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Sweet Solution Analgesia

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Abstract

Mammals' first tasting experience is usually sweet solution. Whether it is milk (breast or formula), sugar water as in some cultures or even dates as advocated by Prophet Mohammed to his followers. Thus, it is no wonder the soothing, calming and even pain relieving effects of oral sweet solutions. Nevertheless, using sweet solution purposely for its pain-relieving effects for infants in the clinical setting is relatively recent; however, the discussion concerning sweet solution effectiveness, mechanism of actions and adverse long-term effects are still ongoing. In this chapter, we present an account of studies on both humans and animals that explored and examined the use of several sweet solutions for analgesia.

Keywords: premature, infants, pain, NICU, sucrose

1. Introduction

Young children are subjected to undergo many painful medical procedures early in their life. Althoughthese procedures are performed even in healthy children, they are more common in sick ones who need an admission to the hospital. Treating pain in the newborn is essential; firstly, for ethical reasons and, secondly, because pain can lead to several physiological and psychological effects. Not only such negative consequences are not related to repeated painful procedures but even short-term pain can have lasting negative effects [1]. Young children, including neonates, are more sensitive to nociceptive stimuli than adults [2]. Research findings emphasized that repeated exposure to painful stimuli during early stage of fundamental development of the nervous system leads to persistent behavioral and sensory changes [3]. Despite this fact, the use of appropriate pain relief interventions during potentially painful procedures is unusual in this population [4]. A paradox is still observed between the frequency of conditions that cause pain among young children and the use of

appropriate pain relief intervention. The most often cited causes for this paradox are the several myths surrounding the painful experience in the neonatal population, particularly the perception that the newborn is too immature to feel pain [5]. It is known that the knowledge about the presence of pain in newborns has greatly increased among health providers who are responsible for neonatal care [6], but it is not known how each professional puts such knowledge into practice [7]. Young children including neonates do not have the ability to verbalize their pain thus health care providers must recognize their pain. Not only unmanaged pain causes distress and delayed recovery but pain in infancy also has short-term (physiological and behavioral) and long-term developmental consequences (increased or decreased behavioral responses to pain). Although infant's pain is not expressed as conscious memory, memories of pain may be recorded biologically and alter brain development and subsequent behavior. Some recent studies have reported that simple and benign interventions such as oral sweet solutions [5, 8, 9], milk [10] or sucking a pacifier [11] reduce pain in neonates during procedures. Pain relieving effects of sweet solutions such as sucrose have been examined in term and preterm neonates [12, 13]. Glucose and other sweet tasting solutions have also been found to have pain relieving effects [9]. The effect of sugar on calming a crying baby during painful procedure is not new but there are historical references pertaining to the analgesic and calming benefits of sweet substances dating back to AD 632, when Prophet Mohammed recommended giving infants a well-chewed date [14]. Also Thorek, in his textbook, *Modern Surgical Technique*, published in 1938, explained his ideas of acceptable pediatric anesthesia: "Often no anesthesia is required. A sucker consisting of a sponge dipped in some sugar water will often suffice to calm a baby" [15].

2. Sweet solutions in the clinical settings and guidelines

The implementation of sweet solution for minor painful and invasive procedures in the NICU has been documented in many studies and extensive review of studies showed that sweet solutions have analgesic effects in young children up to one-year-old [16].

Study findings show that giving sweet solutions to young infants during painful procedures reduces painful responses and crying time tends to be shorter [9]. Different concentrations and dose were examined and showed to have a pain relieving effect. The most widely used sweet solution is sucrose [17]. Glucose is the second most commonly used solution, as it is available as prepared solution at clinics and hospitals [9]. All sweet solutions are administered in the same way, on the infants' lateral side of the tongue prior to or 2 min before the procedure through a syringe slowly over 30 s [9, 18]. Another administration technique is through the use of non-nutritive sucking using pacifier to improve its effectiveness [11, 19].

Sweet solution is a fast acting pain-relief intervention (within 10 seconds) [20]. Although there is no evidence yet about the dose-response effects [21], dose ranging from 0.5 to 2 mL of 12–24% strength show pain-relief effect [11, 22]. For premature neonates, dose is calculated in accordance to their weight/volume ratio. **Table 1** displays the doses according to week's gestation and kilograms. In preterm neonates, it is recommended to use multiple dose regimens instead of given one dose to reduce any risk of adverse effects such as chocking. Several clini-

Age group	27–31 weeks	32 to terms	0–3 months
Suggested doses (single events)	0.2 mL	0.2–0.5 mL	0.2–2 mL
Suggested doses (24 hours)	1 mL	2.5 mL	5 mL
Suggested doses (in kg)	0.5 mL/kg/dose	0.5 mL/kg/dose	0.5 mL/kg/dose
Source: [23, 24].			

Table 1. Doses according to week's gestation and kilograms and the sweetener used.

cal guidelines included the use of sweet solution for analgesia particularly for minor painful procedures. Heel lance followed by venipuncture were the top benefiting procedures of this analgesic measure [25–27]. Sweet solution may be used in infants aged 27 or more-week gestation. The volume administered for each age group should be as follow: 27–31 weeks' gestation (0.1–0.5 mL); 32–36 weeks' gestation (0.5–1 mL) and greater than 37 weeks' gestation (1–2 mL)

- Infants with known sucrose or fructose intolerance

- Infants with sucrase-isomaltase deficiency (CSID)

- Infants with glucose-galactose malabsorption

- Infants who are less than 27 weeks' gestational age

- Infants who are critically ill

- Infants with confirmed or suspected GIT pathology, such as necrotizing enterocolitis

- Infants who are paralyzed or sedated

- Infants with altered gag or swallow reflex

Source: Refs. [28, 29].

Table 2. Contraindications for the use of sweet solution as analgesic.

[5, 8, 9]. Dosage is usually expressed in mg. It is recommended to record the given dose and time on the neonates' medication sheet. Sweet solution does not need a doctor's order but it could be given by a nurse as needed, which is prepared in the pharmacy if not readily available in sterile container at floors. Once the container is open, the solution may be kept at the bedside for 24 hours if not Contaminated. It is important to record the opening date and time on the container. Sweet solution should not be used on infants less than 27-week gestations, infants who have suspected or proven gastrointestinal dysfunction/abnormalities such as ileus, obstruction, necrotizing enterocolitis or who are postoperative. Sweet solution should not be used for unstable or compromised neonates. **Table 2** lists the contraindications for the use of sweet solutions for analgesia.

Around the world more and more hospitals and clinics are implementing the use of sweet substances to reduce pain and discomfort among premature and mature infants. Yet important knowledge and research gaps concerning long-term analgesic effects of repeated administration of sweet solutions still exist. One reason could be related to the fact that the mechanism of sweet-taste-induced analgesia is still not precisely understood, which prevented the uptake of such intervention using research evidence from being used in practice.

3. Sweet solution analgesia in human studies

Sweet solution as analgesic for painful events performed on premature and full term infants is a true revolutionary, novel and relatively current idea [30, 31]. It took long time for the clinical community to recognize and accept the fact that this special group of people does feel pain and this pain has short- and long-term negative consequences [32]. Moreover, available treatments such as opioids were considered unsafe and fear of their adverse effects lead to under treatment or even no treatment at all even for invasive practices [33]. Another obstacle was the lack of proper pain assessment measures for infants and nonverbal children [34]. Physiological and behavioral responses to pain were observed [34], and this lead to the development of pain assessment tools appropriate for measuring premature and infants pain, one of these tools is the premature infant pain profile (PIPP) that is utilized to assess pain and effectiveness of pain management among premature infants [35].

Sweet solution analgesia has been used for painful procedures performed in the NICU, for immunization, injections and circumcision. Heel lances performed quite often in the NICU provoked less physiological and behavioral responses of pain when proceeded with 2 mL of oral sucrose solution of 50% [36]. Same had been noticed for other routinely applied procedures such as intravenous or arterial line insertion, lumbar puncture, tape removal and venipuncture [37–39]. This analgesic effect also extends to even older infants; sucrose was also effective in lowering pain scores due to immunization for babies aged between 1 and 12 months [23, 40]. Sucrose was beneficial when paired with other analgesic for pain relief during circumcision, probably since circumcision is a more intensely painful procedure than other routine procedures undertaken at NICU, yet it gave a synergistic effect with other analgesic methods [41]. The concentration of the sweet agent also mattered; a more concentrated sugar solution was found to be a more effective analgesic than less concentrated ones [21].

Sucrose is the most widely used agent for sweet solution-induced analgesia, nevertheless, other sweeteners were also tried and found to be effective. Fructose, lactose, milk and non-caloric sweeteners had been used for analgesia, although less frequently [21]. Glucose 20–30% solution is effective for heel lance and venipuncture in preterm and term infants [42, 43]. Fructose was as effective as sucrose and both were more effective than glucose [31]. In humans, fructose is as sweet as sucrose and sweeter than glucose; this might explain why fructose and sucrose were more effective than glucose [44]. Non-caloric sweeteners were also as effective as sucrose in reducing pain due to procedures such as heel lance [45].

The effect of sweet solution in reducing pain and calming crying infants is restricted to oral administration [12], providing evidence that it is the taste of sweetness what causes analgesia and not the sugar itself. Further evidence comes from the observation that different sugars and even artificial sweeteners produce the same effect when given orally into the oral cavity. Activating sensory afferents in the oral cavity leads to pleasurable sensation or effect. This positive hedonic effect of sweet tasting substances induced analgesia further supports the theory that it is the taste of sweetness not the caloric value of the food [46].

The mechanism of this sweet-induced analgesia is not fully elucidated. While animal studies provided more convincing evidence for the involvement of the endogenous opioid system, human studies were equivocal [42, 47, 48]. Tolerance to repeated doses of glucose did not develop, and an opioid antagonist, naloxone, given before glucose did not diminish its analgesic effects. On the other hand, babies born to methadone-addict mothers did not respond to the calming effects of sucrose. Thus, so far the evidence support the idea that the mechanism of analgesia induction might be mediated via opioid and non-opioid pathways [8, 47].

This analgesic effect is short lived and repeat administration is needed for repeated procedures. Furthermore, this effect of sweet tasting solutions does not persist beyond infancy [21]. This sweet taste–induced analgesia does not extend to adults, and it seems to be related to the degree of sweetness; thus higher sucrose concentration were preferred by children compared to adults [49]. One explanation is that as we grow, the positive hedonic value of sweet tasting substances decreases thus evoking less pleasure and less analgesia.

Other non-pharmacological methods were also studied, kangaroo mother care KMC was found to be mildly effective at lowering pain responses to heel lance in full and preterm neonates [50]. Skin-to-skin contact between infant and mother alleviated pain occurrence during heel lance as well [51].

4. Sweet solution analgesia in animal studies

Animal studies have shown an analgesic effect of sweet solutions during infancy similar to that of humans [52]. Sweet components of milk including sucrose, glucose or fructose have shown to alleviate neonatal pain [53, 54]. The analgesic effect of sweet solutions is confined to the intraoral route as sucrose reduces pain sensation when administered orally not when applied via gastric gavage [12]. The antinociceptive actions of these solutions are not due to intraoral infusion alone because they are not produced by water or lactose [54, 55].

The most commonly studied is the natural sweetener sucrose. Sucrose has a long history of calming and analgesic effect especially for neonatal pain. The first observation of sucrose pain modulating effects was obtained by Blass et al. 1987 who reported that contact with a small amount of sucrose solution on the tongue of infant rats rapidly increased the paw withdrawal latency (a measure of pain threshold) in a hot-plate test [56]. Sucrose-induced analgesia during infancy develops rapidly and persists for several minutes [57]. In addition, sucrose ingestion for a relatively long period of time produces analgesia [58, 59]. Acute

sucrose-induced analgesia is age-dependent that means it occurs mainly during the pre-weaning period in rats [57].

Artificial sweeteners have also shown analgesic actions when administered orally. Chronic saccharin intake decreases pain sensitivity and increases pain threshold as measured in hot-plate test [60]. Furthermore, acute saccharin administration for 5 hours resulted in analgesia that persists for 3 hours [61]. Aspartame, another sweetener, decreases pain sensitivity, and has shown to produce analgesic effects comparable with sucrose [62, 63].

Although the mechanisms behind sweet substances-induced analgesia are still not clearly defined; endogenous opioid system is implicated. Sweet palatable solutions augment morphine-induced analgesia [64–67], this has suggested that sweet solutions ingestion is associated with the release of endogenous opioids, a mechanism which involves stimulation of gustatory sweet receptors [68]. This mechanism was supported by the observation that sucrose reduces pain sensation when administered orally not when applied via gastric gavage [12, 69]. Furthermore, naltrexone and naloxone, opioid antagonists, were shown to abolish the analgesic effect of sweet-tasting solutions [56, 70–72] In addition, consuming palatable sweet substances increases endogenous β-endorphin activity in rat brain and in human plasma [69, 73–75]. Besides, endogenous opioid system, other neurotransmitters and receptors are probably involved. One study revealed a major involvement of nicotinic cholinergic receptors in the sweet substance-induced analgesia as atropine (cholinergic antagonist) diminished sucrose-induced analgesia [76]. Other studies have shown the involvement of noradrenaline, serotonin and their receptors in the central modulation sweet substance-induced analgesia [71, 77, 78].

Likewise, sweet solutions ability to prevent, decrease or reverse unfavorable long-term effects of neonatal pain had been explored. Unpublished data and a previous study from our lab indicate that early pain experience increases pain sensitivity and impairs spatial memory during adulthood in rats; the interventions using sucrose or saccharin solution prevented these long-term consequences of neonatal pain [75].

5. Short- and long-term effects of using sweet solutions during infancy

The fear of adverse effects following the use of nutritive sweet solutions for analgesia for premature and mature infants might be a hindrance to implementing this analgesic method. Among possible short-term effects are the fear of effect of sweet intake on milk feeding afterward. Also the effect on body weight, weather an increase due to development of sweet tooth or a decrease due to decrease in appetite for healthy food such as milk. Of the long-term effects are potential negative effects on growth and development. Of more concern would be the neurodevelopmental deficits, such as attention/orientation and motor tasks, that might result of higher intake of sugar during infancy, particularly infants who spend lengthier time at the NICU and are exposed to multiple painful procedures daily, thus requiring several doses of sweet solutions. It has been calculated that the amount of sugar a preterm infant will ingest over a period of a few weeks at the NICU will be equivalent to half a can of coke ingested by a 1-year-old [48]. Since few studies have examined the potential adverse effects

of sweet solutions given at infancy, the word is still not out. Despite that, studies have shown no short-term adverse effects, however developmental effects were not examined thoroughly enough to arrive at a conclusive conclusion.

Studies have proclaimed sweet solutions as safe with no or minimum immediate or long-term negative effects [48]. A few on the other hand have challenged this notion and claimed that many long- and short-term adverse effects are associated with the use of sweet solutions for pain management during infancy [79].

In conclusion, oral sucrose (0.5 mL/kg of a 25% solution, 2 min prior to acute painful procedures) for pain relief in preterm neonates was effective and safe, exhibiting no short-term adverse effects in weight gain and feeding patterns, during hospitalization and post discharge [80].

6. Conclusion

Pain due to procedures applied to premature infants has shown to affect, in a negative way, brain development. Newborns, particularly premature infants have brains and nervous systems that are still under development and are very vulnerable to any insults. The plasticity of the brain at this early age makes it ideal for external stimuli to have long lasting effects [1]. Thus it is logical to put forward the hypothesis that managing this pain will in addition to its pain reducing effects be useful in inhibiting or at least reducing the long term unfavorable effects of untreated pain.

Despite availability of analgesia and knowledge about infants' pain, a gap still exists between theoretical knowledge and actual practice. Thus the availability of non-pharmacological analgesia is very important and might be the selling point for the use of analgesia for premature and mature infants [4].

In conclusion, using sweet solutions for pain management, particularly, for this special age group is probably effective and safe, and has the potential of reversing or decreasing long-term adverse effects of pain. More studies need to be done to further explore the safety and the dose of sweet solution for pain during infancy.

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