Behavioral Interventions Reduce Infant Distress at Immunization

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Objective: To assess the effectiveness of simple behavioral interventions at immunization on behavioral and biochemical indicators of distress in infants and parents in a primary care setting.

Design: Subjects were enrolled sequentially to control (standard care) and intervention groups. Intervention parents (n=57) were provided information about techniques to help their infants at immunization. Standard care parents (n=45) did not receive this information. Immunizations were videotaped and coded for infant and parent behaviors. Using a visual analog scale, parents rated their infant's and their own comfort at study enrollment, immediately after immunization, and at check-out. Saliva samples collected from infants and parents at study enrollment and at 15, 30, and 60 minutes after immunization were assayed for cortisol concentration by standard radioimmunoassay. Data were analyzed using χ², analysis of variance, and general linear modeling. Patterns of salivary cortisol change after immunization were analyzed using hierarchical linear modeling.


Subjects: Infants 2 to 24 months of age (n=102) and their parents.

Main Outcome Measures: Duration of infant distress (in seconds); parent use of behavioral intervention; infant and parent salivary cortisol concentrations (in nanomoles per liter).

Results: Intervention parents were more likely to use a behavioral technique with their infants before immunization (P<.05). Total infant distress was shorter for intervention infants at immunization (P<.01), and these infants were rated as more comfortable by their parents (P<.001) immediately after immunization. Salivary cortisol levels were lower for intervention infants at 15, 30, and 60 minutes after immunization (P<.05).

Conclusion: Simple behavioral interventions before immunization are associated with reductions in behavioral and biochemical indicators of infant distress.


Immunization is an important component of children's health supervision visits. It can also be a source of pain, anxiety, and stress for children and their parents. Physicians are concerned about the pain associated with procedures such as multiple immunizations. Despite the evidence that simple behavioral techniques are available and seem to reduce children's distress, many physicians do not routinely use interventions for minor procedures such as immunization.

Interest has grown in helping to lessen children's discomfort and improve their ability to cope with necessary medical procedures. Interventions have employed medical and behavioral methods to reduce pain and behavioral benefits have been found. In general, behavioral distress in infancy has been found to decrease with age. Most studies have assessed whether interventions reduce children's distress at the procedure for which the intervention was applied. Pacifiers and oral sucrose have been used with infants at circumcision and immunization. Distraction and selective attention (eg, deep breathing, cartoons, or music) have been used with preschool-aged and older children at immunization. Cognitive preparation and hypnosis have been used prior to procedures. Behavioral signs of children's distress and children's report of the pain they experience have been reduced with such interventions used by parents and staff. Common to behavioral interventions for improving coping with procedures is beginning the intervention during the...
SUBJECTS AND METHODS

OVERVIEW

This study was conducted at a single, urban pediatric practice during 2 summers (1997 and 1998). Infants 2 to 24 months of age presenting for a health supervision visit between 10 AM and 4 PM were eligible for participation. One hundred fourteen infants and their parents were consecutively enrolled into standard care (control) and intervention groups. Parents were informed that the purpose of the study was to understand infants' response to immunization. Informed consent was signed by the parent. The parents provided background information: parent age, educational level, and occupation; and infant birth and medical history, previous immunization experience, time awakened that day, time of visit, and time from last nap and last food intake. At study enrollment, standard care parents were given no advice or instruction about interventions to use with their infants during medical procedures. Intervention parents received an information sheet at enrollment describing techniques they might use with their infants during medical procedures. The suggested techniques included visual, auditory, oral, and kinesthetic modalities (ie, toys, parent voice, pacifier, and rocking). The study was approved by the Institutional Review Board at the University of Michigan School of Medicine, Ann Arbor.

BEHAVIORAL ASSESSMENTS

Study personnel entered the examination room after the medical history and physical examination to videotape the administration of immunizations. All immunizations were given by a medical assistant. Behaviors were coded for 3 periods—before the immunization (preparation of materials), during immunization (first oral medication [eg, acetaminophen or oral polio vaccine] through last injection [other immunizations]), and after immunization (after last injection until the end of infant distress). Videotapes were rated, blind to subject group status by 3 of us (S.D., G.W., and E.M.). Interrater reliability was calculated using interclass correlations and determined to be 71% to 91% for all variables. The coded infant and parent behaviors included the following:
- infant behavioral state before positioning and placement for immunization (sleeping, neutral alert, happy alert, fussy or crying);
- infant distress type (ie, wince, fussy, and moderate or full cry);
- infant distress duration—each type in seconds (ie, total distress time was computed by summing these categories);
- language used by parent toward infant (positive, neutral, negative or none, eg, “You are doing well”—positive; “Oh”—neutral; “This will hurt”—negative);
- type of behavioral intervention (yes, no);
- infant body position (for immunization—supine, up-right);
- infant facing position (for immunization—facing caretaker or not); and
- infant location (for immunization—examination table, held by parent).

The parents rated comfort level for their infants and themselves at 3 time points: at enrollment, immediately after immunization, and at checkout. The parents placed a mark on a visual analog scale, a line with left and right anchors—“very uncomfortable” and “very comfortable,” respectively. The distance between the very uncomfortable anchor and the parent’s mark was divided by the total line length to give the percent of very comfortable at each time point.

RESULTS

Of 114 pairs of infants and parents enrolled, 7 (3 in the standard care group, 4 in the intervention group) were excluded owing to insufficient infant saliva samples. The
cortisol concentrations and their response to experiences change with age such that younger infants have higher baseline levels and many have a greater increase in cortisol levels to pain or stress. Animal studies on the hypothalamic-pituitary-adrenocorticoid axis have also suggested there may be long-term influences of modifying early stressful experiences on the responsiveness of the hypothalamic-pituitary-adrenocorticoid axis later in life. Salivary cortisol concentration is directly proportional to serum concentration and allows for noninvasive assessment of an individual’s response to stress. Thus, many investigations have adopted this sampling technique in young children. Some studies have described infant salivary cortisol levels in response to immunization, but, to our knowledge, the effect of interventions on cortisol levels has not been explored in the context of immunization.

The purpose of this study was to assess the effectiveness of simple behavioral interventions at immunization on behavioral and biochemical indicators of distress in infants and parents in a primary care setting.
BIOCHEMICAL ASSESSMENTS

Saliva was collected from infants and parents at 4 time points: enrollment; and at 15, 30, and 60 minutes after the immunization. The parents transferred their saliva directly into a clean test tube. For the infants, a cotton dental roll with a small amount of sweetened soft drink mix (to stimulate saliva production) was placed in the mouth until wet. The sweetened soft drink mix was unavailable for a minority of infants (28%). The infant’s saliva was then expressed into a clean test tube. Study enrollment and 15-minute saliva samples were collected in the clinic and refrigerated. Parents obtained the 30- and 60-minute samples and kept them refrigerated at home until collected the next day by study personnel. All saliva samples were then frozen at −20°C until assay in duplicate using radioimmunoaassay kits for cortisol (Magic Cortisol; Chiron Diagnostics Corp, Norwood, Mass).

STATISTICAL ANALYSES

Standard care and intervention groups were compared using the SPSS statistical package (SPSS, Chicago, Ill) for behavioral and biochemical measures: analysis of variance for continuous variables, χ² for categorical variables, and general linear modeling. Variables known to affect infant distress (infant age and sex) and infant salivary cortisol change with a painful experience (infant age, sex, and initial salivary cortisol concentration) were used as covariates.4,18,25 Salivary cortisol concentrations and their log10 transforms were used for the analyses and provided information regarding group changes in cortisol for each time after immunization. To assess the patterns of individual infant and parent salivary cortisol change over time at immunization, we used an additional statistical method, hierarchical linear modeling (HLM). Hierarchical linear modeling (see Figure 2 for details) has been used in growth, educational, and neurodevelopmental analyses and is particularly well suited for assessing with-person and between-person change over time.26,31 While the name HLM specifies a linear model, HLM, like regression, allows an estimation of curvilinear relations. The HLM method establishes an initial level, growth or change over time (associated with a linear term), and a rate of change over time (associated with a quadratic term).

At level 1—Within person:

\[ b_0 = \text{initial cortisol level} \]
\[ b_1 = \text{linear change in cortisol level over time after considering initial cortisol level} \]
\[ b_2 = \text{rate of change in cortisol level over time after considering initial level and change over time} \]

At level 2—Between person:

\[ b_0 = g_{00} + g_{01} (\text{group}) \]
\[ where \ g_{00} = \text{average initial cortisol level} \]
\[ g_{11} = \text{group difference in initial cortisol level} \]
\[ b_1 = g_{10} + g_{11} (\text{group}) \]
\[ where \ g_{10} = \text{average change over time} \]
\[ g_{11} = \text{group difference over time} \]
\[ b_2 = g_{20} + g_{21} (\text{group}) \]
\[ where \ g_{20} = \text{average rate of change over time} \]
\[ g_{21} = \text{group difference in rate of change over time} \]

For all analyses, statistical significance was \( P < .05 \).

distribution of salivary cortisol concentrations at study enrollment were examined for all other infants. Five infants in the standard care group had levels higher than the 97th percentile (6 to 10 times the overall mean). Because we were concerned that these high levels could falsely suggest a benefit of interventions, these subjects were excluded. The remaining 102 subjects give a conservative analysis for this intervention study. The excluded subjects did not differ significantly from the remaining 102 infants on background information or behavioral variables.

The characteristics of the infants and parents (45 in the standard care group, 57 in the intervention group) are given in Table 1. Eighty-seven percent of all infants were full term (>37 weeks’ gestation). The remainder (7 in the standard care group, 6 in the intervention group) were 32 to 36 weeks’ gestation. Most males (86%) in this study were circumcised: this did not differ significantly by group. Sixty-seven percent of infants were white, 18% were Asian, and the remainder were African American or East Indian. Seventy-two percent of all parents reported that their infants calmed readily after previous immunizations. This and the number of previous hospitalizations, surgical procedures, current medication use, time of visit (mean \( \pm SD \) = 1:27 PM \( \pm 1:55 \) hours), time awake for the day, or time from last food intake and nap for the infant did not differ significantly by group.

BEHAVIORAL ASSESSMENTS

Videotapes were available for 37 standard care and 42 intervention infants (77% of the total sample). Twenty-three infants did not have videotape recordings made owing to technical problems. No significant differences were noted on background measures or biochemical assessments between those infants and the other infants. Before immunization, most infants (80%) were in an alert behavioral state. Of the remainder, 6% were sleeping, 8% were fussy, and 5% were crying. Infant state did not differ significantly between standard care and intervention groups.

The standard care and intervention groups were similar for several measures at immunization: duration of immunizations (mean = 1.8 minutes); infant placement, facing and body position; and parent initiation of infant placement and position. Overall, 50% of all parents initiated infant placement and position, while the remainder were directed by the medical assistant. Most infants (59%) were held by the parent in an upright position; the remainder were placed in the supine position on the examination table. Infant distress began before or at the
Table 1. Subject Characteristics*  

<table>
<thead>
<tr>
<th>Demographic Characteristic</th>
<th>Standard Care Group (n = 45)</th>
<th>Intervention Group (n = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mo</td>
<td>6.5 (4.5)</td>
<td>8.6 (5.0)^†</td>
</tr>
<tr>
<td>% Female</td>
<td>40</td>
<td>54</td>
</tr>
<tr>
<td>Birth weight, kg</td>
<td>3.4 (0.6)</td>
<td>3.5 (1.0)</td>
</tr>
<tr>
<td>Previous immunizations, No.</td>
<td>2.4 (1.1)</td>
<td>3.0 (1.3)^††</td>
</tr>
<tr>
<td>Parent</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>30.8 (4.5)</td>
<td>30.9 (5.5)</td>
</tr>
<tr>
<td>% Female</td>
<td>82</td>
<td>93</td>
</tr>
<tr>
<td>SES§</td>
<td>46.9 (13.6)</td>
<td>51.9 (13.2)</td>
</tr>
</tbody>
</table>

*All values expressed as mean (SD) unless otherwise indicated.
†P < .05.
‡P = .23 when controlled for age.
§SES indicates socioeconomic status by Hollingshead score, range 8 to 66; higher number is higher socioeconomic status based on parental level of education and occupation.

Table 2. Unadjusted Infant Distress and Salivary Cortisol Levels

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard Care Group</th>
<th>Intervention Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (± SD), mo</td>
<td>6.5 (4.5)</td>
<td>8.6 (5.0)^*</td>
</tr>
<tr>
<td>Infant distress†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of infants</td>
<td>37</td>
<td>42</td>
</tr>
<tr>
<td>Moderate + full cry</td>
<td>93.6 (69.6)</td>
<td>55.0 (39.2)</td>
</tr>
<tr>
<td>Wince + fuss</td>
<td>43.2 (50.6)</td>
<td>22.7 (26.2)</td>
</tr>
<tr>
<td>Total distress</td>
<td>136.8 (91.6)</td>
<td>77.7 (48.5)*</td>
</tr>
<tr>
<td>Salivary cortisol level‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of infants</td>
<td>45</td>
<td>57</td>
</tr>
<tr>
<td>Initial (baseline)</td>
<td>17.5 (11.4)</td>
<td>14.4 (12.3)</td>
</tr>
<tr>
<td>Time after immunization, min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15§</td>
<td>28.4 (21.6)</td>
<td>15.7 (15.7)*</td>
</tr>
<tr>
<td>30§</td>
<td>23.2 (22.0)</td>
<td>11.5 (12.7)*</td>
</tr>
<tr>
<td>60§</td>
<td>23.0 (19.5)</td>
<td>11.2 (9.9)*</td>
</tr>
</tbody>
</table>

*P < .05.
†Values expressed as mean (± SD) seconds.
‡Values expressed as mean (± SD) nanomoles per liter × 10^6.
§P < .01.

administration of oral medications for 38% of the infants and at or after injections for 61%. The time distress began did not differ significantly by group. Seventy-three percent of all infants received 2 or 3 injections at immunization and 22% received 1 injection. Four infants received 4 injections at the time of immunization. No significant group differences were noted for numbers of injections administered. Location of injections was in the thighs for all but 3 infants.

The main differences in parental behavior were observed prior to immunization. Parents of intervention infants were significantly more likely to initiate use of a behavioral technique than parents of standard care infants (64% vs 35%, P < .04). Visual items and pacifiers were used most often by all parents (48% and 30%, respectively). In addition, intervention parents were significantly more likely to use positive or neutral language with their infants before immunization than standard care parents (59% vs 31%, P < .03). No significant group differences were noted for behavioral intervention or parent language during or after the immunization.

The main infant behavioral differences were observed after immunization. Infant distress duration is reported in Table 2. Total distress was significantly shorter for intervention infants and this difference remains constant when adjusted for covariates (ie, infant age and sex). No significant effect of child placement, facing position, or body position was noted on duration of infant distress for all infants or for circumcision status for male infants.

Parent ratings of infant comfort were similar for both groups at clinic entry. However, immediately after immunization, parents of infants in the intervention group rated their infants as significantly more comfortable than standard care parents rated their infants (58% vs 20% of very comfortable, P < .001). At checkout, parent ratings of infant comfort were not significantly different (mean = 59% of very comfortable). Parents’ ratings of their own comfort level remained in the neutral range (44%-69% of very comfortable) and did not differ significantly by group at any time of self-rating.

BIOCHEMICAL ASSESSMENTS

Mean infant salivary cortisol concentrations are summarized in Table 2. Figure 1 shows the mean salivary cortisol concentrations adjusted for the following covariates—infant age and initial salivary cortisol concentration. The significant group differences were also demonstrated when the log10 transform of the salivary cortisol concentrations were used. Infant salivary cortisol response (maximum concentration at 15 or 30 minutes minus the level on enrollment) was also significantly lower for intervention infants (P < .05). No significant effect of sex on infant cortisol levels or cortisol response was noted for all infants. Circumcision status did not significantly affect cortisol levels or cortisol response for male infants. Since a study published after we had completed enrollment showed that substances like a soft drink mix spuriously increase the cortisol concentrations observed in radioimmunoassay,27 we controlled for presence or ab-
ence of the soft drink mix in analyses. When we did so, all significant group differences remained.

The sequential samples obtained in this study provided an opportunity to assess the patterns of salivary cortisol response to immunization by group. Hierarchical linear modeling is a statistical approach that allows a comparison of response levels and rates of change over time. As shown in Figure 2, top, intervention infants had a significantly lower level of change in salivary cortisol concentrations after immunization compared with standard care infants \( (P<.05) \). The rate of change was also lower for intervention infants \( (P<.05) \).

Parent salivary cortisol levels did not differ by group at any time of assessment. However, significant parent differences by group were observed using HLM (Figure 2, bottom). Intervention parents had a lower level of salivary cortisol change \( (P<.02) \) and slower rate of change \( (P<.05) \) after immunization than the standard care parents. Infant age and sex did not contribute significantly to the parent response patterns observed.

Because previous studies have suggested that behavioral interventions during the anticipatory phase are correlated with reduced distress during procedures, we explored the relation between infant behavioral state before immunization and our behavioral and biochemical findings. Considering all infants (controlling for age and initial salivary cortisol level), behavioral state seemed to predict salivary cortisol level \( (P<.001) \) and cortisol response \( (P<.01) \) at 30 minutes after immunization. Infants who were sleeping, alert, or fussy before the immunization had lower values than infants who were crying before the immunization. Experimental group assignment and infant state also seemed to affect salivary cortisol levels \( (P<.02) \) and cortisol response \( (P<.05) \) at 30 minutes after immunization. Intervention infants who were sleeping or alert before immunization had lower values, whereas infants who were distressed before immunization had higher values. Finally, infant state before immunization predicted duration of distress after the immunization. Considering all infants (controlling for age and group assignment), infant state before the immunization was significantly related to distress duration \( (P<.001) \). Infants who were sleeping or distressed before immunization had longer distress duration than the infants who were alert before immunization.

**COMMENT**

This study demonstrates that behavioral interventions for immunization reduce behavioral and biochemical indicators of distress in infants. Given suggestions to assist their infants, intervention parents were more likely to use behavioral techniques and positive or neutral statements with their infants before the immunization. The infants in the intervention group had reduced duration of behavioral distress, salivary cortisol level, and less intense cortisol response after immunization.

Previous studies of interventions to reduce stress in children have focused primarily on measures of behavioral distress. These studies have demonstrated complex interactions between parent, child, staff, and other contextual factors that seem to affect children's coping abilities. One example is the language parents and medical staff use at procedures. Statements that promote coping (eg, humor, nonprocedural talk, words to engage in coping strategy) seem to assist children even as young as 6 months, while other statements (eg, reassurance, bargaining, and explanations) seem to reduce coping and increase distress. Thus, some types of language may be more effective to assist children's coping. In our study, we suggested several behavioral interventions to parents and, thus, cannot differentiate the effectiveness of one strategy vs others. However, our findings suggest that the behavioral state of the infant prior to procedures may have differential effects. Intervention infants who were alert or fussy demonstrated less behavioral distress after the immunization than infants who were crying or sleeping before the intervention. Perhaps the alert and fussy infants were more available behaviorally, and the techniques assisted them by improving their behavioral organization and/or engaging them to an altered focal point before the immunization. Attempting to use a behavioral intervention with an infant who is already crying may result in further agitation and decreased behavioral organization prior to the immunization. Thus, the behavioral state of the infant may play a role in the effectiveness of behavioral methods to reduce distress in infants.

Studies of salivary cortisol levels for infants at stressors, ie, immunization, other medical procedures, and separation, have demonstrated that infant age, initial cortisol level, ethnicity, car rides, time of day, and interval

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**Figure 2.** Top, Infant salivary cortisol hierarchical linear modeling (HLM) patterns by experimental group at study enrollment and at 15, 30, and 60 minutes after immunization. Level and rate of change are significantly lower for intervention infants \( (P<.05) \). Bottom, Adult salivary cortisol HLM patterns by experimental group at study enrollment and at 15, 30, and 60 minutes after immunization. Level \( (P<.02) \) and rate \( (P<.05) \) of change are significantly lower for intervention parents.
from nap and food intake, are determinants of an individual infant’s cortisol response.18,20,23-25 Other potential modifiers of infant salivary cortisol response have also been explored. In a study by Lewis and Ramsay,26 parent behaviors toward their infants were carefully coded and compared with infant salivary cortisol response to immunization. The study suggested that parental attempts to soothe the infant during or after the immunization were unrelated to infant salivary cortisol levels and response after immunization. However, Lewis and Ramsay suggested that predisposing factors might play a role. In our study, we also found that parent behaviors did not differ by experimental group during or after immunization. However, parent behaviors before the immunization were modified for intervention parents and this was related to lowered salivary cortisol levels and response after immunization. Researchers have described how parent sensitivity to child factors (eg, temperament, development) and degree of the stress affects children’s coping.15,33 Giving a list of behavioral techniques to parents may have taken advantage of their sensitivity to, and knowledge of, what works to assist their infants’ coping with immunizations.

Parents’ impression of their infants’ comfort level immediately after immunization was improved for intervention parents. While this finding is consistent with the reductions in infant distress duration we observed in analysis of the videotapes, it may also reflect intervention parents’ sense of engagement in the immunization process. Similarly, while parents did not report significant changes in their own comfort level before or after their infant’s visit and immunization, group differences were observed in the pattern of parent cortisol level after their infants’ immunization. The brisk salivary cortisol level decline for standard care parents may suggest that the visit ended, in a sense, before the immunization (ie, after the medical history, physical examination, and planning components). Intervention parents, however, had higher levels and a slower rate of salivary cortisol level decline. This may reflect a continued anticipation or engagement related to their role in the immunization for their infant.

Reducing distress at medical procedures remains an important goal and this study suggests behavioral approaches to assist practitioners in this regard. Our efforts with children and parents will have immediate benefits for the medical procedures and studies suggest there may be long-term behavioral and physiological benefits for the developing infant as well.17,21

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REFERENCES