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Modified sensory stimulation using breastmilk for reducing pain intensity in neonates in Indonesia: A randomized controlled trial

Siti Yuyun Rahayu Fitri, M.Sc [a,*], Lely Lusmilasari, Ph.D, MS [b], Mohammad Juffrie, Ph.D, MD [c], Carlo Valerio Bellieni, MD [d]

[a] Pediatric nursing department, Faculty of nursing, Universitas Padjadjaran, Bandung, Indonesia
[b] Pediatric and maternity nursing department, Faculty of medicine, public health and nursing, Universitas Gadjah Mada, Indonesia
[c] Pediatric department, Faculty of medicine, public health and nursing, Universitas Gadjah Mada, Indonesia
[d] Neonatal Intensive Care Unit, Siena University Hospital, Italy

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ABSTRACT

Purpose: Several studies have shown that oral sucrose reduces pain in newborns. However, sucrose has no efficacy in eliminating pain and long-term effects remain unclear. Breast milk may be useful as an alternative, safe sweet solution. Sensorial saturation (SS) is a multisensory analgesic non-pharmacological treatment, which includes touch and sounds as distractors. This study aimed to compare the analgesic effects of SS with sucrose (SSS), SS with breast milk (SSB), and oral sucrose alone (S24%) in neonates undergoing venipuncture.
Design and methods: This was a randomized controlled trial conducted on 108 neonates who underwent venipuncture at neonatology wards. All babies were randomly assigned to one of three groups: two intervention groups and one control group. Pain response was assessed using the premature infant pain profile—revised (PIPP-R). Data analysis was conducted using the Kruskal–Wallis test and Mann–Whitney *U* test.
Results: SSB and SSS were more effective than S24% ($p = 0.001$). No difference was observed between SSB and SSS ($p = 0.669$).
Conclusion: Multisensory stimulation is more effective in reducing pain than unimodal (oral sucrose) analgesia. Breast milk can be used as a sensory gustatory stimulus in multisensory stimulation to reduce pain intensity in neonates, and demonstrates a similar analgesic effect to sucrose.
Practice implications: The study findings suggest that neonatal nurses could use SSB for management of pain. This intervention could serve as an effective, inexpensive, and safe non-pharmacological analgesic. Additional testing of this intervention is warranted to support its use as an evidence-based pain reduction approach.

Introduction

The prevention and treatment of pain in neonates is extremely important due to the short- and long-term impact of pain in this population (Bouza, 2009; Graham, Heim, Goodman, Miller, & Nemeroff, 1999; Mooney-Leber & Brummelte, 2017; Vinall & Grunau, 2014). Numerous procedures cause pain, and the management of pain caused by hospital procedures is still unsatisfactory (Courtois et al., 2016; Stevens, Yamada, Ohlsson, Haliburton, & Shorkey, 2016; Vinall & Grunau, 2014), with the average rate of administration of neonatal analgesia during invasive procedures reported as ranges from 20.8% (Carbajal, Chauvet, & Couderc, 2016) to 27.4% (Carbajal et al., 2008).

The management of pain in infants includes pharmacological and non-pharmacological treatments. Pharmacological treatments are not ideal for routine pain management in neonates because of the excessive chemical effects of drugs, whereas non-pharmacological management is recommended, particularly as the first step (Vinall & Grunau, 2014). Therefore, the development of pain-treating plans in neonates undergoing repeated invasive procedures is important.

Currently, the administration of oral sucrose, the best known non-pharmacological analgesic treatment, is widely used in clinics for minor procedures in newborns (Stevens et al., 2016). More than 100 studies have identified the effect of sucrose on pain in neonates, and the results showed a positive effect, indicating that it can reduce acute pain response caused by minor procedures in neonates. However, the

* Corresponding author at: Pediatric nursing department, Faculty of Nursing, Universitas Padjajdaran, Jl. Raya Bandung Sumedang KM 21 Jatinangor Kab., Sumedang, West Java Province, Indonesia.
E-mail address: siti.yuyun@unpad.ac.id (S.Y.R. Fitri).

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effect of sucrose when used repeatedly and its impact on long-term development remains unclear (Stevens et al., 2016). Moreover, other studies have shown that although the administration of sucrose can reduce behavioral and physiological responses, it does not reduce the EEG response to pain (Slater et al., 2010).

A previous study has shown that the use of oral sweet solution is more effective when combined with other sensory stimuli, called sensorial saturation (SS) (Bellieni et al., 2002). Sensorial saturation includes gustatory, visual, tactile, auditory, and olfactory stimuli. Research has shown that the combination of glucose/sucrose with other multisensory stimuli is more effective in reducing pain than the administration of sucrose alone. The sensory component can increase the analgesic effect of glucose administration because another stimulus will activate the gate control mechanism that inhibits nociceptive transmission in the spinal cord, in addition to the opioid release due to the sweet taste felt throughout the procedure (Bellieni et al., 2002).

An SS protocol without the use of olfactory sensory stimuli showed that the utilization of perfume in infants had no significant impact (Bellieni et al., 2007). SS is best carried out using taste (providing sweet solution orally, e.g., sucrose, glucose), talk (attracting baby's attention with words), and touch (providing gentle massage). The procedure of SS is easy to learn, and any caregiver (mother, pediatrician, or nurse) can effectively use it (Bellieni et al., 2007). Multisensory stimulation to reduce pain is also considered as an effective, safe, and easy method for the screening of retinopathy of prematurity (ROP) (Zeraati, Shahinfar, Behnam Vashani, & Reyhani, 2017).

In a review of the use of SS (Bellieni, Tei, Coccina, & Buonocore, 2012), eight articles used complete SS (oral sugar, massage of the baby, and attracting the baby's attention with words) and two used an incomplete SS. Results showed that SS is effective in reducing pain in neonates. Providing a sweet solution alone (in the form of sucrose or glucose) is less effective than SS, and sensory stimulation without sweet solution is not effective. Therefore, gustatory stimulation in the form of providing sweet liquid is extremely important.

To ensure the safety of long-term intervention for neonatal pain therapy, it is necessary to consider a safer sweet solution that-is, breast milk, the standard norm for infant feeding and nutrition. Compared with other sources of nutrition for infants, breastmilk has more advantages, including infection prevention, immune protection, reducing obesity risk, malignant disease prevention, and reducing sepsis and necrotizing enterocolitis (NEC) risks, as well as advantages for neurological development (American Academy of Pediatrics, 2012; Anatolitou, 2012). In addition, various studies have proved the benefits of breast milk as analgesia in neonates.

A systematic review showed that breastfeeding is effective in reducing pain (Shah, Herbozo, Aliwalas, & Shah, 2012), and breastfeeding has a better analgesic effect than sucrose in infants (Codipietro, Ceccarelli, & Ponzone, 2008; Simonse & Mulder, 2012). However, other studies have shown contrasting results (Bueno, Stevens, Camargo, Toma, & Lúcia, 2012). A study by Shah et al. (2012) revealed that breast milk alone (breast milk given by syringe or spoon) is less effective than direct breastfeeding of mothers or the administration of sweet solution. In contrast, breast milk may be better than sucrose because contains high concentrations of tryptophan, a precursor of melatonin (Heine, 1999), which can increase beta-endorphin concentrations (Barett, Kent, & Voudouris, 1999).

This study aimed to compare the analgesic effect of an SS approach using sucrose (SSS), an SS approach using breastmilk (SSB), and an oral sucrose 24% alone (S24%) on neonates who underwent venipuncture.

Research design and setting

This randomized controlled trial with parallel groups was conducted at the neonatal wards of two provincial government hospitals in West Java, Indonesia (ISRCTN registration). The Medical and Health Research Ethics Committee, Faculty of Medicine Universitas Gadjah Mada, Yogyakarta, Indonesia, approved the study.

Participants

Neonates who underwent blood sampling and met the following inclusion criteria were included: (i) minimum Apgar score of 8 at 5 min, (ii) gestational age > 32 weeks, (iii) minimum postnatal age of 48 h, (iv) positive sucking and swallowing reflex, (v) <8 days from birth, and (vi) receiving breast milk from their mothers. Meanwhile, (i) neonates who received analgesics and sedative drugs and (ii) those with parents who did not provide consent for the study were excluded.

The neonates were randomly categorized into three groups: (i) The first group received SSS; (ii) the second group received SSB; and (iii) the third group received S24%. Randomization was performed as block randomization with a 1:1:1 allocation. Recruitment started April 2018 and ended August 2018.

Sample size

In this study, an equivalence trial was conducted on the three groups (three-arm equivalence trial). Using the sample size formula for randomized control trial with the three-arm equivalence trial (Chang, Tsong, Dong, & Zhao, 2014; Zhong, 2009), the sample size for each group was calculated 36; thus, a total of 108 babies were included. All babies were randomly assigned to an intervention or control group with block randomization (see Fig. 1).

Measures

Pain was measured using the Premature Infant Pain Profile-Revised (PIPP-R), which is an instrument for assessing pain on the basis of behavioral and physiological aspects and modification variables (Stevens, Gibbins, Yamada, & Taddio, 2014). Pain indicators include the following: (i) behavior aspects: brow bulge, eye squeeze, nasolabial furrow; (ii) physiological aspects: heart rate and oxygen saturation; and (iii) contextual aspects: gestational age and behavioral state. The total score ranges from 0 to 21. Using this tool, a score of 0–6 is assigned to mild pain, 7–12 to moderate pain, and 13–21 to severe pain. The PIPP-R in this study has been translated, with permission from the original author.

Procedure

Before starting the study, nurses who were involved in data collection underwent training on the use of PIPP-R and administration of SSS, SSB, and S24% according to the study protocol. The nurses were blinded to the purpose of the study. Different nurses performed the intervention and conducted pain assessment; the previous training minimized the differences due to the action of different nurses.

Eligible babies received the interventions according to a predetermined block code. In terms of SSS intervention, 30 s before collecting blood, the nurses started talking to the baby, looked into the baby's eyes, gently massaged the cheeks and other areas of the baby's face, and administered sucrose 24% until the baby sucked rhythmically; then, the nurse in charge of obtaining the blood sample inserted the needle in the dorsal vein of one of the baby's hands, and smooth massage was carried out. The assessment of pain intensity was conducted by a different nurse from the time of needle puncture until the procedure was completed. SSB is similar to SSS. However, sucrose 24% was replaced with breastmilk. For the control group (S24%), 30 s before and throughout the blood sampling procedure, sucrose 24% was administered.

To assess pain intensity, the PIPP-R scoring form was administered. The nurses assessed the behavior and used a stopwatch to assess the duration of the required parameters. A neonatal oximeter was used to measure heart rate and arterial oxygen saturation (SaO2).

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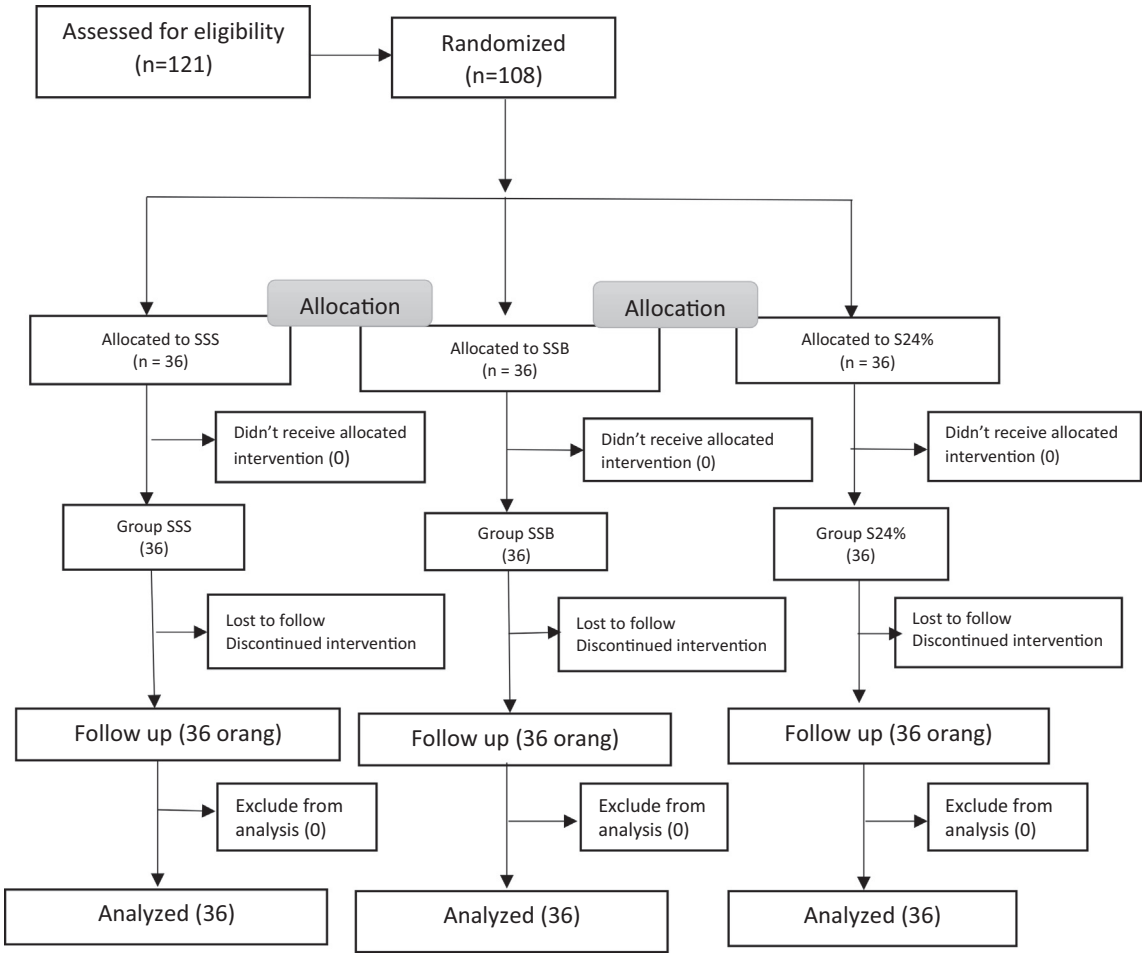

Fig. 1. Flowchart of the study.

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences software version 22 (IBM license online for Gadjah Mada University). The normality of data distribution was assessed using the Kolmogorov–Smirnov test. Because the data obtained were not normally distributed, the Kruskal–Wallis test was used for variance analysis, followed by the post hoc test with the Mann–Whitney *U* test to assess the differences between outcomes. A p-value <0.05 was considered statistically significant.

From the assessment of the normality of residual data about difference in pain intensity based on intervention variations, a Kolmogorov–Smirnov statistics value of 0.171 with a probability of 0.000 was obtained. Testing the normality of residual data about difference in pain intensity based on intervention variations obtained a probability greater than the alpha value (0.05); thus, the residual data were not considered normal.

Results

The babies enrolled met the inclusion criteria, and no statistically significant differences were observed in terms of gender, APGAR score, gestational age, postnatal age, birth weight, and length of hospital stay ($p > 0.05$; Table 1).

Table 2 shows that the average pain intensity in neonates who received SSS was 2.222 ± 1.098 and that in neonates who received SSB was 2.028 ± 1.055. Further, the average pain intensity in neonates who received S24% alone was 5.222 ± 1.290. The average pain intensity in neonates who received SSB was the lowest, whereas the average of those who received S24% alone was the highest. The results of the analysis showed that the intensity of pain in the SSB intervention group was the lowest and significantly different from that in the S24% intervention group ($p = 0.001$) but not significantly different from that in the SSS intervention group ($p = 0.669$). The pain intensity in the S24% intervention group was the highest and significantly different from that in the SSS and SSB intervention groups.

Table 1
Characteristics of the participants.

	Interventions			
	SSS n = 36	SSB n = 36	S24% n = 36	*p* value
Sex				
Male, n (%)	19 (31.1)	22 (36.1)	20 32.8)	0.367
Female, n (%)	17 (36.2)	14 (29.8)	16 (34.0)	
Gestational age (weeks), mean (SD)	35.89 (2.945)	35.44 (2.157)	36.11(1.817)	0.298
Postnatal age (days), mean (SD)	4.17 (3.9)	6.42 (3.97)	4.14 (3.23)	0.444
Birth weight (g), mean (SD)	2465 (786.7)	2123.06 (651.85)	2326.39 (480.31)	0.101
5-min Apgar score, mean (SD)	8.67 (0.48)	8.50 (0.69)	8.75 (0.5)	0.112
Length of hospitalization (day) mean (SD)	3.33 (1.9)	5.06 (2.38)	3.75 (2.11)	0.536

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Table 2
Comparison of intervention SSS, SSB, and S24% regarding PIPP-R scores.

	SSS	SSB	S24%
	Mean ± SD	Mean ± SD	Mean ± SD
PIPP-R	2.222 ± 1.098	2.028 ± 1.055	5.222 ± 1.290

Discussion

The results showed that the intensity of pain in neonates who were provided multisensory and uni-sensory stimulations during invasive procedures (venipuncture) was rated as mild pain according to the PIPP-R scale. However, infants who received multisensory stimulation had lower scores, and this difference is noteworthy. Because of the high sensitivity of the newborns to pain, babies are aware of insult and are disturbed even by apparently low level of pain. Our goal is to eliminate procedural suffering, and it appears that this can be achieved by SS, without pharmacological interventions. We found that the two types of multisensory stimulation (SSS and SSB) did not significantly differ in their analgesic effect.

Previous studies have shown that multisensory stimulation is more effective in reducing pain than uni-sensory stimulation (Bellieni et al., 2002). The various sensory components can enhance the analgesic effect of glucose because another stimulus will activate the gate control mechanism to inhibit nociceptive transmission, in addition to the opioid mechanism of the sweet stimulus (Bellieni et al., 2002). The role of sensory stimulation in reducing pain has also been reported through the concept of cross-modal shaping (Senkowski, Höfle, & Engel, 2014), a term that refers to a situation where a stimulus to a sensory modality influences perceptions, behavioral responses, or neural processing of a stimulus in other sensory modality.

Past trials used glucose or sucrose at different concentrations as a sweet solution for the "taste" stimulus. This research is the first study to assess the effectiveness of breastmilk in SS, and to compare the efficacy of SS using two types of sweet stimulus, sucrose and breast milk. Even though sucrose reduces pain during procedural interventions, it is critically important to uncover procedures that not only reduce but also eliminate pain because even mild pain is detrimental to newborn babies, especially premature babies.

The immature nervous system, both in humans and animals, is extremely responsive to tactile and noxious stimuli, and pain intervention in neonates is different from that in infants and children. In addition, neonates respond rapidly to sensory stimulation, such as caressing, rocking, non-nutritive sucking, and maternal intervention in the form of breastfeeding, as age-specific distracting strategies (Smith, 2011).

SSB can be considered similar to the behavior of a mother who is breastfeeding her baby. The efficacy of breast milk and breastfeeding is attributed to the presence of the person who makes breastfeeding comforting (the mother), physical sensations (from tactile stimulation in the form of massage and embraces), distraction (by visual and auditory stimuli), calming (from olfactory stimuli), and sweetness from the milk (the presence of lactose) (Shah et al., 2012). It appears that these stimuli are similar to those provided with SS; thus, it is intuitive to conclude that the mechanisms through which both processes express their analgesic effect are similar.

Based on near-infrared spectroscopy (NIRS), compared with glucose, breastmilk causes extensive cortical activation during blood tests (Bembich et al., 2013); thus, it is considered effective analgesia. In addition, in contrast to formula milk, breast milk contains tryptophan, which is a precursor of melatonin (Heine, 1999). Melatonin can increase beta-endorphin levels (Barett et al., 1999), which represents a mechanism for the nociception blockade of breast milk. Therefore, premature babies who are not breastfed directly by the mother can still receive the benefits of breast milk by administration of breast milk on the tongue of the neonate or via naso/orogastric tube (supplemental breast milk). In addition, breast milk does not have any side effects (Shah et al., 2012).

The scent of breast milk has been compared with that of vanilla, and breast milk has been shown to have significant on heart and oxygen saturation during and after venipuncture and to decrease heart rate variability and saturation of premature infant. Conversely, the aroma of vanilla did not cause significant changes in heart rate and oxygen saturation (Neshat et al., 2016). Moreover, other studies have shown that the scent of breast milk and lavender both prevented increased pulse rate, decreased Neonatal Infant Pain Scale (NIPS) score, decreased oxygen saturation, and reduced pain during the neonatal procedure (Akcan & Polat, 2016).

Through the NIRS investigation, Aoyama et al. (2010) showed that the aroma of breast milk increases the hemoglobin–oxygen bond in the orbitofrontal cortex, indicating that the aroma of breast milk can increase cerebral blood flow and that pain conditions decrease blood flow to the brain. These results strengthen the evidence that the aroma of breast milk can have a calming effect and that neonates can distinguish the aroma of formula milk from that of breast milk.

Infants who are treated in the neonatology and neonatal intensive care unit (NICU) wards are not supposed to be hip-carried, thus making it difficult for the mother to perform breastfeeding directly. With the SSB method, feeding breast milk can resemble breastfeeding activities because other sensory stimuli in addition to the gustatory stimulus (namely, tactile, visual, auditory, and olfactory stimuli) resemble the components present in the breastfeeding process, as mentioned above.

In sum, multisensory stimulation with the SS approach can include breast milk as a substitute for glucose or sucrose in sensory gustatory stimulation. The use of breast milk as part of this type of analgesia has numerous benefits, as mentioned above. In addition, breast milk is safer than other sweet solutions because it has no harmful side effects at repeated doses and frequencies, and in terms of cost-efficacy, breast milk is cheaper than other artificial sweet solutions.

Limitations

The pain assessment in this study only took place at the time of needle insertion in the venipuncture procedure. Pain intensity data collected throughout a sequence of blood collection procedures would show which method of analgesia has the longest duration. Future studies can design and carry out data collection methods based on a sequence of invasive procedures.

Video recording was not employed during the study observations as this was not permitted in the hospitals. The use of video cameras would allow data storage and objective validation during the observation phase. However, interrater observer assessment and the use of a stopwatch when calculating pain responses reduced research bias.

In this study, sample selection did not differentiate between neonates who underwent other painful procedures and those who did not. Painful procedures in addition to the study intervention of venipuncture, such as intravenous therapy, might have influenced pain intensity.

Conclusions

As findings indicate, pain in neonates who undergo venipuncture can be reduced with SSS and SSB, which are more effective than unisensory stimulation. The use of breast milk as a substitute for sucrose for multisensory stimulation shows a similar analgesic effect. However, research demonstrates that breast milk offers many other health benefits for the baby. Moreover, breast milk can replace sucrose in SS, which confirmed that such intervention is an effective, inexpensive, and safe non-pharmacological analgesia. Thus, such a method can be used in various clinical settings, including those in developing countries. In future studies, the use of SSB in treating pain caused by other invasive procedures can be investigated.

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Author statement

All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, or revision of the manuscript. Furthermore, each author certifies that this material or similar material has not been and will not be submitted to or published in any other publication before its appearance in the Journal of Pediatric Nursing.

CRediT authorship contribution statement

Siti Yuyun Rahayu Fitri: Conceptualization, Funding acquisition, Writing - original draft. **Lely Lusmilasari:** Conceptualization, Funding acquisition, Writing - original draft, Methodology, Formal analysis. **Mohammad Juffrie:** Conceptualization, Funding acquisition, Writing - original draft, Supervision. **Carlo Valerio Bellieni:** Conceptualization, Funding acquisition, Writing - original draft, Investigation, Writing - review & editing.

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