

β -Endorphin Concentration After Administration of Sucrose in Preterm Infants

Anna Taddio, PhD; Vibhuti Shah, MD; Prakesh Shah, MD; Joel Katz, PhD

Background: Sucrose is an effective analgesic for procedural pain in preterm infants. It has been hypothesized that its analgesic effects are mediated by the release of endogenous opioid neurotransmitters such as β -endorphin.

Objective: To determine whether intraoral administration of sucrose was associated with an increase in serum β -endorphin concentrations in preterm infants with a gestation period less than 29 weeks who were not exposed to a painful stimulus.

Methods: We performed a prospective open-label study in preterm infants admitted to 2 tertiary neonatal intensive care units. Each infant received a single dose of 30% sucrose intraorally during a 1- to 2-minute period. A blood sample was obtained using an indwelling arterial catheter to determine β -endorphin concentration immedi-

ately before and 2 to 5 minutes after the commencement of sucrose administration.

Results: We enrolled 11 preterm infants with a mean \pm SD gestational age of 27.2 ± 0.9 weeks and a mean \pm SD birth weight of 1018 ± 238 g (1.02 ± 0.24 kg) at a mean \pm SD postnatal age of 3.0 ± 2.5 days. The mean \pm SD β -endorphin concentration before and after sucrose administration was 60.4 ± 30.5 pg/mL and 57.4 ± 22.4 pg/mL, respectively ($P = .45$). No adverse events were observed during the study procedures.

Conclusion: Intraoral administration of sucrose in preterm infants did not lead to an increase in serum β -endorphin concentrations at a point in time when the analgesic effects of sucrose were presumed to be present.

THERE IS a considerable body of research demonstrating the analgesic effectiveness of oral sucrose solutions in newborns undergoing painful cutaneous procedures.^{1,2} Sucrose reduces pain from various procedures including heel lance, venipuncture, immunization, and circumcision. Sucrose has ideal antinociceptive properties for most cutaneous procedures because it has a peak onset of action of 2 minutes³ and a duration of action of 5 to 10 minutes. These characteristics coupled with its ease of administration, low cost, and lack of documented systemic effects⁴ have led to its promotion in the clinical setting as an analgesic for managing neonatal pain during noxious medical procedures.⁵

The mechanism underlying sucrose-induced analgesia is not fully established. It has been hypothesized that the sweet taste induces the release of endogenous opioids.³ A preabsorptive mechanism for sucrose-induced analgesia is supported by data demonstrating analgesic

effects following direct administration onto the tongue but not after administration into the stomach via a nasogastric tube.⁶ However, to date, no study has investigated whether endogenous opioid concentrations in the serum are changed following sucrose administration.

This study was undertaken to further elucidate the mechanism of action of sucrose as an analgesic in preterm infants. Our objective was to determine whether serum β -endorphin concentrations in these infants were increased following intraoral administration of sucrose.

METHODS

We conducted an open-label prospective study in 2 neonatal intensive care units in Toronto, Ontario (The Hospital for Sick Children and Sunnybrook and Women's College Health Sciences Centre, Women's College campus), between February 2000 and October 2001. Preterm infants with a gestational age between 26 and 29 weeks who had indwelling arterial catheters, were within the first 10 days of life, and were judged clinically stable by the attending

From the Department of Pharmacy and Population Health Sciences, Research Institute, The Hospital for Sick Children, and Graduate Faculty of Pharmaceutical Sciences, University of Toronto (Dr Taddio), Department of Paediatrics, Mt Sinai Hospital, and Faculty of Medicine, University of Toronto (Drs V. Shah and P. Shah), Department of Psychology and School of Kinesiology and Health Science, York University (Dr Katz), and the Department of Anesthesia, Toronto General Hospital, Mount Sinai Hospital, and University of Toronto (Dr Katz), Toronto, Ontario.

Table 1. Infant Characteristics

Characteristic	Mean ± SD
Gestational age at birth (wk)	27.2 (0.9)
Birth weight (kg)	1.02 (0.24)
Apgar score at 1 min	6.6 (1.3)
Apgar score at 5 min	8.3 (1.0)
Male %	5 (46)
Maternal delivery %	5 (46)
Postnatal age at time of study (d)	3 (2.5)
Respiratory distress syndrome %	7 (64)
Received ventilation %	9 (82)
Received antibiotics %	6 (55)
Received morphine %	1 (9)

*n = 11.

Table 2. β -Endorphin Concentrations*

Subject No.	Baseline	After sucrose
1	48.7	38.6
2	18.8	48.2
3	39.7	19.7
4	13.7	39.7
5	38.0	39.3
6	38.9	37.4
7	51.6	48.6
8	67.4	38.2
9	58.3	48.2
10	120.1	38.3
11	41.8	66.9
Mean ± SD	60.4 ± 30.5	57.4 ± 22.4

*Data are presented as pg/mL. $P = .45$ (baseline vs after sucrose).

neonatologist were eligible to participate. Each infant received 1 dose of 30% wt/vol sucrose solution on the tongue with a syringe, administered slowly during a 1- to 2-minute period. The volume of sucrose given ranged from 0.2 to 0.75 mL and was based on the infant's weight. This method of administration was chosen to standardize the dose intensity among infants to 0.1 to 0.15 g/kg. Immediately before and between 2 and 5 minutes after the commencement of sucrose administration, blood samples (0.8-1.0 mL) were obtained using an indwelling arterial catheter to determine serum β -endorphin concentration. Infants were observed for adverse events during the administration of sucrose, including choking, vomiting, apnea, or bradycardia. The infants did not undergo a painful procedure during the study period.

Infants were not eligible for the study if they had congenital anomalies, were clinically unstable, or were receiving opioid analgesics. The research ethics boards of both participating institutions approved the study protocol, and informed parental consent was obtained for all infants.

Blood samples were centrifuged, and the serum was frozen until later analysis for β -endorphin concentration by the biochemistry laboratory at The Hospital for Sick Children using a commercially available radioimmunoassay kit (β -endorphin 60T kit; Nichols Institute Diagnostics, San Juan Capistrano, Calif). The reported sensitivity of the assay was 14 pg/mL, and the intra-assay coefficient of variation was less than 5%.⁷ All samples were analyzed in duplicate, and the mean of the 2 values was reported.

There were no previous studies with which to estimate sample size. We determined that 10 infants would suffice if there

was a 2-fold increase in β -endorphin concentration following the administration of sucrose, with a standard deviation equal to half this difference, $\alpha = .05$, and power set at 80% (Sample Power version 1.00; SPSS Inc, Chicago, Ill). The difference in β -endorphin concentrations before and after the administration of sucrose was compared using a paired t test (SPSS version 10.1.0; SPSS Inc).

RESULTS

Eleven preterm infants participated in the study. In 1 infant, we discovered that morphine had been administered after the study procedures had been performed; consequently, an additional infant was recruited. However, the data for the infant who received morphine were retained in the analysis. The characteristics of all participating infants are listed in **Table 1**. All participants were medically stable preterm infants with gestational ages at birth ranging from 25 to 28 weeks. Six infants were receiving antibiotics for the following indications: possible sepsis ($n = 2$), prolonged rupture of amniotic sac membranes ($n = 2$), maternal chorioamnionitis ($n = 1$), and a blood culture result positive for coagulase-negative *Staphylococcus epidermidis* ($n = 1$). The infant with the positive blood culture result was 10 days old at the time of the study and had an indwelling, peripherally inserted central venous catheter. Ten infants were receiving supplemental oxygen; of those, 8 were receiving conventional ventilation, 1 was given continuous positive airway pressure, and 1 was receiving low-flow oxygen. The 1 infant receiving morphine was also being given a tapered dose of dopamine for blood pressure support. None of the infants had intraventricular hemorrhages.

All infants were calm at the time of the study. Four infants had been exposed to painful cutaneous procedures (lumbar puncture [$n = 2$] and peripheral intravenous cannula insertion [$n = 2$]) in the preceding 24 hours. In 1 infant, the procedure was performed 3 hours prior to the study. In all other infants, the procedures were performed 14 to 24 hours before the study. No adverse events were observed during the intraoral administration of sucrose in any of the infants. Serum β -endorphin concentrations before and after sucrose administration are indicated in **Table 2**. Postsucrose blood samples were collected between 2 and 5 minutes (median, 2 minutes) after commencement of sucrose administration. Mean \pm SD presucrose and postsucrose serum β -endorphin concentrations were 60.4 \pm 30.5 pg/mL and 57.4 \pm 22.4 pg/mL, respectively ($P = .45$). Although subject 3 had received morphine prior to the study procedures, there was no difference in the results after the exclusion of this infant from the analysis.

COMMENT

This study did not demonstrate a statistically significant difference in serum β -endorphin concentrations in preterm infants before and after a single dose of sucrose. To our knowledge, this is the first study to measure β -endorphin concentrations before and after sucrose administration. The results are inconsistent with those of animal studies that suggest β -endorphin release after the

administration of sucrose. In rats, intraoral administration of sucrose reduced vocalization and lengthened paw lift latency from a hot plate compared with the administration of distilled water. In addition, these analgesic effects were reversed by the opioid antagonist naltrexone hydrochloride but not by normal saline injections.⁸ Studies in humans have demonstrated that sucrose is not effective in calming infants of women treated with methadone hydrochloride, suggesting that the effects of sucrose are mediated by a common pathway.⁹

We studied preterm infants with stable cardiorespiratory status who followed their expected medical course. Preterm infants are exposed to numerous painful procedures; previous clinical trials have demonstrated the efficacy of sucrose for procedural pain in this population.² The concentrations of β -endorphin that were observed are similar to those reported in other studies of infants of similar gestational and postnatal ages.¹⁰⁻¹⁴ Therefore, our results are representative of this population and are probably not related to the assay technique used. β -endorphin concentrations were elevated in preterm infants receiving mechanical ventilation compared with control infants matched for age and weight.¹³

We specifically targeted infants with indwelling arterial catheters in situ to obtain blood samples for the measurement of β -endorphin. This was done to avoid subjecting the infants to unnecessary pain from heel lance or venipuncture for the sole purpose of obtaining the blood samples. Sampling in this manner meant that sucrose was not administered before a painful procedure, as it is in the clinical setting. Nevertheless, the infants in our study were similar to preterm infants in other sucrose studies because they had been exposed to painful and stressful events during their neonatal intensive care unit stay. The absence of a significant difference between β -endorphin concentrations before and after sucrose administration raises the possibility that sucrose-induced β -endorphin release occurs only in response to a painful procedure. However, we know of no mechanism that would lead to increased β -endorphin concentration after sucrose administration in response to a painful procedure but not otherwise. Such a mechanism would require the sucrose (or its effects) to interact with a pain-related factor to increase β -endorphin levels rapidly enough to induce analgesia after the painful procedure had occurred.

The lack of a difference in serum concentrations in this study may be due to improper timing of the blood sampling after sucrose administration. Blood sampling for β -endorphin concentrations was started between 2 and 5 minutes after the commencement of sucrose administration. It is possible that an insufficient period elapsed between the administration of the dose and blood sampling¹⁵ so that the increases in β -endorphin concentrations were not yet evident in the peripheral circulation. Alternatively, plasma β -endorphin concentration may not be directly related to the concentration at receptor sites. Rather, local concentration at the receptor site could vary without any detectable difference in plasma concentration.¹⁶

Another possible explanation for the negative result is that neurotransmitters other than β -endorphin are responsible for mediating the analgesic effects of sucrose. There are 3 main families of endogenous opioids: endor-

phins, enkephalins, and dynorphins. They act on 3 basic receptor types— μ , Δ , and κ , respectively—although no endogenous opioid is specific for 1 receptor. All opioids are derived from different precursor molecules and are present in the periphery, spinal cord, and brain.¹⁷ Of the numerous naturally occurring opioids, we chose to investigate β -endorphin because it produces the most powerful and longest-lasting analgesia. It is also the most studied one, and the role of other endogenous opioids is less clear. Moreover, only β -endorphin has been demonstrated to increase following the ingestion of sweet foods in animals.¹⁸

β -endorphin is derived by selective cleavage of the precursor molecule proopiomelanocortin. The main source of circulatory β -endorphin is the pituitary gland, but it may be produced in the brain and peripheral organs as well.¹⁹ During acute stress and pain, the hypothalamic-pituitary-adrenal system produces an increase in β -endorphin concentration in the blood. This circulatory release of β -endorphin can be reduced by systemic analgesia²⁰⁻²²; thus, plasma β -endorphin concentrations have frequently been used to determine analgesic efficacy. Early studies performed in animals demonstrated an inconsistent relationship between plasma and cerebrospinal fluid (CSF) β -endorphin concentrations. However, numerous methodologic shortcomings precluded an unequivocal interpretation of the results, including uncertain validity of assay techniques, concurrent administration of potentially interfering substances, and lack of control data.¹⁹ Although recent studies suggest that short-term variations occur in both plasma and CSF concentrations of β -endorphin, they are not closely correlated,^{19,20,23} and it is not clear whether β -endorphin is secreted within the brain but rapidly metabolized or resorbed without significantly altering the concentration in the CSF.¹⁹ The inconsistent relationship between plasma and CSF levels may be further complicated by certain neurological or inflammatory conditions involved in the pain system that act independently to influence β -endorphin release peripherally and/or centrally.²⁴ Because the relationship between peripheral and CSF β -endorphin concentrations as well as the mechanism of action of sucrose is unclear, we measured peripheral β -endorphin concentrations rather than CSF concentrations. Measuring CSF concentrations was neither feasible nor ethical (without more data to suggest a central mechanism of action).

Finally, it is possible that the dose of sucrose used in our study was subtherapeutic and failed to elicit changes in β -endorphin concentration. However, this is unlikely because the dose was within the range of effective analgesic doses used in this population.² In previous studies of preterm infants, sucrose doses varying from 0.01 g to 1 g^{25,26} (corresponding to approximately 0.01 g/kg to 1 g/kg) have been effective. In this study, we standardized the dose based on the weight of the infant. Our previous meta-analysis suggested that 0.24 g was the minimally effective dose for full-term infants (approximately 0.1 g/kg if the infant weighs 2.5 kg), so we used a similar exposure level (0.1 g/kg) for preterm infants. The method of sucrose administration was consistent with other studies; therefore, it is unlikely that the dose of sucrose or the mode of administration can explain why β -endorphin concentrations did not rise postdose.

What This Study Adds

The analgesic effects of sucrose are hypothesized to be mediated by the release of endogenous opioid neurotransmitters such as β -endorphin. We investigated whether β -endorphin concentrations in the serum were increased following sucrose administration in preterm infants. We found no significant effect of a single dose of sucrose on β -endorphin concentrations at a point in time when the analgesic effects of sucrose were presumed to be present. Our results do not support a β -endorphin-mediated mechanism of action of sucrose. However, the sampling techniques used (timing of blood samples; body fluid analyzed) may have been inappropriate or insensitive to changes in central nervous system β -endorphin concentration. Future research is needed to support or refute an opioid-mediated mechanism of action of sucrose.

In summary, we found no detectable increase in serum β -endorphin concentrations in preterm infants after a single dose of sucrose at a point in time when its analgesic effects were expected to be present. This study is only the first step in trying to identify the biochemical response to sucrose, so future studies are needed. Animal experiments involving measurements of β -endorphin concentration changes in the central nervous system after treatment with sucrose and the time course of these changes in the periphery may help to further elucidate the mechanism of action of sucrose and identify the cause of this apparently conflicting result.

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Corresponding author and reprints: Anna Taddio, PhD, Department of Pharmacy, The Hospital for Sick Children, 555 University Ave, Toronto, Ontario, Canada M5G 1X8 (e-mail: anna.taddio@sickkids.ca).

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