Comparison of 24% sucrose as analgesic during 2nd and 3rd diphtheria-pertussis-tetanus vaccinations with 1st diphtheria-pertussis-tetanus vaccination

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Received – 03 October 2016 Initial Review – 31 October 2016 Published Online – 28 December 2016

ABSTRACT

Background: International clinical guidelines recommend oral sucrose to be given to relieve procedural pain in neonate.

Objective: The aim of this is to study analgesic effect of 24% sucrose beyond neonatal age up to 4 months by comparing its effect during the 2nd and 3rd diphtheria-pertussis-tetanus (DPT) vaccinations with the 1st DPT.

Materials and Methods: This prospective study was conducted in 150 healthy infants undergoing for their 1st, 2nd and 3rd DPT vaccination of 50 each and received 24% Sucrose 2 ml 2 min before vaccination. The outcome variables were total duration of cry, first cry, change in heart rate and modified facial coding score (MFCS). The data were analyzed statistically.

Results: Mean total duration of cry was significantly longer in 3rd DPT babies 36.3 (25.34) s than 1st DPT babies 36.3 (25.34) s. Mean duration of the first cry was significantly higher in 3rd DPT 52.1 (13.12) s and 2nd DPT babies 37.3 (15.14) s than 1st DPT babies 18.2 (14.12) s. Mean change, that is, rise in heart rate (beats/min) from baseline was significantly higher in 3rd DPT 16.6 (4.9) and 2nd DPT babies 10.3 (5.2) than 1st DPT babies 3 (2.3) Change in median MFCS at 1 and 3 min was significantly higher with 3rd DPT (3, 2) and 2nd DPT (2, 1) groups as than 1st DPT (1, 0). Longer mean total and first cry, and increase in heart rate was maximum in 3rd DPT group.

Conclusion: Nearly 24% sucrose had less analgesic activity in babies receiving 3rd and 2nd DPT vaccination compared to those receiving 1st DPT, and it suggested 24% sucrose had less analgesic effect between 2 and 4 months of age babies.

Key words: 24% sucrose, Analgesia, Diphtheria-pertussis-tetanus vaccinations, Infants

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage [1]. Newborns have all the necessary anatomical, physiological and chemical systems to perceive pain [2]. The neurological system needed for this perception has already been formed between the 24th and 28th weeks of pregnancy [3]. Newborns are even more sensitive to pain than adults. Their suppressive mechanisms are immature which lowers the threshold of pain perception [4]. Treating pain in the newborn is essential; first, for ethical reasons and, second, because pain can lead to decreased oxygenation, hemodynamic instability, or increased intracranial pressure [5]. Moreover, painful experience very early in life can promote somatization later in life [6]. Many newborn babies undergo painful procedures such as heel pricks, venepuncture, and intramuscular injections.

International clinical guidelines recommend oral sucrose to be given to relieve procedural pain in neonate [7]. These recommendations are based on results from several randomized controlled clinical trials that conclude that sucrose is effective in reducing pain in preterm and term neonates [8]. Vaccination is the most common procedure performed in infancy, although new parents might have significant concerns regarding the pain associated with routine vaccination and may disturb mother-infant bonding [9]. There are limited studies where sucrose was used beyond neonatal age [10]. The aim and objective of this study was to assess analgesic effect of 24% sucrose beyond neonatal age up to 4 months of age by comparing its analgesic effect during 2nd and 3rd diphtheria-pertussis-tetanus (DPT) vaccinations with 1st DPT in healthy infants.

MATERIALS AND METHODS

This prospective study was carried out in the immunization clinic of the Department of Pediatrics Dr. D.Y. Patil Medical College, Kolhapur, Maharashtra. Written informed consent was obtained from the parents, and ethical clearance was taken from the Ethical Committee of College. Healthy term infants less than four months of postnatal age who were on exclusive breastfeed, and attended the immunization clinic for first, second, and third DPT vaccinations were included in the study. The following babies were excluded: Preterm deliveries (<37 week of gestation), intrauterine growth retardation, birth asphyxia (Apgar score <5), infants who had required hospital admission for more than 48 h, developmental delay with neurological deficit. The babies were divided into three predefined groups comprising 50 infants each receiving 1st DPT, 2nd DPT, and 3rd DPT.
The name, age, sex, weight, length, and head circumference of babies were recorded. Oral sucrose (arbincino 24% w/v oral solution by Raptakos, Brett and co. Ltd.) 2 ml was given orally by a sterile syringe 2 min before intramuscular vaccination. Whole DPT vaccine, 0.5 ml by a 2 ml disposable syringe with 23 G” needle was given on the anterolateral aspects thigh (left/right) after cleaning the skin with spirit, in the mother’s lap by single nursing staff, so that depth of needle insertion and duration should remain apparently same in all babies. All events were recorded by audio video camera (Sony camcorder DCR SX 63) by the investigator for total duration of 3 min from the insertion of needle. A different investigator analyzed the outcome variables from the audio-video recordings in all babies. 

The outcome variables were total duration of cry, first cry, change in heart rate from baseline and modified facial coding score (MFCS). Crying time was defined as the number of seconds the baby had distressed vocalization after needle insertion within the first 3 min. Duration of first cry was defined as duration of continuous crying before a quiet interval of 5 s. The MFCS was calculated immediately and after 1 and 3 min of needle insertion. This was a composite score obtained from the sum of the following: Brow bulge, eye squeeze, nasolabial furrow, open mouth, chin quiver, and trunk movement [11]. Each parameter was scored “0” if absent and “1” if present and the total score was obtained. Heart rate in beats/min were counted just before and after vaccination at 3 min by a single investigator to avoid interpersonal error.

Every effort was made to ensure that the infant was awake before vaccination. The mothers were allowed to hold, talk or rock the baby during procedure in all groups. Non-nutritive sucking was not done during the procedure. All tests were performed between 10 am and 1 pm to avoid diurnal variation in pain response. All babies had been fed within 3 h before the interventions but had not received a feed in the previous 30 min. All data were analyzed by analysis of variance test for multiple comparisons except MFCS which was analyzed using Kruskal-Wallis test in which p<0.05 was significant.

### RESULTS

A total of 150 babies were divided into 3 predefined groups of 50 babies each. The postnatal age, weight, sex, and time since last breastfeed was comparable in all three groups (Table 1). Mean total duration of cry was significantly longer in 3rd DPT group babies 94.4 (30.12) s and 2nd DPT babies 50.6 (26.14) s as compared to 1st DPT babies 36.3 (25.34) s. The mean duration of the first cry was significantly higher in 3rd DPT babies 52.1 (13.12) s and 2nd DPT babies 37.3 (15.14) s than 1st DPT babies 18.2 (14.12) s (Table 2).

Mean change, that is, rise in heart rate (beats/min) from baseline was significantly higher in 3rd DPT babies 16.6 (4.9) and 2nd DPT babies 10.3 (5.2) as compared to 1st DPT babies 3 (2.3) (Table 3). Change in median MFCS was significantly higher with 3rd DPT (3, 2) and 2nd DPT (2, 1) groups as compared to 1st DPT (1, 0) group at 1 and 3 min post-vaccination respectively (Fig. 1). Longer mean total and first cry, rise in heart rate and higher MFCS was maximum in 3rd DPT group.

### DISCUSSION

Currently, the standard practice during routine vaccination is not to administer any analgesia. Sucrose as analgesic was first studied almost 20 years back. Even though previous neonatal studies demonstrated the effectiveness of sucrose, it was not used during routine vaccination. We hope that this study will inspire practice change in this area.

Unexpectedly our study demonstrated 24% sucrose had less analgesic activity in 3rd and 2nd DPT babies compared to 1st DPT babies suggested 24% sucrose had less analgesic effect between 2 and 4 months of age babies. Two meta-analysis of 10 and 14 randomized clinical trials on infant pain by Shah et al. [12] and Harrison et al. [13] found sucrose was effective in pain management strategy for infants and children up to 12 months of age. Lewindon et al. [14] found that 2 ml of 25% sucrose was effective during vaccination up to 6 months of age. Dilli et al. [15] explored pain relieving qualities of sucrose in children

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**Table 1: Baseline demographic characteristics of the study subject**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1st DPT vaccination (n=50)</th>
<th>2nd DPT vaccination (n=50)</th>
<th>3rd DPT vaccination (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (weeks)</td>
<td>6.2 (2.4)</td>
<td>10.1 (2.3)</td>
<td>14.2 (2.2)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>4.1 (0.4)</td>
<td>5.0 (0.4)</td>
<td>6.1 (0.3)</td>
</tr>
<tr>
<td>Time since last fed (m/n)</td>
<td>44 (8.4)</td>
<td>43 (8.3)</td>
<td>45 (8.2)</td>
</tr>
</tbody>
</table>

Mean (SD). DPT:Diphtheria-pertussis-tetanus, SD: Standard deviation

**Table 2: Duration of cry in each minute, total duration of cry and duration of first cry in seconds in study groups after DPT vaccination**

<table>
<thead>
<tr>
<th>Duration of cry in seconds</th>
<th>1st DPT vaccination</th>
<th>2nd DPT vaccination</th>
<th>3rd DPT vaccination</th>
<th>F-statistics</th>
<th>df</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st min</td>
<td>26.3 (12.94)</td>
<td>30.4 (10.34)</td>
<td>52.2 (8.25)</td>
<td>84.9</td>
<td>149</td>
<td>0.000</td>
</tr>
<tr>
<td>2nd min</td>
<td>8.8 (11.68)</td>
<td>16.2 (11.68)</td>
<td>30.6 (14.20)</td>
<td>38.85</td>
<td>149</td>
<td>0.000</td>
</tr>
<tr>
<td>3rd min</td>
<td>1.3 (3.34)</td>
<td>7.2 (4.2)</td>
<td>10.4 (3.22)</td>
<td>81.62</td>
<td>149</td>
<td>0.000</td>
</tr>
<tr>
<td>Total duration of cry</td>
<td>36.3 (25.34)</td>
<td>50.6 (26.14)</td>
<td>94.4 (30.12)</td>
<td>61.57</td>
<td>149</td>
<td>0.000</td>
</tr>
<tr>
<td>First cry</td>
<td>18.2 (14.12)</td>
<td>37.3 (15.14)</td>
<td>52.1 (13.12)</td>
<td>72.12</td>
<td>149</td>
<td>0.000</td>
</tr>
</tbody>
</table>

Mean(SD). DPT:Diphtheria-pertussis-tetanus, SD: Standard deviation, DF: Degrees of freedom
Comparison of 24% sucrose as analgesic during 2nd and 3rd DPT vaccinations with 1st DPT

Table 3: Mean change i.e., rise in heart rate (beats/min) from baseline after DPT vaccination at 3 min in study groups

<table>
<thead>
<tr>
<th>Study groups</th>
<th>Mean heart rate (beats/min), mean (SD)</th>
<th>Change in heart rate</th>
<th>t-test</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before vaccination</td>
<td>After vaccination</td>
<td></td>
</tr>
<tr>
<td>1st DPT vaccination</td>
<td>110.9 (10.9)</td>
<td>113.9 (11.9)</td>
<td>3 (2.3)</td>
</tr>
<tr>
<td>2nd DPT vaccination</td>
<td>102.4 (9.4)</td>
<td>112.6 (10.2)</td>
<td>10.3 (5.2)</td>
</tr>
<tr>
<td>3rd DPT vaccination</td>
<td>94.2 (8.9)</td>
<td>110.6 (9.8)</td>
<td>16.6 (4.9)</td>
</tr>
</tbody>
</table>

DPT: Diphtheria-pertussis-tetanus, SD: Standard deviation, DF: Degrees of freedom

Figure 1: Median change in modified facial coding score in various study groups. At 1 min: H=24.519 with 2 degrees of freedom; p=0.000. At 3 min: H=21.615 with 2 degrees of freedom; p=0.000

up to 48 months of age and found effectiveness compared to no treatment. Mowery [16] did not find similar analgesia for three vaccinations. Barr et al. [17] reported a lack of effectiveness of sucrose at younger ages. Effect of sucrose was short lasting for more invasive procedures, especially in infants beyond newborn period [18]. Rogers et al. [19] found 2 ml of 24% of sucrose was not effective for possibly more painful procedures like bladder catheterization.

Evaluation of pain in neonates is difficult due to subjective nature of pain. Various behavioral, physiological and biological responses present in neonates can be used to assess pain [20]. Validated scores for the assessment of pain include PIPP (premature infant pain profile), CRIES (crying, the requirement of oxygen for saturation above 95%, increased vital signs, expression and sleeplessness), N-PASS (neonatal pain, agitation and sedation scale), MFCS and FLACC (face, leg, activity, cry and consolability pain scale). In this study, we used four easily detectable parameters namely first cry, total duration of cry, heart rate, and MFCS. Our choices of outcome measures were a result of a review of the literature. Without direct verbal corroboration from the infants, we cannot be entirely sure that any of the above outcome measures actually reflect the degree of pain. Slater R et al. [21] used electroencephalography for specific nociceptive brain activity and electromyography for spinal nociceptive reflexes for direct assessment of pain in neonate. Limitation of this study was that we had used MFCS pain score beyond neonatal age. We had not found any adverse effects of 24% sucrose in the present study.

The mechanism for analgesic effect of sucrose in newborn occurs by activation of central endogenous opioid system an action similar to that of opioid analgesic. Endorphins act by binding to opioid receptors in the central nervous system to inhibit the feeling of pain [17]. Sucrose solution puts two mechanisms into action: First, a tactile stimulation of fluid in the mouth provides an initial effect and, second, the sense of taste stimulation prolongs the effect through the release of those endogenous opiates, termed as “sweetness effect” [22,23]. Sucrose also reduces the response of sensory systems to noxious stimuli called as antinociception [24].

The reasons for less analgesic effect of 24% sucrose during 3rd and 2nd DPT vaccinations as compared to 1st DPT in our study could be, first, we might had used lower concentration and lower dose of sucrose. According to Harrison et al. [13], and Ramenghi et al. [25], higher concentrations of sucrose solution might be more effective as the infant ages. There was insufficient evidence to recommend optimum dosing and age parameters for sucrose administration [8]. However, Lefrak et al. [26], in a review, highlighted that it was the sweet taste that produced the analgesic effect and not the volume of sucrose administered. Second, Sucrose might be more effective at calming infants during the recovery period after a painful procedure than during the actual procedure when pain is at its peak [17]. Third, repetitive procedural pain and advancing age could lead to changes in the pain sensitivity threshold because of rapid progressive neurological development. Other pharmacological measures were rarely used during vaccinations because of concerns about their effectiveness and potential adverse effects. Therefore, the effect of sucrose can be further enhanced by utilizing other nonpharmacological measures such as breastfeeding, swaddling or cuddling, skin to skin contact, and non-nutritive sucking.

CONCLUSION

Nearly 24% sucrose had less analgesic activity in 3rd and 2nd DPT babies compared to 1st DPT babies suggested 24% sucrose had less analgesic effect between 2 and 4 months of age babies. The analgesic effect of sucrose decreases as age advances.

ACKNOWLEDGMENTS

The authors are grateful to Dr. Sharma Rakesh Kumar Dean Dr. D. Y. Patil Medical College for his continuous guidance and support.

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Kavthekar et al. Comparision of 24% sucrose as analgesic during 2nd and 3rd DPT vaccinations with 1st DPT

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Funding: None; Conflict of Interest: None Stated.

How to cite this article: Kavthekar SO, Bharati HP, Kurane AB, Patil RR. Comparision of 24% sucrose as analgesic during 2nd and 3rd diphtheria-pertussis-tetanus vaccinations with 1st diphtheria-pertussis-tetanus vaccination. Indian J Child Health. 2017; 4(1):49-52.