Mechanisms of sucrose and non-nutritive sucking in procedural pain management in infants

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Pain Res Manage 2001;6(1):21-28.

The administration of sucrose with and without non-nutritive sucking (NNS) has been examined for relieving procedural pain in newborn infants. The calming and pain-relieving effects of sucrose are thought to be mediated by endogenous opioid pathways activated by sweet taste. The orogustatory effects of sucrose have been demonstrated in animal newborns, and in preterm and full term human infants during painful procedures. In contrast to sucrose, the analgesic effects of NNS are hypothesized to be activated through nonopioid pathways by stimulation of orotactile and mechanoreceptor mechanisms. Although there is uncertainty as to whether the effects of sucrose and NNS are synergistic or additive, there is sufficient evidence to support the efficacy of combining the two interventions for procedural pain relief in infants. In this review article, the underlying mechanisms of sucrose and NNS, separately and in combination for relieving procedural pain in preterm and full term infants, are examined. Clinical and research implications are addressed.

Key Words: *Infants; Mechanisms; Non-nutritive sucking; Pain; Sucrose*

Mécanismes de l'administration du sucrose et de la succion non nutritive dans le traitement de la douleur associée aux interventions chez les enfants en bas âge

RÉSUMÉ : L'administration du sucrose associée ou non à la succion non nutritive (SNN) pour soulager la douleur associée aux interventions chez les nouveau-nés a fait l'objet de recherche. Les effets calmants et analgésiques du sucrose seraient liés à la libération d'opioïdes endogènes, déclenchée par la saveur sucrée. Les effets orogustatifs du sucrose ont été démontrés chez des animaux nouveau-nés, ainsi que chez des nourrissons prématurés et nés à terme pendant des interventions douloureuses. Contrairement au sucrose, les effets analgésiques de la SNN seraient liés à l'activation des voies non opioïdes, déclenchée par la stimulation des mécanismes orotactiles et mécano-récepteurs. Même si l'incertitude règne quant aux effets du sucrose et de la SNN, à savoir s'ils sont synergiques ou complémentaires, il existe suffisamment de preuves pour appuyer l'efficacité de l'association des deux mesures pour soulager la douleur associée aux interventions chez les nouveau-nés. Le présent rapport de synthèse porte sur les mécanismes sous-jacents de l'administration du sucrose et de la SNN, appliquées seules ou en association, pour soulager la douleur associée aux interventions chez les enfants prématurés et nés à terme. Il est également question de la portée clinique et de l'incidence sur la recherche.

Newborn infants hospitalized in neonatal intensive care units (NICUs) are subjected to many painful procedures during efforts to improve their clinical status. In one study (1), infants born between 27 and 31 weeks of gestation received a mean of 134 painful procedures within the first two weeks of life, and approximately 10% of the youngest and/or sickest infants received over 300 painful procedures.

There is sufficient evidence that preterm and full term infants are capable of responding to noxious stimuli by mid-gestation (2-7), and that their immediate responses include both physiological (3,8-21) and behavioural indicators (22-32). The long term effects of pain are poorly understood, but emerging evidence suggests that pain may be detrimental to neurobehavioural outcomes (7,19,33-37). In light of this

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evidence, clinicians and researchers need to identify safe and efficacious interventions to reduce the immediate and long term effects of procedural pain.

Sucrose is a disaccharide consisting of fructose and glucose. The soldiers of Alexander the Great, who entered India in 325 BC, first introduced sucrose to the West (38). In later centuries, the use of sucrose as a sweetening agent was spread by the Arabs and the Crusaders, and was introduced into the New World by Columbus in 1493. Today, sucrose is used as a common household sweetening agent. Compared with sucrose, the sweeteners fructose, glucose, maltose and lactose are 1.7, 0.75, 0.33 and 0.6 times as sweet, respectively (39). The soothing and calming properties of these agents have been anecdotally described by generations of parents and grandparents who claim that sweet tastes calm distressed infants. Current medicinal uses include sucrose in suspensions for oral medications, possibly to conceal the bitter taste of the pharmacological agent. These traditional uses of sucrose were not likely based on rigorous scientific study.

The administration of sucrose has been the most frequently studied nonpharmacological intervention for the relief of procedural pain in newborn infants. Sucrose has been shown to promote calming behaviours and reduce acute procedural pain in preterm and full term infants. The efficacy of sucrose for procedural pain in infants has been addressed in two systematic reviews (40,41). In the first review (40), only one study with preterm infants ($n=16$) and four studies with full term infants ($n=255$) met the inclusion criteria for a meta-analysis. The primary outcome in the meta-analysis was the proportion of crying time during the 3 min after the painful stimulus. Sucrose doses greater than 0.24 g (2 mL of 12% weight/volume [w/v] sucrose) given orally by syringe or pacifier approximately 2 min before a painful stimulus were the most effective in decreasing cry duration. In some studies, heart rate, facial expressions and composite assessments of pain were also decreased. There were no significant clinical benefits of administering doses greater than 0.50 g. In the second systematic review (41), smaller doses of sucrose were shown to be effective in decreasing more specific physiological and behavioural pain responses in preterm and full term infants. However, the optimal dose of sucrose to reduce procedural pain could not be identified because methodological and conceptual limitations in the studies prevented accurate comparisons. Across studies, there were differences in the definition of pain, painful stimuli, delivery method of sucrose, pain outcomes and study methods.

Non-nutritive sucking (NNS) is the provision of a pacifier or nonlactating nipple into an infant's mouth to promote sucking behaviours without the provision of breast milk or formula for nutrition. Caregiver activities such as positioning, rocking, swaddling and holding, and providing pacifiers have been used for many years to calm infants and provide comfort during painful and stressful events. Pacifiers are readily available in NICUs and have been reported by NICU nurses as the first choice of pain relieving

intervention (42). Providing NNS has reduced behavioural pain responses during circumcision (28,43,44), immunizations (45,46), mechanical ventilation (47) and heel lances in full term (48) and preterm infants (1,49). Composite pain scores were also reduced in preterm infants who received NNS during heel lances (1). Pain relief was further reduced in infants who received NNS and sucrose in combination.

Compared with swaddling (22) or rocking (49) during painful procedures, NNS reduces the duration of crying and soothes infants more rapidly. However, unlike swaddling, there is a rebound in distress when the pacifier is removed from the infant's mouth. The efficacy of NNS is immediate but terminates almost immediately upon cessation of sucking. In a systematic review (50), the efficacy of NNS for many infant outcomes, including weight gain, energy intake, heart rate, oxygen saturation, transition to oral/nipple feedings and length of hospitalization in NICUs, was evaluated. The primary outcome selected for the review was length of stay. Preterm infants who were provided with a pacifier during gavage feedings were discharged from hospital earlier than preterm infants who were not provided with NNS. The review did not reveal any other benefits of NNS, but infants were not followed past discharge. Although family members, as well as health care professionals, have historically used NNS, very little rigorous research exists to determine the efficacy of NNS for procedural pain relief.

In summary, although there is evidence to support the efficacy of sucrose and NNS for the management of pain in preterm and full term infants, the mechanisms underlying the efficacy of these interventions have not been clearly delineated. In the present review, the individual and combined mechanisms of sucrose and NNS are examined, and the most likely hypotheses are proposed.

MECHANISMS OF SUCROSE

Animal research

The effectiveness of sweet tasting substances in reducing pain responses was initially derived from animal models (51-53). In rat pups, milk infusion, corn oil, polydose and sucrose have increased paw-lift latency and decreased the number of ultrasonic distress vocalizations in response to thermal pain (54). Conversely, water infusions did not affect lift-paw latency or vocalizations. Sweet taste-induced analgesia, however, was altered in the presence of opioid antagonists such as naltrexone and high levels of competing sweet tastes. Rat pups receiving intraoral saccharine for 28 consecutive days did not respond to exogenous morphine treatment for painful thermal stimuli. Furthermore, the pain responses were not affected by the administration of naltrexone (55). Therefore, although the efficacy of sweet tastes appears to provide opioid-mediated analgesia in the rat model, repeated doses of sweet tastes may result in tolerance to subsequent opioid administration. Further research to examine this hypothesis is required.

Several different hypotheses regarding the underlying mechanisms of sucrose exist; however, there is one hypoth-

esis that is the most plausible and has the most support. The sweet taste of sucrose is proposed to promote analgesia through activation of endogenous opioids that attenuate nociceptive information at the level of the dorsal horn (56). Rat pups preferentially ingested sucrose over milk and other nonsweet solutions during painful and stressful events (57). Rat fetuses that received intrauterine injections of apple juice preferentially ingested apple juice over milk 15 days after birth. Compared with control rats, rats that received intrauterine apple juice consumed greater amounts of apple juice (58). These data indicate that rat fetuses can discriminate tastes and that memory of tastes exists after birth. Opioids also appear to enhance feeding and food choice. In particular, fat and sweet consumption increases with the administration of opioids and is suppressed by opioid antagonists (59,60). The relationship among dietary choice, taste preference and the modulation of pain appears to be opioid-mediated.

Human research

Because of ethical reasons, much of what has been studied in animal models cannot be replicated with human infants. Therefore, although the efficacy of sucrose is reduced in animal models in the presence of high levels of endogenous opioids, the relationship in human infants remains theoretical. In one study, pain responses of post-term infants were compared with those of healthy full term infants (61). Term infants were significantly more calmed by sucrose, as measured by cry duration, than were post-term infants ($P < 0.01$). The authors hypothesized that the release of B endorphins associated with postmature infants resulted in tolerance to sucrose. Similar to animal models, high levels of endogenous opioids appear to alter responsiveness to sucrose (55). In a second study involving term infants ($n=4$), infants born to mothers who were maintained on methadone during their pregnancy were used to draw comparisons between endogenous opioids and responsiveness to sucrose (48). Infants of mothers exposed to methadone were not calmed by sucrose. Furthermore, sucrose did not prevent these infants from becoming agitated when a pacifier to promote NNS was removed. Although the sucrose was taken avidly, the infants only stopped crying when the pacifier was returned to their mouth or the infant placed his or her hand into the mouth. Sucrose also failed to reduce the infant's physiological stress responses associated with crying (heart rate). These preliminary data suggest that the mechanisms underlying sucrose and NNS are likely different.

Taste receptors that detect sweetness are found at the anterior tip of the tongue, where sucrose is administered. Taste receptors are evident in human infants by the end of the eighth week of gestation, and sensory nerve fibres from the receptors of the tongue to the brainstem are established by 26 to 28 weeks' gestation (62). Taste fibres unite in the medulla oblongata, where they synapse with fibres for touch, pain and temperature (55). Impulses are then relayed to the cerebral cortex for interpretation. In preterm, full term and older infants, sweet tastes are preferred over fats, pro-

teins, lactose and water (48,63). Sucrose preference, as measured by intake, was related to sweetness in all age groups (48). Rank ordering of sugars by adults was shown to be identical to that of infants, with sucrose preferred over fructose, which is preferred over glucose, which is preferred over lactose (64). Similar to animal models, adults, and full term and older infants preferentially ingest sweets or fats over nonsweets when stressed; this relationship is probably opioid mediated. Responses to nonsweet tastes during stressful situations are similar across age groups and include raised cheeks and narrowed or tightly closed eyes, wrinkled nose and eyebrows pulled together (65). Conversely, responses to sweet tastes include facial relaxation, hand-mouth behaviours and sucking.

Taste-induced analgesia in animal (52,57) and human (62-67) newborns is rapid, enduring and dependent on the ability to detect sweet taste. Only trace amounts of sucrose have been detected chemically in saliva within 1 min after administration (48). Term infants who receive small amounts of sucrose remain in awake and alert states, and place their hands in their mouths. Hand-mouth behaviours only appear after crying stops – disputing the argument that crying only stops because it is incompatible with hand-mouth or sucking behaviours.

Sucrose has been administered to preterm, full term and older infants by syringes (17,18,68,69), droppers (70), drinks (67,71) or on pacifiers (1,63,71). In one study (71), different routes of sucrose administration were compared in preterm infants. In a crossover design, including two consecutive heel lances, infants received randomly allocated sterile water or sucrose before the first heel lance. The solution was given through a nasogastric tube, which passed directly into the stomach. For the second heel lance, the infant received the same solution via syringe onto the tongue. Pain responses were measured by behavioural pain scores comprised of facial expressions (brow bulge, eye squeeze, nasolabial furrow and open mouth). Compared with sterile water, sucrose administered directly on the tongue significantly reduced crying time and behavioural pain scores. Neither sucrose nor sterile water delivered directly into the stomach via the nasogastric tube reduced responses to procedural pain. Sucrose is hydrolyzed into glucose and fructose through the intestinal epithelium, which is present, by 26 weeks' gestation (38,72,73). Given the rapid effects of intraoral sucrose, it is unlikely that hydrolysis in the small intestine is responsible for its pain-relieving properties.

A variety of sucrose concentrations (7.5%, 12%, 24% and 50%), volumes and administration schedules have been implemented to reduce procedural pain in newborn infants. Sucrose has calmed infants as early as 9 h after birth, and the calmness persisted 5 to 10 min after a painful stimulus (48). Various time delays between sucrose intake and the initiation of painful procedures have been used (40,41,67). Reductions in crying time have been found 2 min after sucrose is administered onto the tongue. A 2 min interval appears to be required for taste receptors in the mouth to

mediate opioid responses and inhibit nociceptive impulses. When duration of cry was used as an indicator of pain, 0.24 g sucrose (2 mL of 12% w/v sucrose) is efficacious for heel lances (10,68,69) and venepunctures (18) in preterm infants, and heel lances (63,66,70) in term infants, but not for circumcision (74), eye examinations (75) or intramuscular injections (45). Although there is a trend toward a reduction in crying time with greater concentrations of sucrose (76), no benefit to administering doses greater than 0.5 g has been found. A few researchers (1,68,69) have reported that very small doses of sucrose (0.12 g) reduce composite pain scores comprised of heart rate, respiratory rate and facial expressions in infants less than 34 weeks of gestation. However, these smaller doses of sucrose are not efficacious in full term infants and do not appear to be sustained in older infants (45).

Age and maturation appear to decrease the efficacy of sucrose. Sucrose administered to full term infants (32) before a heel lance reduced crying by 40% compared with water, but did not reduce crying in older infants. Similarly (45), sucrose reduced crying time in two-week-old infants during immunizations but did not reduce crying in infants older than two months of age. In a multiple regression analysis that included age, infant condition and time required for a nurse to perform immunization, age of the infant at the time of data collection was the only variable that predicted percentage of crying, with younger infants crying longer. The age effect may be related to the time when other behavioural and environmental interventions such as eye-to-eye contact, distraction, relaxation, swaddling or positioning, or co-ordinated NNS are implemented.

In summary, existing studies on the efficacy of sucrose in human neonates have incorporated varying doses, painful procedures and pain outcomes. Although the variability of data and study methods prevents meaningful conclusions, it appears that the sweet taste of sucrose detected on the tongue 2 min before a painful procedure is the mechanism by which opioid responses are mediated in preterm and full term infants. Sucrose is readily taken by preterm and full term infants; however, its efficacy as a pain-relieving intervention decreases with age and maturation. Other factors related to the administration of the intervention, such as dose and concentration, may alter the magnitude of pain responses, but they are unlikely to be responsible for mediating the endogenous opioid response. Perhaps once a threshold of sucrose concentration or volume has been crossed, all volumes and concentrations are equally efficacious in reducing pain (48).

MECHANISMS OF NNS

The calming effects of NNS have been observed in human and rat neonates, but the mechanisms underlying its effectiveness remain unclear. NNS is thought to produce analgesia in human infants through stimulation of orotactile and mechanoreceptors when a pacifier or nonlactating nipple is introduced into the infant's mouth (48). Unlike the mechanisms of sucrose, the orotactile-induced analgesia associ-

ated with NNS does not appear to be mediated through opioid pathways; it is not affected by the administration of naltrexone, and its efficacy is terminated once sucking has ceased.

In rat neonates, orotactile stimulation with a nonlactating anesthetized dam to promote NNS has been found to decrease distress vocalization associated with thermal pain. Rat pups at 10 days of age showed delayed withdrawal latencies from heat when NNS was provided (77). Relative to isolated rats, rats lying in contact with other rats doubled their heat-withdrawal latencies. Rats provided with NNS increased their heat-escape latencies by four times, while rats positioned in hyperextension and allowed to receive milk infusion did not withdraw from thermal pain at all. Unlike the heat-escape latencies in the isolated or contact groups, the pain relief associated with NNS was not blocked by large doses of naltrexone or norbinaltorphimine. In addition, morphine added to the pain-relieving effects in the contact group but multiplied the effects in the NNS and sucking/feeding groups. Suckling pups given morphine had increased heat-escape latencies by 15 min, and the effects were observed for 60 min. Contact or isolated rats did not achieve maximum latency for 45 min, and the effects were not observed by 60 min. These notions suggest that the effects of NNS, although not opioid mediated, may potentiate the effects of opioid analgesics. Research examining synergism between NNS and opioids is required.

Limited data are available to support the underlying mechanisms of NNS as a pain-relieving intervention. However, there are several possible mechanisms underlying efficacy. The gate control theory (78) purports that pain impulses travel from the periphery to the central nervous system (CNS) by ascending pathways in the spinal cord. Impulses are modulated via descending pathways from the CNS by a 'gating' mechanism at the level of the spinal cord. Analgesia likely occurs at the level of the dorsal horn. Interventions such as distraction and relaxation may reduce arousal during and after painful procedures (79,80); however, they have only been evaluated to a limited extent with respect to infant pain management. Other cognitive therapies such as patient education, anticipatory guidance, coping strategies and imagery are not possible for use with infants. Physical strategies such as environmental modification and/or reduction of bright light, noise and frequent handling may reduce infant pain by reducing excessive and cumulative noxious stimuli and promoting behavioural state stability, but limited data exist. NNS is widely used to calm infant pain because of relative ease and accessibility. NNS may reduce pain responses by inhibiting nociceptive impulses from the periphery along the ascending fibres or activating tactile afferent fibres that stimulate the descending influencing systems to close the 'gate' and reduce pain.

The involvement of serotonergic systems in the modulation of pain is well documented in the management of adult pain (81,82). Serotonin and serotonin reuptake inhibitors appear to facilitate the release of B endorphins. In contrast, serotonin receptor blockers cause significant decreases in

B endorphins (83). Previous data suggest that B endorphins play a role in analgesia in post-term infants (61). Serotonin-mediated analgesia, as measured by B endorphin levels, is observed when serotonin and serotonin reuptake inhibitors are injected into the arcuate nucleus and nucleus accumbens of adult rats (83). Compared with control rats, rat pups that had had a surgical transection of their serotonergic system had decreased B endorphins despite injections of serotonin or serotonin reuptake inhibitors. The ability to relieve pain appears to be related to neuronal reuptake of serotonin. In the rat model, intracerebroventricular boluses of serotonin reuptake inhibitors decreased pain responses associated with subcutaneous injections of formaldehyde, thermal pain and neuropathic pain created by tight ligation of spinal nerves. The pain inhibitory effects of serotonin and serotonin reuptake inhibitors were prevented by injection of serotonergic antagonists. However, the inhibitory effects were not prevented by the opioid antagonist naloxone. These results indicate that serotonin provides analgesia through nonopioid mechanisms.

A systematic review (81) comprised 19 studies that examined the efficacy of serotonin reuptake inhibitors for the management of pain. Although none of the studies included infants or children, serotonin reuptake inhibitors consistently reduced chronic pain associated with headaches, diabetic neuropathy, postherpetic neuralgia and fibromyalgia. No data on acute procedural pain exist, but studies with animals have indicated that pain responses to mechanical stimuli are reduced with selective serotonin reuptake inhibitors (83-86).

There is some evidence that the serotonergic system promotes calming through attachment and suckling behaviours (85,86). In one animal study, serotonin reuptake inhibitors reduced the frequency of rat pups detaching and re-attaching to a non-lactating anesthetized dam (85). There was a trend for a dose-related decrease in re-attaching behaviours with larger doses. Serotonin reuptake inhibitors also decreased the frequency of nipple switching and increased the time spent attached to the nonlactating breast. Serotonin reuptake inhibitors did not increase suckling behaviours when weight gain was used as a proxy for suckling. Control rats had significantly more weight gain than rats that received serotonin. Weight gain may not be a valid indicator of suckling.

Similar results were found when serotonin receptor blockers, which prevent the neuronal reuptake of serotonin, were injected into rat pups (86). Serotonin receptor blockers increased the percentage of suckling in rat pups between 10 and 25 days. These agents also reinstated suckling behaviours in weaned pups. Rats younger than 10 days of age all suckled, regardless of whether they received serotonin or saline. Similar to the previous study (86), serotonin reuptake inhibitors did not increase suckling behaviours in rats older than 35 days. However, these older rats were more settled than the control group. The age-related differences might reflect developmental maturation of the serotonin system, whereby younger rats have immature serotonergic systems and older rats may have other mechanisms that contribute to

the abandonment of suckling at weaning. These data support the hypothesis that serotonin modulates attachment behaviours to a nipple, similar to NNS, but does not appear to influence suckling, which is associated with ingestion. Further research to examine possible mechanisms for serotonin mediation, in the absence of feeding, is required.

In vitro brainstem-spinal cord preparations from newborn rats have been used to locate the area in the brain responsible for suckling reflexes (87). A rhythmical suckling-like activity of the hypoglossal nerve as the index of suckling was used, and a fluorescent dye was injected. The induced suckling action persisted after removal of the dorsal medulla oblongata, the caudal pons and trigeminal spinal nucleus. The researchers concluded that the central rhythm generator for suckling is localized in the ventromedial medulla oblongata. Stimulation to the central rhythm generator was derived from only suckling. Further research to clearly identify the area responsible for suckling is required.

In summary, NNS temporarily reduces the physiological and behavioural responses to procedural pain and promotes calmness in preterm, full term and older infants. The mechanisms underlying the efficacy of NNS remain unclear, but unlike sucrose do not appear to be mediated through opioid systems. It is hypothesized that stimulation associated with suckling mediates the production of serotonin that contributes to immediate but transient analgesia. The fibre stimulation associated with continuous, rhythmic suckling may explain why the efficacy of NNS dissipates within 30 s of suckling termination (88). Unlike the efficacy of orogustatory-induced analgesia, which endures several minutes after sucrose is administered, NNS does not have lingering effects. Further research of the role of NNS and production of serotonin is required.

COMBINED MECHANISMS OF SUCROSE AND NNS

In an attempt to understand better the interaction of sucrose and NNS, Blass and Watt (88) examined 40 full term infants undergoing heel lances. Infants randomly received sucrose alone, water alone, pacifier with water (NNS), or pacifier with sucrose. Sucking movements were recorded in real time and quantified during the treatment phase. NNS with sucrose was more effective – as measured by cry duration, grimace and heart rate changes – than NNS or sucrose alone. NNS was analgesic when the suck rate exceeded 32 sucks/min. The authors suggested that antinociceptive mechanisms associated with NNS are engaged when suckling thresholds have been reached. Infants with fewer than 30 sucks/min were also comforted during the treatment phase. However, these infants received the combination of sucrose and NNS. The authors further suggested that the orotactile threshold previously described does not have to be reached if orogustatory mechanisms associated with sucrose taste are activated. Unlike NNS, the pain-relieving effects associated with sucrose persisted long after the painful stimulus had terminated.

Stevens and colleagues (1) examined the combined efficacy of sucrose and NNS for relieving procedural pain in preterm infants. Each infant received four interventions in random order: prone positioning, a pacifier dipped in water, a pacifier dipped in 24% sucrose or standard care (containment and side-lying position). Behavioural and physiological responses were used to calculate a composite pain score. Significant differences in pain scores between the pacifier with water and control group ($P < 0.005$), and pacifier with sucrose and control group ($P < 0.0001$) were found. There was a trend ($P < 0.05$) toward lower pain scores with the sucrose and NNS group compared with the water and NNS group.

The comforting and pain-relieving behaviours observed with the combination of sucrose and NNS may be similar to behaviours observed during breastfeeding. Mothers initially calm their agitated infant by orotactile or body contact (48). The calming associated with warmth, positioning and containing is immediate and thereby allows the infant to locate and attach to the nipple. The infant stops crying and remains in a quiet and attentive state to obtain sufficient milk for satiation. The cessation of crying, reduced heart rate, gross motor movements and calm state associated with orotactile stimulation with the nipple are required for infant feeding. Following the orotactile stimulation with the nipple, the infant draws milk from the breast by rhythmic, sucking behaviour. Infants are further calmed after milk is detected through orogustatory stimulation (47). It is hypothesized that the orotactile mechanism associated with nipple attachment is transferred to the orogustatory mechanisms where opioid mediation occurs. To date, few investigators have evaluated the efficacy of breastfeeding or breast milk for reducing pain during painful procedures. Ors and colleagues (89) randomly assigned 102 healthy term infants to receive 2 mL of 25% sucrose, human milk or sterile water 2 min before heel lancing. Crying time, median recovery time and the percentage change in heart rate were significantly lower in the group that received sucrose than in the groups that received human milk or sterile water. Similarly, Skogsdal et al (90) randomly assigned 120 newborns infants to receive no treatment, 1 mL of 30% glucose, 10% glucose or breast milk 2 min before heel lance. Significant reductions in crying and heart rate increases were noted in the group that received 30% glucose. Therefore, although the mechanisms for sucking may be similar in nutritive and non-nutritive sucking, the effectiveness of breast milk as an analgesic, based on these limited data, has not yet been supported.

CLINICAL IMPLICATIONS

Sucrose and NNS have potential clinical benefits because they are readily available in hospital nurseries, are inexpensive, are easily administered and have few known risks. The combination of sucrose and NNS has both calming and pain-relieving properties and, therefore, can be used for a variety of diagnostic and therapeutic activities that are painful. Given the rapid and enduring effects of sucrose and NNS, they can be given together in advance of minor to moderate procedural pain. In addition, pharmacological

interventions can be used as an adjunct with the combined therapy for severe acute or chronic pain.

Both sucrose and NNS have been used safely for single painful procedures in animal and human preterm, full term and older infants. Only one study (91) has suggested that sucrose administration predisposes preterm infants to necrotizing enterocolitis, but the lack of methodological rigour within the study precludes any supportable conclusions. Many pathogenetic mechanisms such as prematurity, alteration of bowel flora, presence of umbilical lines or nasogastric route of administration may contribute to necrotizing enterocolitis. No other data concerning the safety of NNS are available. Although sucrose and NNS appear to be safe, further study is required to determine tolerance, potential risks and safety.

RESEARCH IMPLICATIONS

There are sufficient animal data to draw parallels to human infants; sucrose appears to be mediated through endogenous opioid pathways, and the mechanism underlying efficacy is sweet taste. However, the mechanisms underlying NNS remain unclear, and although a few animal studies suggest that multiple pathways including contact, vestibular or serotonergic pathways may be involved, there are insufficient data to draw comparisons with human infants. Further research identifying the role of sucking in relation to serotonin production in animals is required. In addition, research examining possible feedback mechanisms between sucking and further production of serotonin may explain the rapid but transient analgesic properties of NNS. Data from animal models can then be used to infer mechanisms of NNS in human infants.

Sucrose and NNS are safe for single painful procedures, but no studies have examined the use of the interventions alone or in combination for repeated painful stimuli in a heterogeneous population such as extremely low birth weight or neurologically impaired infants. Similarly, no data on chronic infant pain-relieving interventions are available. Researchers conducting the meta-analyses on sucrose and NNS were not able to identify the most efficacious dose of sucrose for a variety of gestational ages or painful procedures. Prospective randomized, controlled trials with a validated composite measure of pain and a sufficient sample size to detect significant clinical and statistical differences are required.

The efficacy of sucrose appears to decrease with age and maturation. Studies using sucrose with other environmental and behavioural interventions such as positioning, skin to skin contact or visual/auditory stimuli may be combined to improve pain management for older infants. The efficacies of sucrose and NNS appear to be synergistic rather than additive; the presence of one therapy accentuates the action of the other therapy. Although both interventions are efficacious as analgesics, the magnitude and duration of effect are enhanced with combined therapy, although the magnitude of the enhancement has not been well delineated. Animal data indicate that morphine adds to the pain-relieving effects of

contact but multiplies the effects of NNS. Efficacy of the interventions for infant pain relief may be similar, but prospective, randomized, controlled trials that examine each intervention alone and in combination for specific painful stimuli are needed.

CONCLUSIONS

The frequency of acute procedural pain in NICUs and the potential for immediate and long term detrimental effects of pain necessitate the need for safe, efficacious and clinically effective interventions to reduce procedural pain in infants. Sucrose appears to be antinociceptive, mediated through endogenous opioid systems, effective with a short latency and effective after the painful stimulus has ceased. The mechanisms underlying sucrose appear to be orogustatory. In contrast, the mechanisms underlying NNS are unclear but probably involve orotactile receptors that stimulate serotonin production. NNS is not mediated through opioid pathways; efficacy is transient and not affected by opioid antagonists.

Sucrose and NNS are efficacious for rat pups, and preterm and full term human infants. The combination of

sucrose and NNS involves both opioid and nonopioid pathways and, therefore, offers the most potent nonpharmacological intervention for procedural pain. The common use of sucrose in the human diet and the frequent use of pacifiers to calm infants from earliest times suggest that there are few concerns over adverse effects. Although the combination of orogustatory and orotactile-induced analgesia is not sufficient for severe pain, these interventions can be incorporated into clinical practice and used with other pharmacological or nonpharmacological interventions in a multifocused pain-relieving strategy. Further research on the underlying mechanisms to explain the efficacy of sucrose and NNS for repeated or chronic pain is required.

ACKNOWLEDGEMENTS: We gratefully acknowledge the financial support of The Hospital for Sick Children, Toronto, Ontario, Canada for the Research Training Award (Sharyn Gibbins) and the Ontario Ministry of Health, Toronto, Ontario, for the Career Scientist Award (Bonnie Stevens). We also acknowledge Drs Ellen Hodnett, Janet Pinelli, and Arne Ohlsson (PhD thesis committee members for Sharyn Gibbins) and Dr Dorothy Pringle for their support and critique of this work.

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