Oral sucrose for pain management in infants: Myths and misconceptions

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Abstract There is a large body of evidence demonstrating the analgesic efficacy of oral sucrose during minor painful procedures in young infants. Despite this evidence, sucrose is not utilized in many settings for management of acute procedural pain (Harrison, D., et al. 2006. Pain assessment and procedural pain management practices in neonatal units in Australia. J. Paediatr. Child Health 42(1—2), 6—9). Many factors may play a role in this poor uptake of research findings in the clinical setting. One of these factors may be what the author of this paper has termed, sucrose myths; i.e. myths concerning the use, safety and effectiveness of single and repeated doses of oral sucrose in premature and term newborn neonates, and infants ranging up to 18 months of age. This paper explores the foundation and evidence behind eight sucrose myths, providing the reader with current evidence with which to base practice upon, with the aim of improving pain management during painful procedures for both sick and healthy infants.
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Background

Oral sucrose and other sweet tasting solutions have long been used for management of pain in infants. There are numerous historical references pertaining to the analgesic benefits of sweet substances dating back to 632 AD, when Prophet Mohammed recommended giving infants a well chewed date (Islamic Voice, 2002). Sugar solutions, often mixed with a combination of alcohol and cocaine or opium were used to calm infants in the late 1840s and early 1900s (Holbrook, 1959; Norberry, 1996), whilst Perry Davis pain killer, an over-the-counter concoction of sugar, alcohol and opium, was promoted as a cure for infantile colic (Holbrook, 1959). Sugar mixed with wine or whisky

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was also given to infant boys undergoing circumcision (Blanton, 1917), and in 1938, recommendations were made that anaesthesia for infants during surgery was often not required, and that ''a sucker consisting of a sponge dipped in some sugar water will often suffice to calm a baby'' (Thorek, 1938, p. 2021). The underlying mechanism of the analgesic effects of sweet tasting solutions is considered to be due to an orally mediated release of endogenous opioids (Blass and Ciaramitaro, 1994).

Blass and colleagues first reported calming effects of sweet tasting solutions in human infants in 1989 (Blass et al., 1989), however it was in 1991, that the first blinded, randomised, controlled trial demonstrating the efficacy of sucrose in the reduction of procedure-related pain in infants was published (Blass and Hoffmeyer, 1991). There are now over 45 published studies of the analgesic effects of sucrose in infants, 21 of which were included in a systematic review of sucrose for analgesia in newborn infants undergoing painful procedures (Stevens et al., 2004). Findings of the systematic review were that small volumes of sucrose or other sweet tasting solutions, compared with either placebo solutions or no treatment, were effective in reducing behavioural signs of pain and multi-dimensional behavioural and composite pain scores during and following completion of either heel lance or venepuncture. Despite this large body of evidence demonstrating the analgesic properties of oral sucrose in infants, and despite recommendations that sucrose be used during painful procedures, by national and international professional bodies concerning pain management in infants (American Academy of Pediatrics, Canadian Paediatric Society, 2000; Anand, 2001; Harrison, 2006; Royal Australasian College of Physicians, 2005) infrequent utilisation of oral sucrose in the clinical setting has been reported (Fernando et al., 2001; Gray et al., 2006; Harrison et al., 2006; Rohrmeister et al., 2003).

Over the past five years, in the course of delivering lectures on pain management and sucrose use in infants, the author of this paper identified that the same eight questions were consistently being asked from the audience, in relation to concerns about the use, safety and effectiveness of oral sucrose in infants of different gestational and postnatal ages. These questions have been titled the eight sucrose myths, and are summarised as follows:

(1) Not ''baby friendly''
(2) Grows bacteria
(3) Risk of dental caries
(4) Increased risk of poor neurological outcomes in infants <32 weeks
(5) Increases risk of necrotising enterocolitis
(6) Results in hyperglycaemia
(7) Not effective in older babies
(8) Repeated doses lead to development of tolerance to sucrose

Presenting current and relevant evidence in relation to these eight sucrose myths may impact on sucrose utilisation in the clinical setting. Therefore, in the remainder of this paper, evidence to either support or refute these ''myths'' is presented. Health professionals caring for healthy and sick infants will then be equipped with the current evidence on which to base their pain management practices during acute minor painful procedures.

Sucrose is not ''baby friendly''

The Baby Friendly Health Initiative (BFHI), launched in 1991, is an international effort by the United Nations Children's Fund (UNICEF) and the World Health Organization to promote maternity settings as centres of breastfeeding support. One of the primary strategies has been to encourage maternity settings to refuse free or low-cost breast-milk substitutes, feeding bottles or teats (UNICEF, World Health Organization, 1991). It was stated by many members of different audiences attending the author's lectures, that oral sucrose contravened the BFHI due to it being perceived as a breast-milk substitute. The manager of the BFHI in Australia (Australian Government, Department of Health and Ageing) was therefore contacted in order to establish exactly what stance has been taken with regard to the administration of oral sucrose. In a personal communication dated November 24th 2006, the manager of the Australian BFHI stated that oral sucrose for the purposes of procedural pain management in infants did not contravene the BFHI principles, and furthermore, was endorsed by the BFHI as an evidence-based pain management strategy (Kylie Campbell, Manager Baby Friendly Health Initiative, 2006). Health professionals caring for infants can therefore be assured that oral sucrose used for procedural pain reduction is not viewed as a feed substitute, and for that reason, this first sucrose ''myth'' can easily be refuted.

Sucrose grows bacteria

Although sucrose is well known for its preservative properties (Chirife et al., 1983), Abu-Arafeh et al. (1998) reported significant bacterial contamination of a 10% sucrose solution occurring 24 hours after preparation. In order to test this report,

and as a quality audit activity, bacterial testing of the 33% weight/volume (w/v) sucrose solution used in routine care in a neonatal intensive care unit, within a tertiary paediatric hospital was conducted (Harrison, 2001, updated 2006; Harrison et al., 2003). Over a one-month period, weekly cultures of four bottles of multi-use refrigerated sucrose, one non-refrigerated bottle and one control bottle of sucrose (stored in a refrigerator in the microbiology department) took place. A record was kept of the number of times each bottle was accessed, whilst the control bottle was accessed only for weekly microbiological testing. Results demonstrated no sustained growth of any bacteria, including in the bottle of sucrose most frequently accessed by clinical staff (105 times in the four-week period) (Harrison et al., 2007a). Although further studies are recommended to evaluate the risk of bacterial overgrowth in lower concentrations of sucrose solutions used for pain reduction in infants, this study provides sufficient evidence to refute the myth that sucrose or other sweet tasting solutions, in concentrations high enough to evoke an analgesic effect in infants, do not support bacterial growth.

Sucrose predisposes infants to dental caries

The risk of dental caries associated with the use oral sucrose in infants has been raised (Bucher et al., 1995; Ramenghi et al., 1996a). However there have been no published studies examining dental health in infants and children who had received sucrose for pain management in the neonatal or early infancy period. Nevertheless, it is unlikely that the small volumes of sweet solutions given to infants prior to painful procedures would be associated with the development of dental caries (Lewindon et al., 1998). In addition, the amount of sucrose administered for pain reduction is in all likelihood less than the volume and sugar content of commonly administered medications in the neonatal intensive care unit (NICU), including that of proprietary syrups, such as antibiotics, antipyretics (Lewindon et al., 1998) and oral anti-fungal preparations. The important issue of dental health in infants following discharge from a NICU is difficult to evaluate, as the effect of illness, antibiotics, orally placed endotracheal tubes, gavage tubes and oral suction all potentially predispose sick infants to poor dental health. There are no published studies identified which have examined dental health in this complex group of infants, and in fact, there is little known about infants'

dental health in the general population, as dental attendance for all infants and children before the age of two years is rare (Gussy et al., 2006). Therefore, the sucrose myth pertaining to the associated risk of dental caries cannot be confirmed and cannot be refuted. Common sense informs us that the appropriate use of small volumes of sucrose during painful procedures should not contribute to the risk of dental caries. However, as health professionals caring for sick infants and their families, we must be cognisant of the risk of over using sucrose, and ensure that oral sucrose is not promoted as an agent to be frequently used in the promotion of calming in crying infants, outside of the realm of procedural pain reduction.

Increased risk of poor neurological outcomes in infants < 32 weeks

This myth arose from a study conducted to examine the role of sucrose for consistent reduction of procedural pain in the first week of life, in long-term developmental outcomes (Johnston et al., 2002). The authors hypothesised that, given the emerging data on the potential negative behavioural sequelae to untreated pain in premature neonates, if procedural pain were adequately managed in the first week of life, there may be a positive effect on subsequent outcomes. To test this hypothesis, 103 premature infants less, than 32 weeks gestational age, during the first week of life, were randomised to receive either oral sucrose (24% w/v), or water, prior to all invasive and noxious procedures. Procedures in which the study solutions were administered included insertion of gastric tubes, adhesive tape removal and endotracheal suction, as well as heel lances and venepuncture. A mean number of 63 doses of sucrose per infant in the treatment group and 58 doses of water per infant in the control group were administered over the first week of life. Results showed no differences in neurobehavioural outcomes between infants in the control group compared to the infants in the sucrose group, at any of the three assessment points (32, 36 and 40 weeks gestational age). However, a secondary analysis of the data, of neurobehavioural outcomes in the sucrose group only, indicated that higher doses of sucrose, compared to lower doses of sucrose, predicted poorer neurobehavioural outcomes at 36 and 40 weeks gestational age. This finding however requires further discussion.

One explanation put forward by the authors for this finding, was, as a possible consequence of ceasing all sucrose administration during invasive

procedures after the seven-day trial period, an increased sensitivity to pain developed, affecting the infants' neurobehavioural scores of alertness, orientation, movement and vigour (Johnston et al., 2002). Another possibility was that the multiple doses of sucrose given to the newborn premature infants repeatedly stimulated the immature endogenous opiate system, consequently interfering with the normal development and functioning of the infants' endogenous opiate system. Alternatively, the authors offered a methodological explanation, relating to the inadequate sample size included in the secondary analyses; differences in the neurobehavioural scores between those infants who received higher doses of sucrose compared to those infants who received less doses, may have been due to chance alone. Despite acknowledgment of the limitations of their study, cautionary use of repeated doses of sucrose in premature infants was nevertheless recommended (Johnston et al., 2002).

In contrast, a subsequent study of a similar design, which also evaluated adverse events, clinical outcomes, and neurological outcomes following consistent use of sucrose in premature infants, did not show any such association between sucrose use and adverse outcomes (Stevens et al., 2005). Stevens et al. (2005) randomised 66 premature infants to receive either standard care, water and pacifier, or sucrose and pacifier during all invasive procedures during the first 28 days of life; this was a noticeably longer study period than the seven days in Johnston et al. (2002). The results showed no differences in the neurobiological risk scores between the sucrose group and the other two groups, thereby ruling out an association between consistent use of oral sucrose during the first month of life during invasive procedures, with poor neurological outcomes in infants younger than 32 weeks gestational age. As this study period was over an extended time frame, the lack of association between consistent use of sucrose and adverse long-term outcomes is more likely to be an accurate reflection of the truth; therefore this fourth sucrose myth can be refuted with some degree of confidence.

Increases risk of necrotising enterocolitis

Concerns have been raised relating to an association between necrotising enterocolitis in premature infants and the oral administration of sweet solutions (Acharya et al., 2004; Ramenghi et al., 1996b). This concern stems from a report published

30 years ago in which there was an increased incidence of necrotising enterocolitis in premature infants administered multiple doses of calcium suspended in a 20% sucrose solution (Willis et al., 1977). The high incidence of necrotising enterocolitis was attributed to the hyperosmolar effects of the suspension. However many medications currently used in routine care of sick infants have a higher osmolality than the 25—50% sucrose and 30—50% glucose solutions used in the majority of trials to date (Bucher et al., 2000; Mutz and Obladen, 1985; Women's & Children's Hospital Pathology Royal Children's Hospital, personal communication, 30th November, 2004). It is unlikely that the small volumes of oral sucrose or glucose required for procedural pain reduction would be associated with an increased risk of necrotising enterocolitis. However, a small number of studies have sought to ascertain whether administration of sucrose does indeed lead to an increased incidence of necrotising enterocolitis.

In two studies which evaluated the efficacy of 25% oral sucrose compared to placebo during a single painful procedure, incidence of necrotising enterocolitis was included as one of the reported outcome measures (Acharya et al., 2004; Ramenghi et al., 1996b). In both these studies, there were no differences in the incidence of necrotising enterocolitis following administration of either sucrose or placebo. Adding greater weight to this evidence, due to the large numbers of study solutions administered over a period of 28 days, Stevens et al. (2005) also reported no differences in the incidence of necrotising enterocolitis between premature infants randomised to receive oral sucrose to those infants randomised to either of the two non-sucrose arms of their study.

Although there is sufficient evidence to dispel this fifth sucrose myth, health professionals caring for sick infants should always let caution prevail. It must be remembered that only small volumes of sucrose are required for procedural pain reduction, and that sucrose should be used only for management of short-lived acute pain. Due to the short acting analgesic effects of sucrose (Blass and Shah, 1995), it is not effective and not recommended for use in situations of ongoing distress, irritability, hunger or chronic pain.

Results in hyperglycaemia

It has been suggested that hyperglycaemia may be a risk for premature infants subsequent to oral sucrose administration. The evidence for this theoretical risk however, is lacking. For those

randomised, controlled trials of sucrose efficacy, in which blood glucose measurements were included as an outcome measure, there were no differences in blood glucose levels between the sucrose and water groups, including the two studies by Johnston et al. and Stevens et al. in which multiple doses of sucrose were administered to premature infants (Bucher et al., 1995; Gormally et al., 2001; Johnston et al., 2002; Stevens et al., 2005). In addition, a study conducted nearly 30 years ago, in which systemic absorption of oral glucose in adult participants was measured, there was negligible absorption of glucose through the oral mucosa, demonstrating that substantial volumes of the solution needed to be swallowed in order for an increase in blood sugar level to occur (Gunning and Garber, 1978). As only small volumes of sucrose are required for sucrose-induced analgesia (Blass and Smith, 1992; Stevens et al., 2004), it is improbable that infants would be administered large enough volumes to effect blood glucose levels. This sixth sucrose myth can therefore be easily refuted.

Sucrose is not effective in older babies

This sucrose myth is grounded in evidence originating from findings of animal studies. Anseloni et al. (2002) reported that sucrose analgesia in the rat model began to decline from 15 days of age, and was ineffective beyond 17 days of life (Anseloni et al., 2002). As the maturity of a rat pup at 17 days of age is estimated to be equivalent to early infancy in humans (Fitzgerald and de Lima, 2001), the decline and loss of sucrose-induced analgesia with increasing age in rodents, may also suggest the same age-related decline in sucrose-induced analgesia in human infants.

There is however, evidence of sucrose-induced analgesia in older human infants, which has primarily originated from studies conducted during routine immunisation in infants from two months of age, and ranging up to 18 months of age (Allen et al., 1996; Barr et al., 1995; Lewindon et al., 1998; Lindh et al., 2003; Reis et al., 2003). With the exception of one study (Barr et al., 1995), these studies have all been randomised, controlled trials evaluating the efficacy of oral sucrose or glucose administered prior to either a single injection, or two or more injections given during one episode of routine immunisation. The study by Barr et al. (1995) was a longitudinal randomised, controlled trial, following a cohort of 57 infants receiving immunisations at two and four months of age. Results of all these studies showed evidence of analgesic benefits of oral sucrose or glucose during immunisation, however the effects were demonstrated to be more moderate compared with the profound analgesia exerted by sweet tasting solutions in the neonatal period (Stevens et al., 2004). In addition, a number of studies used higher volumes or concentrations of sucrose than described in studies including newborn infants (Lewindon et al., 1998; Reis et al., 2003). For example, in the study by Lewindon et al. (1998), 2 ml of a 75% sucrose solution was used. A blinded, randomised, controlled trial of 33% (w/v) sucrose solution compared to sterile water during heel lancing, which included 30 infants older than 28 days of life, also showed that sucrose, compared to water, was effective in reducing pain. However, the authors also reported that the analgesic effects were more modest than that observed in younger infants (Harrison et al., 2003, 2005).

In contrast, a recently published study reported that 24% (w/v) sucrose failed to reduce behavioural signs of pain when administered to infants aged up to 90 days prior to urethral bladder catheterisation (Rogers et al., 2006). Effective sucrose analgesia was evident only in a subgroup of infants aged less than 30 days, whilst, for the infants older than 30 days of age, sucrose was reported to be no more effective than water. Although Rogers et al. acknowledged that their study was not adequately powered to detect differences within subgroups of infants, and the limited numbers of infants older than 30 days of age may have been too small to detect any such differences in pain scores (Rogers et al., 2006), the findings nevertheless, add to the evidence suggesting that sucrose analgesia beyond the first month of life may be less evident than that observed in the neonatal period and higher volumes or concentrations may be required to elicit the sweet taste mediated analgesic effect.

In contrast again, findings of a study of a different nature; a descriptive longitudinal cohort study, evaluating the effectiveness of oral sucrose (33% w/v) in sick hospitalised infants, were that analgesic effects of sucrose in reducing behavioural responses to heel lance pain were sustained throughout an entire hospitalisation, ranging from one to five months (Harrison et al., 2007b). Although a 33% sucrose solution is more concentrated than that used in the majority of trials included in the systematic review of sucrose for analgesia in newborn infants undergoing painful procedures (Stevens et al., 2004), and higher than the 24% solution used in Rogers et al. (2006), the lack of any increase in pain responses over time is suggestive of ongoing sucrose analgesia.

In summary, there is adequate evidence to refute this seventh sucrose myth, and to recommend that oral sucrose does provide some analgesia in infants beyond the neonatal period, however some of the evidence is conflicting. Further adequately powered randomised, controlled trials of sucrose efficacy in older infants undergoing painful procedures are therefore warranted to resolve uncertainties regarding sucrose analgesia beyond the neonatal period, and throughout infancy.

Repeated doses lead to development of tolerance to sucrose

The question has been posed; do repeated doses of sucrose result in the development of a tolerance to sweet-tasting solutions, with the end result being a reduction of sweet taste-mediated analgesia (Eriksson and Finnstrom, 2004)? Studies conducted in animal laboratories have indeed shown that repeated doses of sweet-tasting solutions or prolonged uninterrupted periods of sweet solution consumption could induce either sucrose tolerance, as demonstrated by reduced thermal pain thresholds (Holder and Bolger, 1988) or morphine tolerance (Fidler et al., 1993; Lieblich et al., 1983). However, these effects were demonstrated in rats following consumption of either large volumes of sweet solutions, up to 50 ml daily for up to 28 days, or having an uninterrupted supply of sweet solution for three to six hours. It is inconceivable that such doses or duration of sucrose consumption would ever be given to any infant in a NICU. In addition, Lieblich et al. (1983) showed that the same sweet taste-induced opioid tolerance was not evident in a different strain of rat, which consumed an average of 24 ml of saccharin solution daily for 28 days; an amount still vastly in excess of what would be administered to infants for pain reduction.

Although there are a small number of studies conducted in human infants, which have evaluated the analgesic effects of repeated doses of oral sucrose (Eriksson and Finnstrom, 2004; Harrison et al., 2007b; Johnston et al., 2002; Mucignat et al., 2004; Stevens et al., 2005), only three of these evaluated the analgesic effects of oral sucrose over a period longer than one week (Harrison et al., 2007b; Mucignat et al., 2004; Stevens et al., 2005). Mucignat and colleagues compared pain scores in 33 healthy former premature infants over a six-week period, during 265 subcutaneous injections of erythropoietin factor, during four different conditions: 30% oral sucrose, topical anaesthetic cream (EMLA®), non-nutritive sucking (NNS),

or a combination of all three interventions. Although results of this cross-over study showed a significant reduction in pain scores during the oral sucrose intervention compared to both NNS and EMLA® alone, with the combination of interventions resulting in a further reduction in pain scores, results were not analysed in terms of comparison of successive pain scores over the six-week period. Although this information added to the considerable body of literature concerning analgesic effects of oral sucrose in infants, and its superior analgesic properties over both NNS and EMLA® when used alone, it did not contribute to the knowledge gap around effectiveness of repeated doses or prolonged use of sucrose.

Only Stevens et al. (2005) and Harrison et al. (2007b) have analysed the analgesic effects of prolonged sucrose use over a prolonged period, and in both studies, sucrose was reported to remain effective subsequent to multiple doses. Stevens et al. (2005) randomised 66 premature infants to receive either standard care, or water and NNS or sucrose and NNS, during all invasive minor procedures during the first 28 days of life. Findings were that there was evidence of ongoing efficacy of the combination of oral sucrose and NNS throughout the 28-day period, as demonstrated by lower Premature Infant Pain Profile (PIPP) scores during weekly heel lancing compared to PIPP scores of the infants randomised to the control group. In addition, there was no increase in pain scores in the sucrose and NNS group over the period of the study. Harrison et al. (2007b) conducted a longitudinal study of 55 sick hospitalised infants in which the effectiveness of oral sucrose during heel lancing, over the duration of a hospitalisation, ranging from one to five months, was evaluated. Findings were that pain scores remained consistently low throughout the entire hospitalisation. As oral sucrose was given prior to, and during, all 443 pain assessments conducted during heel lancing, and no increase in either behavioural or physiological responses over consecutive procedures was evident, this suggests a lack of development of sucrose tolerance despite multiple doses (Harrison et al., 2007b).

In reality, the actual sucrose consumption for many infants nursed in NICUs is underestimated as the administration of oral sucrose also occurs outside the prescribed sucrose solution specified for pain reduction. Medications administered to infants in the NICU are frequently suspended in sucrose solutions, including most preparations of the frequently prescribed antifungal medication, nystatin. For example, in this author's NICU setting, the oral antifungal preparation, nystatin is

administered orally three times each day, to all infants, to reduce the risk of systemic *Candida* infection. The sugar content in different nystatin preparations may vary widely, and, in fact, due to changing costs and availability, during the 15-month data collection period for the aforementioned study (Harrison et al., 2007b), four different nystatin preparations were used. All preparations had varying concentrations of sucrose, and included a sugar-free solution, one suspended in a 12.5% (w/v) sucrose solution, one suspended in a 50% sucrose (w/v), and, in addition, one of the infants in the cohort was specifically prescribed a more concentrated formulation of nystatin, which was suspended in a preparation containing 62.5% sucrose. Yet, despite the substantial numbers of sucrose doses given to the infants in the longitudinal study, in addition to other sources of sucrose contained within frequently administered oral medications, no increase in pain responses over successive heel lance procedures were observed, suggestive of a lack of evidence to support development of sucrose tolerance (Harrison et al., 2007b).

Conclusion

In this literature review, current evidence relating to eight common questions, or myths, concerning the use, efficacy, safety, and effectiveness of oral sucrose for procedural pain management in infants has been presented. It has been highlighted that further evidence is warranted concerning analgesic effects of oral sucrose in infants up to 18 months of age, and there is a paucity of information concerning dental health in infants following discharge from a NICU. There is no evidence to support that appropriate use of oral sucrose for reduction of pain during acute minor painful procedures in newborn and young infants, including premature infants, increases the risk of necrotising enterocolitis, hyperglycaemia, adverse neurodevelopmental outcomes, or leads to tolerance to sucrose analgesia. In addition, the use of oral sucrose for procedural pain reduction does not contravene the BFHI, and there is no evidence that sucrose, in concentrations sufficient for pain management, supports the growth of bacteria. In conclusion, oral sucrose, when administered to both healthy and sick hospitalised infants, in small volumes prior to acute painful procedures, is a safe, effective, economic, and feasible pain reduction strategy. As health professionals caring for infants, we have an ethical responsibility to consistently utilise evidence-based pain reduction strategies such as oral sucrose, during acute minor painful procedures.

Acknowledgments

References

Abu-Arafeh, I., et al., 1998. Randomised controlled trial of sucrose by mouth for the relief of infant crying after immunisation. Arch. Dis. Child 79 (5), 465—466.

Acharya, A.B., et al., 2004. Oral sucrose analgesia for preterm infant venepuncture. Arch Dis. Child Fetal Neonatal Ed. 89 (1), F17—F18.

Allen, K.D., et al., 1996. Sucrose as an analgesic agent for infants during immunization injections. Arch. Pediatr. Adolesc. Med. 150 (3), 270—274.

American Academy of Pediatrics, Canadian Paediatric Society, 2000. Prevention and management of pain and stress in the neonate. Pediatrics 105 (2), 454—461.

Anand, K.J., International Evidence-Based Group for Neonatal Pain, 2001. Consensus statement for the prevention and management of pain in the newborn. Arch. Pediatr. Adolesc. Med. 155 (2), 173—180.

Anseloni, V.C., et al., 2002. Age-dependency of analgesia elicited by intraoral sucrose in acute and persistent pain models. Pain 97 (1—2), 93—103.

Barr, R.G., et al., 1995. ''Sucrose analgesia'' and diphtheria-tetanus-pertussis immunizations at 2 and 4 months. J. Dev. Behav. Pediatr. 16 (4), 220—225.

Blanton, M.G., 1917. The behavior of the human infant during the first thirty days of life. Psychol. Rev. 24 (6), 456—483.

Blass, E., Ciaramitaro, V., 1994. A new look at some old mechanisms in human newborns. Monogr. Soc. Res. Child. Dev. 59 (1).

Blass, E.M., Hoffmeyer, L.B., 1991. Sucrose as an analgesic for newborn infants. Pediatrics 87 (2), 215—218.

Blass, E.M., Shah, A., 1995. Pain-reducing properties of sucrose in human newborns. Chem. Senses 20 (1), 29—35.

Blass, E.M., Smith, B.A., 1992. Differential effects of sucrose, fructose, glucose, and lactose on crying in 1- to 3-day-old human infants: qualitative and quantitative considerations. Dev. Psychol. 28 (5), 804—810.

Blass, E.M., et al., 1989. Sensorimotor and motivational determinants of hand-mouth coordination in 1—3-day-old human infants. Dev. Psychol. 25, 963—975.

Bucher, H.U., et al., 1995. Sucrose reduces pain reaction to heel lancing in preterm infants: a placebo-controlled, randomized and masked study. Pediatr. Res. 38 (3), 332—335.

Bucher, H.U., et al., 2000. Artificial sweetener reduces nociceptive reaction in term newborn infants. Early Hum. Dev. 59 (1), 51—60.

Campbell, K., Manager, Baby Friendly Health Initiative, 2006. Oral sucrose does not contravene the Baby Friendly Health Initiative, Melbourne; November, 24, 2006, Personal Communication.

Chirife, J., et al., 1983. In vitro study of bacterial growth inhibition in concentrated sugar solutions: microbiological basis for the use of sugar in treating infected wounds. Antimicrob. Agents Chemother 23 (5), 766—773.

Eriksson, M., Finnstrom, O., 2004. Can daily repeated doses of orally administered glucose induce tolerance when given for neonatal pain relief? Acta Paediatr. 93 (2), 246—249.

Fernando, A., et al., 2001. Changing attitudes and practice of pain relief for commonly performed neonatal procedures. Paper presented at the International Paediatric Conference, Beijing.

Fidler, P., et al., 1993. Early onset of reduced morphine analgesia by ingestion of sweet solutions. Physiol. Behav. 53 (1), 167—171.

Fitzgerald, M., de Lima, J., 2001. Hyperalgesia and allodynia in infants. In: Finley, A., McGrath, P. (Eds.), Acute and Procedure Pain in Infants and Children, Vol. 20. IASP Press, Seattle, WA, pp. 1—10.

Gormally, S., et al., 2001. Contact and nutrient caregiving effects on newborn infant pain responses. Dev. Med. Child Neurol. 43 (1), 28—38.

Gray, P.H., et al., 2006. Pain relief for neonates in Australian hospitals: a need to improve evidence-based practice. J. Paediatr. Child Health 42 (1—2), 10—13.

Gunning, R.R., Garber, A.J., 1978. Bioactivity of instant glucose. Failure of absorption through oral mucosa. J. Am. Med. Assoc. 240 (15), 1611—1612.

Gussy, M.G., et al., 2006. Early childhood caries: current evidence for aetiology and prevention. J. Paediatr. Child Health 42 (1—2), 37—43.

Harrison, D., 2001. Neonatal Unit Guideline: Oral Sucrose for Procedural Pain Management in Infants. Royal Children's Hospital, Melbourne, Australia, updated 2006.

Harrison, D., Australian College of Neonatal Nurses, 2006. Management of pain in sick hospitalised infants. Neonatal Paediatr. Child Health Nursing 9 (1), 27—29.

Harrison, D., et al., 2003. Oral sucrose for procedural pain in sick hospitalized infants: a randomized-controlled trial. J. Paediatr. Child Health 39 (8), 591—597.

Harrison, D., et al., 2005. Erratum: Re: Oral sucrose for procedural pain in sick hospitalized infants: a randomized-controlled trial (J. Paediatr. Child Health 2003, 39, 5917). J. Paediatr. Child Health 41 (9—10), 535.

Harrison, D., et al., 2006. Pain assessment and procedural pain management practices in neonatal units in Australia. J. Paediatr. Child Health 42 (1—2), 6—9.

Harrison, D., et al., 2007a. Bacterial contamination of oral sucrose solutions. Arch. Dis. Child Fetal Neonatal Ed. 92 (2), 55.

Harrison, D., et al., 2007b. The effectiveness of repeated doses of oral sucrose in reducing procedural pain during the course of an infant's prolonged hospitalisation. J. Paediatr. Child Health 43 (Suppl. 1), A20.

Holbrook, S., 1959. The Golden Age of Quackery. Macmillan, New York.

Holder, M.D., Bolger, G.T., 1988. Chronic sweet intake lowers pain thresholds without changing brain mu- or delta-opiate receptors. Behav. Neural Biol. 50 (3), 335—343.

Islamic Voice, 2002. Relief of pain: a medical discovery. http://www.islamicvoice.com/april.2001/quran.htm; (accessed 7th October, 2004).

Johnston, C.C., et al., 2002. Routine sucrose analgesia during the first week of life in neonates younger than 31 weeks' postconceptional age. Pediatrics 110 (3), 523—528.

Lewindon, P.J., et al., 1998. Randomised controlled trial of sucrose by mouth for the relief of infant crying after immunisation. Arch. Dis. Child 78 (5), 453—456.

Lieblich, I., et al., 1983. Morphine tolerance in genetically selected rats induced by chronically elevated saccharin intake. Science 221 (4613), 871—873.

Lindh, V., et al., 2003. Emla cream and oral glucose for immunization pain in 3-month-old infants. Pain 104 (1—2), 381—388.

Mucignat, V., et al., 2004. Analgesic effects of Emla cream and saccharose solution for subcutaneous injections in preterm newborns: a prospective study of 265 injections. Arch. Pediatr. 11 (8), 921—925.

Mutz, A.E., Obladen, M.W., 1985. Hyperosmolar oral medication and necrotizing enterocolitis. Pediatrics 75 (2), 371—372.

Norberry, J., 1996. Illicit Drugs, Their Use and the Law in Australia. Department of the Parliamentary Library, Parliament of Australia, Canberra. (No. 12).

Ramenghi, L.A., et al., 1996a. Effect of non-sucrose sweet tasting solution on neonatal heel prick responses. Arch. Dis. Child 74 (2), F129—F131.

Ramenghi, L.A., et al., 1996b. Reduction of pain response in premature infants using intraoral sucrose. Arch. Dis. Child 74 (2), F126—F128.

Reis, E.C., et al., 2003. Effective pain reduction for multiple immunization injections in young infants. Arch. Pediatr. Adolesc. Med. 157 (11), 1115—1120.

Rogers, A.J., et al., 2006. A randomized, controlled trial of sucrose analgesia in infants younger than 90 days of age who require bladder catheterization in the pediatric emergency department. Acad. Emerg. Med. 13 (6), 617—622.

Rohrmeister, K., et al., 2003. Pain and stress management in the neonatal intensive care unit-a national survey in Austria. Wien Klin. Wochenschr. 115 (19—20), 715—719.

Royal Australasian College of Physicians, 2005. Guideline Statement: Management of Procedure-Related Pain in Neonates. Paediatrics & Child Health Division. The Royal Australasian College of Physicians, Sydney.

Stevens, B., et al., 2005. Consistent management of repeated procedural pain with sucrose in preterm neonates: is it effective and safe for repeated use over time? Clin. J. Pain 21 (6), 543—548.

Stevens, B., Yamada, J., Ohlsson, A., 2004. Sucrose for analgesia in newborn infants undergoing painful procedures (Cochrane Review). In: The Cochrane Library, Issue 1. John Wiley & Sons, Ltd, Chichester, UK.

Thorek, M., 1938. Modern Surgical Technique, Vol. 111. Lippincott, Montreal.

UNICEF, World Health Organization, 1991. Baby-friendly hospital initiative. http://www.unicef.org/programme/breastfeeding/baby.htm; (accessed June 17, 2007).

Willis, D.M., et al., 1977. Unsuspected hyperosmolality of oral solutions contributing to necrotizing enterocolitis in very-low-birth-weight infants. Pediatrics 60 (4), 535—538.