial and total crying time in infants receiving multiple immunization injections. In addition, parents of infants who received this intervention reported a strong preference to use the same intervention for future immunizations. Nurses found that administering multiple injections to infants on their parents’ laps was as easy as their traditional practice of vaccinating infants on the examination table.

A combination of pain management approaches was used in this study because there is no research, to our knowledge, on how individual characteristics may influence the effectiveness of one method relative to another in infants receiving multiple injections. The pain reduction methods used, including the use of the non-pharmacologic approaches of oral tactile stimulation and holding, are theorized to act via the activation of endogenous opioid pathways.27,28 The mechanism of oral sucrose’s analgesic effect in human infants has been studied in animal models. In rat pups, oral sucrose produces an immediate increase in pain threshold, which is blocked by opioid antagonists.29 Because of its rapid onset, the effect is thought to be preingestive gustatory stimulation of opioid receptors in pain pathways, which persists 3 to 5 minutes.29

From our study design, it is not possible to determine whether the 3 pain reduction techniques are required in combination to achieve the beneficial effect we observed. Further investigations using the techniques individually and in pairs would distinguish the relative contribution of each pain reduction component. Our goal was to evaluate the effectiveness and applicability of this approach in a natural clinical setting.

The similarity in HR data between study groups merits discussion. A potential discordance exists between cardiovascular reactivity and behavioral measures of in-

### Table 1. Demographic and Clinical Characteristics of the 2 Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Intervention Group (n = 56)</th>
<th>Control Group (n = 60)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, wk†</td>
<td>9.9 ± 2.2</td>
<td>9.2 ± 1.8</td>
<td></td>
</tr>
<tr>
<td>Weight, kg‡</td>
<td>5.1 ± 0.7</td>
<td>5.2 ± 0.9</td>
<td></td>
</tr>
<tr>
<td>Male sex</td>
<td>30 (54)</td>
<td>29 (49)</td>
<td></td>
</tr>
<tr>
<td>Race or ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>39 (70)</td>
<td>42 (70)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>11 (20)</td>
<td>11 (18)</td>
<td></td>
</tr>
<tr>
<td>Biracial</td>
<td>3 (5)</td>
<td>6 (10)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>3 (5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>0</td>
<td>1 (2)</td>
<td></td>
</tr>
<tr>
<td>Prior painful procedures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heel stick</td>
<td>54 (96)</td>
<td>56 (93)</td>
<td></td>
</tr>
<tr>
<td>Circumcision (boys)</td>
<td>25 (89)‡</td>
<td>28 (97)</td>
<td></td>
</tr>
<tr>
<td>Intravenous cannulation</td>
<td>12 (21)</td>
<td>7 (12)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B vaccine</td>
<td>4 (7)</td>
<td>5 (8)</td>
<td></td>
</tr>
<tr>
<td>Venipuncture</td>
<td>3 (5)</td>
<td>4 (7)</td>
<td></td>
</tr>
<tr>
<td>Lumbar puncture</td>
<td>1 (2)</td>
<td>2 (3)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>1 (2)</td>
<td>1 (2)</td>
<td></td>
</tr>
</tbody>
</table>

*Data are given as number (percentage) of each group unless otherwise indicated. The χ² or Fisher exact test was used to test for group differences.
†Data are given as mean ± SD. The t test was used to test for group differences.
‡n = 28 in the intervention group; n = 29 in the control group.

### Table 2. Measures of Infant Injection Pain

<table>
<thead>
<tr>
<th>Measure</th>
<th>Intervention Group (n = 56)*</th>
<th>Control Group (n = 60)*</th>
<th>P Value</th>
<th>95% CI for Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cry duration, s‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First cry</td>
<td>19.0 (5.8 to 62.8)</td>
<td>57.5 (31.0 to 81.5)</td>
<td>.002</td>
<td>−11 to −42</td>
</tr>
<tr>
<td>Total cry</td>
<td>92.0 (60.0 to 140.5)</td>
<td>117.5 (77.0 to 156.5)</td>
<td>.05</td>
<td>−1 to −38</td>
</tr>
<tr>
<td>Vaccination time, s‡</td>
<td>65.0 (58.5 to 87.0)</td>
<td>60.0 (49.0 to 74.0)</td>
<td>.01</td>
<td>3 to 16</td>
</tr>
<tr>
<td>HR, beats/min†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>155.4 ± 18.1</td>
<td>154.5 ± 16.0</td>
<td>.80</td>
<td>−7 to 6</td>
</tr>
<tr>
<td>Maximum</td>
<td>204.3 ± 16.5</td>
<td>202.0 ± 15.7</td>
<td>.49</td>
<td>−9 to 4</td>
</tr>
<tr>
<td>Maximum elevation</td>
<td>49.0 ± 21.6</td>
<td>48.0 ± 18.0</td>
<td>.62</td>
<td>−9 to 7</td>
</tr>
<tr>
<td>Preference VAS score, mm§</td>
<td>97.0 (82.0 to 100.0)</td>
<td>44.0 (5.0 to 77.2)</td>
<td>&lt;.001</td>
<td>39 to 65</td>
</tr>
<tr>
<td>Ease of administration VAS score, mm§</td>
<td>15.5 (5.2 to 32.5)</td>
<td>15.0 (3.0 to 29.0)</td>
<td>.31</td>
<td>−3 to 8</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; HR, heart rate; VAS, visual analog scale.
*For cry duration, vaccination time, and preference and ease of administration of the VAS score, data are given as median (25th–75th percentile) and the Mann-Whitney test was used to test for group differences. For HR, data are given as mean ± SD and the t test was used to test for group differences.
†This is an investigator observation (J.L.S).
‡This is a 100-mm linear VAS assessing parent preference for the infant to receive future injections using study visit methods (100 indicates definitely prefer).
§This is a 100-mm linear VAS assessing nurse ease of vaccine administration (0 indicates very easy).
This observation is supported by existing reports of infant procedural pain management, in which other investigators found that their interventions were associated with changes in some measures of pain response, such as cry duration or serum β-endorphin level, but not with changes in HR. While it is possible that HR elevation is not a primary indicator of the efficacy of an intervention, it is also possible that our HR recording methods were not sensitive enough to detect a difference.

To provide oral tactile stimulation, study infants were given either a pacifier or a formula bottle at the parents’ discretion. While formula does provide some taste-induced hypoalgesia, it is unlikely that the infants who received formula obtained additional benefit. First, the milk effect (from either formula or human milk) is modest relative to the potent sucrose effect. Second, the taste-induced effect has been shown to be an on-off, rather than a graded, function. The study dose of sucrose exceeded the minimum dose (0.24 g) required to achieve an analgesic effect. The advantage of including a choice of pacifiers or milk is that parents’ preferences are respected and their own infant supplies can be used, both of which enhance the acceptability and feasibility of this approach in practice.

In this study, we demonstrated that combining oral sucrose, oral tactile stimulation (sucking on a pacifier or a bottle), and parental holding was associated with reduced crying in young infants receiving multiple injections. This simple approach is inexpensive and convenient, allowing it to be easily adopted into practice. Use of commercially prepared oral sucrose may further enhance convenience. It is critical that nurses, who are typically responsible for administering injections, reported that vaccine administration was easy using this method. Furthermore, this approach enables parents to actively participate in ameliorating their children’s pain, which may explain their overwhelming preference for its use.

Reducing the pain of multiple immunization injections in infants is challenging. To be adopted by busy pediatric practices, pain management approaches must be simple, convenient, fast acting, inexpensive, and effective. The simple pain reduction methods that have been previously described, such as cognitive-behavioral techniques (eg, blowing on a pinwheel), are effective for older children but not for infants. Use of topical anesthetics, which are effective for reducing procedural pain in infants, may be limited by concerns about safety, delayed onset, or cost when applied to multiple sites.

This study demonstrated that combining oral sucrose, oral tactile stimulation (sucking on a pacifier or a bottle), and parental holding was associated with reduced crying in young infants receiving 4 immunization injections. Parents strongly preferred this method, and nurses reported that vaccines were easily administered. Because it is effective, convenient, and inexpensive, this pain reduction approach can be easily adopted as part of standard infant immunization practice.
In conclusion, combining sucrose, oral tactile stimulation, and parental holding was associated with significantly reduced crying in young infants receiving multiple injections. Parents of infants who received this intervention reported a strong preference to use this method in the future. In addition, nurses found this injection technique easy to apply. This simple, effective, and feasible intervention was popular among parents, and can be readily incorporated into standard infant immunization practice.

Accepted for publication May 16, 2003.

From the Department of Pediatrics, University of Pittsburgh School of Medicine (Dr Reis), the Department of Pediatrics, Children’s Hospital of Pittsburgh (Dr Reis and Ms Roth and Sypham), and the Department of Epidemiology, University of Pittsburgh Graduate School of Public Health (Dr Holubkov), Pittsburgh, Pa; and the Department of Psychiatry and Behavioral Science, Feinberg School of Medicine, Northwestern University Medical School, Children’s Memorial Hospital, Chicago, Ill (Dr Tarbell). Dr Holubkov is now with the Department of Family and Preventive Medicine, University of Utah, Salt Lake City.

This study was presented as an abstract at the annual Pediatric Academic Societies Meeting; May 5, 2002; Baltimore, Md.

We thank the Children’s Hospital of Pittsburgh Research Advisory Committee for its support of this study; and the nurses and families of the Children’s Hospital of Pittsburgh Primary Care Center who participated in this study.

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