Sucrose for analgesia in newborn infants undergoing painful procedures

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Administration of oral sucrose (in dosages of 0.5–2 ml of 12%–50% solution) approximately two minutes prior to single heel lance is effective in providing pain relief in both term and preterm infants. However, the longer-term effects of sucrose, especially for extremely premature babies, who are at the greatest risk of receiving repeat doses, is not known.

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1. INTRODUCTION

Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. The experience of pain is always subjective. Hence, verbalization of nociceptive sensation is the gold standard for assessment of pain (1). Since neonates cannot verbalize their pain, the recognition and management of pain in newborn babies is still suboptimal in neonatal intensive care units. Studies have documented that babies born at less than 32 weeks of gestation are exposed to 10–15 painful procedures each day during the first few weeks of life, and in almost 80% no treatment for pain relief is offered (2). Pain in neonates is known to cause adverse short and long-term effects. A host of physiological, biochemical and behavioural responses have been noted during painful episodes. When exposed to prolonged pain, neonates enter a state of passivity with few, if any, body movements; they have an expressionless face, decreased heart rate and respiratory variability, and decreased oxygen consumption, all suggestive of a marked conservation of energy. Prolonged or repeated pain also increases the response elicited by future painful stimuli (hyperalgesia) and even by usually non-painful stimuli (allodynia). The consequences include altered pain sensitivity (which may last into adolescence) and permanent neuro-anatomical, behavioural, emotional and learning disabilities (3).

Several strategies have been devised to help clinicians recognize pain in neonates. These take into account various autonomic and behavioural responses of neonates. Strategies to manage pain due to surgery, illness, and major procedures exist, but means to prevent or reduce pain from diagnostic procedures including heel lance and venepuncture have until recently been lacking. This Cochrane review examined the efficacy, effect of dose and safety of oral sucrose for relieving procedural pain in neonates (4).

2. METHODS OF THE REVIEW

The review authors sought to include published randomized controlled trials involving term and/or preterm neonates (maximum postnatal age of 28 days after reaching 40 weeks postmenstrual age) allocated to either
a treatment or placebo group. The main outcome measures were behaviour (duration of crying, proportion of time crying, facial reactions), physiological measurements [heart rate, respiratory rate, pulse oximeter oxygen saturation (SpO2), transcutaneous partial oxygen pressure (TcPO2), transcutaneous partial carbon dioxide pressure (TcPCO2), cortisol levels], pain indicators, and composite pain scores (including a combination of behavioural, physiological and contextual indicators). Intervention-related adverse events were also recorded. Studies were retrieved from MEDLINE (1950 to April 2009), EMBASE (1980 to 2009), CINAHL (1982 to April 2009) and CENTRAL (The Cochrane Library). The quality of trails was assessed based on methods used for sequence generation, allocation concealment, blinding, and completeness of outcome data, selective reporting and any other source of bias. Two review authors’ extracted the data independently. They then compared the data and resolved the differences. Additional data were provided by investigators of four studies.

3. RESULTS OF THE REVIEW

The 44 studies that met the inclusion criteria included 3496 infants. Twenty-two studies included term infants, 20 included preterm infants, and in two studies both term and preterm infants were included. In twenty-one studies (48%), allocation sequence had been adequately generated and in 23 (52%) allocation was adequately concealed. Blinding of participants, personnel and outcome assessors were adequate in 35 studies (79%). Incomplete outcome data were adequately addressed in 39 studies (89%). Heel lance was the intervention in 29 studies. Other interventions included: examination for retinopathy of prematurity (n=5), venepuncture (n=5), subcutaneous or intramuscular injections (n=4), bladder catheterization (n=1) and nasogastric tube insertion (n=1), and combination of procedures (n=1). The delivery method of sucrose differed between studies (syringe, dropper or sucrose dipped pacifier). Sterile water was one of the control arms in all except one study, in which sucrose was compared with breast-feeding. The outcomes evaluated differed in many of the studies. Crying behaviour was assessed in 30 studies and similar composite pain scores were reported in only 10. Outcomes were reported inconsistently – as means with standard deviation (SD) or standard error (SE), medians with ranges and often in graphic form without reporting numerical data. This prevented the use of comprehensive meta-analysis. No categorical data were reported that could be used in meta-analyses. Adverse effects were reported in 12 studies, but the length of observation was not reported. Subgroup analysis to explore heterogeneity was not performed as there were too few studies to conduct such analyses.

Compared with sterile water, sucrose (administered via oral syringe, dropper or pacifier in doses ranging from 0.5 ml to 2 ml of 12%–50% solution) was effective in reducing crying, grimacing, vagal tone, and unidimensional or multidimensional composite pain scores during heel lance. Sucrose significantly reduced crying time in 18 studies evaluating pain at heel lance. Significant reductions in crying during the first three minutes following heel lance were found in groups receiving both high (50%) or low (12%) sucrose concentrations. A meta-analysis was performed on data from three studies (n=192 infants) where the mean duration of first cry (seconds) with heel lance was assessed. Duration of the first cry was not significantly reduced in infants who were administered sucrose (dose range 2 ml of 12.5% to 2 ml of 50% sucrose) compared to the control groups [weighted mean difference (WMD) ?8.99, 95% confidence interval (CI) ?20.07 to 2.10]. However, when data from two studies (n=88) that had evaluated total crying time (seconds) were combined, the mean duration of crying was significantly reduced (WMD ?39.26, 95% CI ?44.29 to ?34.24) in infants who received sucrose (dose 2 ml of 20–30% sucrose), but significant heterogeneity was noted in the two studies. When premature infant pain profile (PIPP) scores were pooled across three studies involving heel lances, the scores were significantly reduced in infants who received sucrose (dose range 0.012–0.12 g) compared with the control group at 30 seconds (WMD ?1.64, 95% CI ?2.47 to ?0.81) (n=220 infants) and at 60 seconds (WMD ?2.05, 95% CI ?3.08 to ?1.02) (n=95) after heel lance.

Studies that had evaluated physiological measures such as changes in heart rate (pooled analysis of four studies), respiratory rate and oxygen saturations (total six studies: five showing no difference and one showing significant dip in oxygen saturation) did not find any significant differences between the groups.
Some effectiveness of sucrose administration was evident during venipuncture with respect to reducing the heart rate. The effectiveness of sucrose use for tests of retinopathy of prematurity (ROP) was less clear. A decrease in oxygen saturation was observed in the sucrose group. For other painful procedures such as bladder catheterization, subcutaneous injections, nasogastric tube insertions and circumcision, data were limited and efficacy may not have been achieved with sucrose alone.

Repeated doses of sucrose were assessed in five studies, all of which reported varied outcomes and meta-analysis was not possible. The duration of administration varied between 1 week and 6 weeks. Reduction in PIPP scores was noted, but no difference in cortisol levels was noted in any study.

The combination of sucrose with pacifier in some of the studies made it difficult to tease out the effect of pacifier from that of sucrose. Pacifier has been shown to have a calming effect as long as contact exists, but loses the effect in the absence of contact. Results from this review indicate that the use of sucrose with pacifier appears to have a synergistic effect with both single and repeated doses of sucrose.

4. DISCUSSION

4.1 APPLICABILITY OF THE RESULTS

The authors of this review conclude that sucrose given in dosages of 0.5ml–2 ml of 12%–50% solution administered approximately two minutes prior to single heel lance is safe and efficacious in providing pain relief to term and preterm infants.

Heel lance is a very common procedure in the neonatal intensive care unit. For this procedure and similar others, pain relief may be achieved with sucrose, pacifiers, breast-feeding, positioning and other sweet solutions. The results of this review are applicable to all settings.

4.2. IMPLEMENTATION OF THE INTERVENTION

Although table sugar is easily available, sucrose in concentrations of 12.5–50% is not commercially available in most under-resourced settings. Advising the use of sucrose prior to breastfeeds or for infants on exclusive breast-feeding would breach the protocols of the baby-friendly hospital initiative. Hence, if sucrose is to be used as a routine treatment for pain relief, it should be a prescribed medication.

The reduction in pain with sucrose varied between 16% and 28% on pain assessment scales (6). This magnitude of reduction has also been seen with other non-pharmacological measures like kangaroo mother care and facilitated tucking, although data on those interventions are limited.

While this review did not report any adverse events with sucrose, the long-term effects, especially of repeated administration, are largely unknown. The safety of sucrose in extremely premature babies (< 27 weeks), which are at greatest risk of receiving repeat doses, is not clear. To date only one study on long-term consequences has reported negative outcomes in preterm infants who received repeated administration of sucrose (>10 times during the first week of life) (7). The mechanism of action of sucrose is poorly understood. Several pathways have been proposed, including activation of endogenous opioids, modulation of dopaminergic and acetylcholine pathways. The effect of a seemingly simple drug and its complex interplay with the neurochemicals of a developing brain cannot be ignored.

4.3. IMPLICATIONS FOR RESEARCH

The long-term effects of sucrose need to be addressed in randomized controlled trials. There is also a need to study the safety and efficacy of sucrose in extremely premature neonates. Future studies should concentrate on other pain relieving measures such as breast-feeding, kangaroo mother care and non-nutritive sucking.
Studies should also focus on the mechanisms of action of sucrose for pain relief.

References

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