A RANDOMIZED DOUBLE-BLIND TRIAL COMPARING THE EFFECT ON PAIN OF AN ORAL SUCROSE SOLUTION VS. PLACEBO IN CHILDREN 1 TO 3 MONTHS OLD UNDERGOING SIMPLE VENIPUNCTURE

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Abstract—Background: Few clinical trials evaluating the efficacy of oral sweet solutions for procedures in the emergency department (ED) have been published. Objectives: To compare the efficacy of an oral sucrose solution vs. a placebo in reducing pain in infants undergoing venipuncture without cannulation. Methods: A randomized, double-blinded clinical trial was conducted in a pediatric ED. Infants 1 to 3 months old were randomly allocated to receive 2 mL of 88% sucrose or 2 mL of placebo, 2 min prior to venipuncture. The outcome measures were the difference in pain levels as assessed by the Face, Legs, Activity, Cry and Consolability Pain Scale (FLACC) and Neonatal Infant Pain Scale (NIPS) scores, crying time, and variations in heart rate. Results: Eighty-two participants were recruited. Data were analyzed for 38 patients from each group (excluding protocol deviations). The mean difference in FLACC scores 1 min post venipuncture compared with baseline was 2.84 ± .64 (sucrose) vs. 2.71 ± .62 (placebo) (p = 0.98). For the NIPS score, it was 2.32 ± .47 (sucrose) vs. 1.63 ± .49 (placebo) (p = 0.60). The difference in the median crying time was not statistically significant between the two groups: 63.0 ± 3 (sucrose) vs. 48.5 ± 5 s (placebo) (p = 0.17). No significant difference was found in participants’ heart rate variations and crying time were not significantly changed.

Keywords—pediatric; pain; sucrose solution; venipuncture; pain scales

INTRODUCTION

In emergency departments (EDs), children undergo many painful procedures. Weisman et al. found that inadequate analgesia in young children during procedures diminished the effects of adequate analgesia during subsequent procedures (1). There is evidence nowadays on the negative effects of early life negative experiences on growth and development in infants, and there is good evidence on the effectiveness of several nonpharmacological interventions for pain relief in neonates and infants (2,3). Many studies have suggested that the prompt and accurate recognition and treatment of pain in young infants is important for their immediate comfort and for their best possible lifelong development (4).

Use of sucrose has been widely studied for procedural pain in the neonatal intensive care unit and in the newborn nursery settings, particularly for venous blood sampling, capillary blood tests, and circumcision (5–11). In these studies, infants receiving oral sucrose solutions prior to...
procedures cried less and had overall decreased behavioral pain responses when compared with those receiving a placebo. Furthermore, sucrose is considered safe, with no serious life-threatening adverse events and only few reported side effects. Although the evidence of efficacy has been established in neonates, there have been a limited number of published clinical trials in older infants for the commonly performed painful procedures in any setting. Uncertainties remain on the effectiveness beyond the newborn period (11,12).

We hypothesized that providing an oral sucrose solution prior to venipuncture would decrease pain levels in infants 1 to 3 months of age. The objective of our study was to compare the efficacy of an oral sucrose solution vs. a placebo in reducing pain in infants 1 to 3 months of age undergoing venipuncture without cannulation in the ED.

MATERIALS AND METHODS

Study Setting – Population

This study took place in the ED of a tertiary care pediatric university-affiliated hospital with an annual patient census of 80,000 visits.

Eligible infants were those from 28 days to 3 months of actual age (not corrected) requiring a venipuncture as part of their planned ED management. Infants were excluded if they were born prior to 37 weeks of gestation, had acute respiratory illness, had a chronic cardiopulmonary condition, had assisted ventilation (such as tracheostomy or oxygen dependence), were technology dependent (such as enteral feeding tube), had a developmental delay, had an oropharyngeal malformation or dysfunction (such as cleft palate or micrognathia), or had a metabolic disease. Infants were also excluded if their parents were unable to understand the study and provide informed consent due to language barriers. Finally, infants who had previously participated in this study or who underwent a painful procedure in the preceding 60 min (bladder catheterization, bladder puncture, lumbar puncture, capillary blood tests) were also excluded.

Study Design

This was a randomized, double-blinded, placebo-controlled clinical trial. From April 2011 to September 2014, a convenience sample of infants presenting to the ED and requiring venipuncture was recruited when one of the two designated research nurses was available daytime during weekdays. The painful procedure chosen for our study was simple venipuncture without cannulation for withdrawal of blood samples. Venipuncture is frequently performed in the ED with infants of this age group. For patients in whom venipuncture was not successful at the first attempt, the ED nurse or laboratory technician performed subsequent venipuncture as required by the patient’s care after the study was completed (5 min post intervention). These participants were included for analysis because they also had an attempt at venipuncture while penetrating skin surface.

Outcomes Measures

The primary outcome measure was the difference in pain levels as assessed by the Face, Legs, Activity, Cry and Consolability Pain Scale (FLACC) 1 min post venipuncture vs. baseline. To date, there are no pain scales that have been validated precisely for the age group studied in our project. However, the FLACC scale is recommended by expert consensus groups to assess pain in children 2 months to 7 years, as its validity and reliability have been previously established (13,14). FLACC is an easily applicable pain scale in which the observer scores a patient for five categories, from 0 to 2 points, for a total maximal score of 10 points (Appendix 1) (14). Therefore, this pain scale was chosen as the measure of our primary outcome, in our population of infants from 1 to 3 months old.

Our secondary outcome measures included: variations in heart rate and crying time, differences in pain levels as assessed by the Neonatal Infant Pain Scale (NIPS) 1 min post venipuncture vs. baseline. The NIPS (Appendix 2) is a well-validated pain scale for newborns up to 1 month of age (15,16). The two recruiting research assistants had prestudy training with the two selected pain scales. Excellent unweighted kappa values were obtained between both of them (0.88 for FLACC and 0.91 for NIPS scales, respectively) on a sample of five potentially eligible patients prior to start of recruitment.

Side effects and adverse events were also recorded.

Interventions

The randomization process was performed by the institution’s pharmacy via computer-generated blocks of four. The randomization allotment was known only by a pharmacist who was not involved in the study. All providers involved in the patient’s care, research assistants, and parents were blinded to group assignment. Participants were randomly assigned to either study group: 2 mL of 88% sucrose solution (Syrup BP) or 2 mL of a placebo solution (sterile water).

Systematic reviews of the current literature have been unable to demonstrate superiority of one concentration of a sweet solution over another, but many studies suggest that higher concentrations of sweet solutions seem more effective (17–21). Therefore, we chose to study the
effect of syrup BP (product by Laboratoire Atlas Inc.,
Anjou, QC, Canada), which is 88% sucrose. This syrup
is of particular interest as it is of low cost, universally
available, and stable for approximately 3 months.
The placebo was color, consistency, and odor
matched, and was provided in identical packaging.
Two syringes were available per patient in case a sec-
ond dose had to be provided if the patient vomited.
All packaging with the intervention solutions was pro-
vided by the pharmacy in a locked cabinet in the ED.
Each package contained either the study medication or
the placebo, as randomly selected by the pharmacy.
Once eligibility was verified and consent obtained,
the research assistants took the package in the locked
cabinet in sequential order.
Timers were used to coordinate all the events. At
baseline, just prior to any intervention, the FLACC
score, the NIPS, and heart rate were recorded. Two
minutes prior to venipuncture, the solution contained
in a syringe was administered to the participant. The
solution was administered a second time if the infant
vomited < 2 min after the first dose. A maximum of
two trials was offered. A pacifier was given to the in-
fant only at parental request, and this co-intervention
was recorded. The venipuncture was performed by
an ED nurse or laboratory technician 2 min after the
administration of the study solution. The FLACC
score and the NIPS were assessed at 1 min and
5 min after venipuncture. Heart rate was measured
by pulse oximetry every minute for 5 min after the
venipuncture. The crying time was recorded with a
timer starting from the beginning of a cry until the in-
fant stopped crying (for a maximum of 5 min).

Sample Size

Sample size was calculated using a standard deviation
of ± 2.5, an alpha value of 0.05, and a power of
90% to detect a 2-point difference in mean FLACC
scores between the placebo and the sucrose group as
a clinically significant difference. Approximately 38
patients per group were needed, given a potential
dropout rate of 15%, mostly failed first trial of simple
venipuncture.

Data Collection

Baseline and clinical characteristics data were extracted
from the ED medical records for the recruited partici-
pants. A sociodemographic questionnaire was completed
by the research assistants. The FLACC and NIPS pain
scores, as well as crying time and heart rate, were re-
corded by the research assistants in real time during the
study.

Analyses

Data were entered into an Excel® database version 14.1.0
(Microsoft Corporation, Redmond, WA). Statistical ana-
lyses were performed using SPSS v.21 (IBM, Armonk,
NY) for all recruited patients. Intention-to-treat analysis
was performed. Means and medians with standard devia-
tion, difference of means, and p-values were reported.

If distributions for results of a variable followed a
normal distribution, a Student’s t-test was performed.
For the results that did not follow normal distributions,
Mann-Whitney U tests were performed to compare me-
dians or mean ranks.

Similar subgroup analyses were performed for the per-
protocol group: patients in whom venipuncture was not
successful at the first attempt. For these participants, the
ED nurse or laboratory technician performed subsequent
venipuncture after the study was completed (5 min post
intervention).

Ethics

The infants’ parent or legal guardian provided informed
consent after the study was explained by the research as-
sistants. This study received approval from the hospital’s
institutional Ethics and Review Board.

This trial was registered with ClinicalTrials.gov
(NCT01293812).

RESULTS

During the study period, 111 patients were eligible
(Figure 1). Of these, 17 families refused to participate
and 12 participants were missed while the research assis-
tants were not available. A total of 82 patients were re-
recruited: 41 in the sucrose group and 41 in the placebo
group. However, 3 patients in the sucrose group had pro-
tocol deviation: for one infant, it was impossible to give
him the solution because he cried all the time, one infant
was in fact born prematurely, and the other had an i.v.
insertion instead of simple venipuncture. In the placebo
group, three protocol deviations were also encountered:
one infant had just had a painful procedure (urethral cath-
terization in the preceding 60 min), one infant had just
had capillary blood tests instead of venipuncture, and
one infant immediately vomited the two allowed doses
of the study solution (no further evaluation was recorded).

Data were analyzed on the 76 participants who completed
the study.

Baseline demographic and clinical patient characteris-
tics are shown in Table 1; both groups were similar. Nin-
teen patients (50%) had undergone painful procedures
during a previous episode of care in the sucrose group,
and 20 patients (53%) in the placebo group. The
frequency of administration of any analgesic agents pre-procedure either at triage if presence of fever, or by parents in the previous 4 h, was similar in each group, 58% for the sucrose group and 53% for the placebo group. The use of a pacifier during the procedure at parental request was similar (54% vs. 50%).

A Mann-Whitney U test was performed to determine whether there was a difference in FLACC scores at 1 min post intervention compared with baseline between both study groups. The mean difference in FLACC pain scores between 1 min post venipuncture and baseline was 2.84 ± .64 in the sucrose group vs. 2.71 ± .62 in the placebo group (p = 0.98). For variations in NIPS scores, a Mann-Whitney U test was also performed. There was no statistically significant difference in scores between 1 min post venipuncture and baseline between groups: 2.32 ± .47 (sucrose) vs. 1.63 ± .49 (placebo) (p = 0.60).

The difference in the median crying time after venipuncture was not statistically significant between the two groups: 63.0 ± 3 (sucrose) vs. 48.5 ± 5 s (placebo) (p = 0.17). No significant difference was found in the difference of participants’ heart rates 1 min post venipuncture compared with baseline: 33 ± 6 (sucrose) vs. 24 ± 5 beats/min (placebo) (p = 0.44). Success rates for achieving a simple venipuncture at the first attempt were similar in both groups: 32 (84%) in the sucrose group and 31 (82%) in the placebo group (p = 0.74). No side effects or adverse events were noted up to 5 min post venipuncture.

**DISCUSSION**

We studied the use of oral sucrose solution prior to venipuncture to decrease pain levels in infants 1 to 3 months of age. Our results show that there were no significant statistical differences in the change in pain levels after venipuncture as measured by the FLACC and NIPS scores, or in the variation of heart rates between the sucrose and the placebo groups. However, the crying time was slightly diminished by providing sucrose instead of a placebo while performing venipuncture, but that was not statistically significant.

To our knowledge, only three previous studies have examined the effectiveness of sweet solutions as an analgesic for procedural pain in pediatric EDs. A randomized controlled trial in an emergency setting, comparing sucrose or pacifier for infants 0 to 6 months undergoing venipuncture with cannulation, demonstrated a trend in decreasing pain among the subgroup of infants of 0 to 3 months (22). The study was not powered to be statistically significant in this subgroup. Furthermore, this study showed no difference in pain scales in the subgroup of older infants (3 to 6 months). Our group has conducted a similar study specifically to evaluate the group of infants 1 to 3 months of age (23). We aimed to assess the impact of an 88% sucrose solution vs. a placebo in pain levels as evaluated by the FLACC and NIPS scores while performing venipuncture with cannulation. We have found no statistical differences in pain levels; however, the crying time was significantly reduced with the use of a sucrose solution. The third study examined the effect of sucrose during bladder catheterization for infants of 1 to 90 days (24). The subgroup of infants 1 to 30 days old who received a sweet solution showed smaller changes in pain scores, were less likely to cry during catheterization, and returned to baseline pain scores more quickly in comparison with the placebo group. However, among children of 31 to 90 days, there was no statistically significant difference.

**Limitations**

We found some limitations in our study. First, about the scores selected. We hypothesized that using one pain scale validated in infants up to 1 month of age (NIPS) and another validated in infants older than 2 months of age (FLACC) allowed us to assess pain in infants from

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**Table 1. Patients’ Baseline Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Sucrose n=38</th>
<th>Placebo n=38</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean weight kg (±1 SD)</td>
<td>5.4 (0.9)</td>
<td>5.6 (0.8)</td>
<td>0.74</td>
</tr>
<tr>
<td>Male (%)</td>
<td>23 (56)</td>
<td>22 (54)</td>
<td>0.82</td>
</tr>
<tr>
<td>Previous painful procedure (%)</td>
<td>16 (42)</td>
<td>17 (45)</td>
<td>0.73</td>
</tr>
<tr>
<td>At triage (means)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Temp °C (±1 SD)</td>
<td>37.9 (0.7)</td>
<td>37.9 (0.8)</td>
<td>0.31</td>
</tr>
<tr>
<td>HR (±1 SD)</td>
<td>165 (20)</td>
<td>163 (24)</td>
<td>0.97</td>
</tr>
<tr>
<td>RR (±1 SD)</td>
<td>42 (2)</td>
<td>42 (1)</td>
<td>0.91</td>
</tr>
<tr>
<td>Analgesia in previous 4 h (%)</td>
<td>23 (58)</td>
<td>20 (53)</td>
<td>0.67</td>
</tr>
<tr>
<td>Pacifier used during study (%)</td>
<td>20 (57)</td>
<td>19 (50)</td>
<td>0.81</td>
</tr>
</tbody>
</table>

HR = heart rate; RR = respiratory rate; SD = standard deviation.

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**Figure 1. Study flow.**
1 to 3 months of age, but this can be debated. No score was validated exactly for our age group. These scores were the best available tools, as far as we know. Similarly, it would be difficult to use the selected scores while performing a procedure because many items of these scores involve parts of the body that are not easily assessed due to different factors such as immobilization of the patients.

We have also included in our analyses patients with a failed first attempt at venipuncture for the following reasons. We considered that even if it was a failed attempt, the skin barrier was broken and it was also a painful procedure. Also, we had a similar rate of missed venipuncture between both groups (16% vs. 18%). It might have underpowered our study. However, our sample size was calculated incorporating a potential dropout rate of 15%, mostly failed first trial of simple venipuncture. In future studies, more data could be collected to improve power.

We do realize that a proportion of families (17 out of 111) refused to participate in the study. It was mostly attributed to their level of anxiety with their young infant and perceived possible delays in the interventions despite reassurance while participating in the study. Unfortunately, 12 participants were missed. It was related to a single research assistant coverage for multiple studies. Furthermore, we had six protocol deviations (three in each group), mostly secondary to changes of procedures ordered by physicians after the patients were randomized. Data were analyzed on the 76 participants who completed the study.

We also questioned whether, if we had given the sucrose solution closer in time to the procedure, the effect would have been more beneficial. In future studies, it would be interesting to test this hypothesis.

CONCLUSIONS

In infants 1 to 3 months of age undergoing simple venipuncture in the ED, administration of an oral sweet solution did not statistically decrease pain scores as measured by the FLACC and NIPS scales. The participants’ heart rate variations and crying time were not significantly changed by providing sucrose instead of a placebo.

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REFERENCES

Appendix 1. The Face, Legs, Activity, Cry and Consolability Pain scale (FLACC)

<table>
<thead>
<tr>
<th>Categories</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Face</td>
<td>No particular expression or smile</td>
</tr>
<tr>
<td>Legs</td>
<td>Normal position or relaxed</td>
</tr>
<tr>
<td>Activity</td>
<td>Lying quietly, normal position, moves easily</td>
</tr>
<tr>
<td>Cry</td>
<td>No cry (awake or asleep)</td>
</tr>
<tr>
<td>Consolability</td>
<td>Content, relaxed</td>
</tr>
</tbody>
</table>


Appendix 2. Neonatal Infant Pain Scale (NIPS)

<table>
<thead>
<tr>
<th>Categories</th>
<th>Scoring</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Facial expression</td>
<td>Relaxed</td>
</tr>
<tr>
<td>Cry</td>
<td>No cry</td>
</tr>
<tr>
<td>Breathing patterns</td>
<td>Relaxed</td>
</tr>
<tr>
<td>Arms</td>
<td>Relaxed</td>
</tr>
<tr>
<td>Legs</td>
<td>Relaxed</td>
</tr>
<tr>
<td>State of arousal</td>
<td>Sleeping/awake</td>
</tr>
</tbody>
</table>

ARTICLE SUMMARY

1. Why is this topic important?
   A lot of data on the efficacy and safety of sugar oral solutions exist in the neonatal population, but there is a lack of knowledge about the efficacy of the sugar oral solution after this period of life.

2. What does this study attempt to show?
   This study helps to develop knowledge and evidence regarding an easy, safe, and low-cost way of reducing the experience of pain in infants in the emergency department (ED).

3. What are the key findings?
   In infants 1 to 3 months of age undergoing simple venipuncture in the ED, administration of an oral sweet solution did not statistically decrease pain scores as measured by the Face, Legs, Activity, Cry and Consolability Pain (FLACC) and Neonatal Infant Pain Scale (NIPS) scales. The participants' heart rate variations and crying time were not significantly changed by providing sucrose instead of a placebo.

4. How is patient care impacted?
   Other modalities to alleviate pain need to be studied to improve pain management for pediatric patients while undergoing interventions in the ED.