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Does Noninvasive Electrical Stimulation of Acupuncture Points (NESAP) reduce heelstick pain in neonates?

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Abstract

Aim—Noninvasive electrical stimulation at acupuncture points (NESAP) for analgesia is used in children, but has not been widely studied in neonates. The purpose of this study was to determine if NESAP alone or in combination with sucrose relieved heelstick pain in neonates.

Methods—Term neonates (n=162) receiving routine heelsticks for newborn screening were enrolled following parental consent. All infants received facilitated tucking and nonnutritive sucking. Neonates were randomized to standard care, sucrose, NESAP, or sucrose plus NESAP. NESAP (3.5 mA, 10 Hz) or sham was administered over 4 acupuncture points. The Premature Infant Pain Profile (PIPP), heart rate variability (HRV), and salivary cortisol were used to measure heelstick pain.

Results—PIPP scores among all 4 treatment groups increased during heelstick, $F(9,119) = 1.95$, $p = 0.05$, and NESAP therapy had no significant effect on PIPP scores. However, PIPP scores from baseline to heelstick increased the most in the two groups not receiving sucrose ($p < 0.01$). Mean

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Conflict of Interest Statement

The authors declare no conflict of interest.

PIPP scores remained below 5 during the heelstick in all four groups, indicating minimal or no pain. Differences in HRV and salivary cortisol among groups were insignificant.

Conclusion—NESAP at 3.5 mA, 10 Hz is not effective in relieving pain during heelsticks in neonates.

Keywords

neonates; NESAP; sucrose; pain; PIPP

Introduction

Hospitalized infants undergo many painful procedures for treatment or diagnostic purposes, but health care providers continue to struggle with the best methods to provide pain relief for infants during these procedures. Additionally, infants have a lower sensory threshold to pain, making them more sensitive and vulnerable during procedures [1]. Further, procedural pain leads to harmful short-term physiologic effects such as oxygen desaturation [2], and repeated pain may also trigger long-term consequences such as alterations to brain development and pain processing systems [3]. Systemic analgesics are not always appropriate and may not be effective for acute, localized procedural pain [4,5]. It is essential for health care providers to focus on a variety of pain relief methods for infants during painful procedures [6].

Acupuncture has been used extensively in infants and children [7] and demonstrates an excellent safety profile. It has also been used to treat neonatal abstinence syndrome [8]. NESAP, a non-invasive method of stimulation of acupuncture points, has been shown to be safe in neonates [9].

NESAP and sucrose act by different biological mechanisms, but it is unknown if their effects would be additive. The purpose of this study was to determine if NESAP alone or in combination with sucrose relieves heelstick pain in neonates. The following two hypotheses were proposed for this study:

- NESAP at selected acupuncture points (ST36, SP6, BL60, KI3) or oral use of 24% sucrose will reduce the newborn infant's responses to heelstick pain, as measured by the Premature Infant Pain Profile (PIPP), heart rate variability (HRV), and salivary cortisol levels.
- The effects of combined therapies will be additive, as compared to either NESAP or sucrose alone.

Methods

Study Design

A double-blind 2×2 factorial randomized controlled trial was designed to evaluate the response to pain during heelsticks for routine newborn metabolic screening at two medical centers. The study was registered with Clinical Trials (NCT01800318). After IRB approval and parental consent, 162 healthy infants born at 37 – 42 weeks gestational age were

randomized into four treatment groups using randomization number tables. The research team was blinded to infant group assignment. All treatment groups received facilitated tucking and a pacifier. In addition, treatment groups received 24% sucrose and/or NESAP. The underlying mechanism for sucrose analgesia is activation of the endogenous opioid system [10]. Similarly, NESAP activates endorphins [11] and the descending pain inhibitory pathways [12]. Facilitated tucking was administered by a trained advanced practice nurse researcher and was applied by providing gentle support to the head and flexing the knees to midline.

Group A received sham NESAP with 24% oral sucrose; Group B received NESAP with water; Group C received NESAP with 24% oral sucrose, and Group D received Sham NESAP with water (control). Table 1 presents a time line of the heel stick, treatment and data collection process.

Sample

Infants were enrolled at two study sites: University of Arkansas for Medical Sciences (UAMS), Little Rock, AR and Lucille Packard Children's Hospital, Stanford University, Palo Alto, CA. Inclusion criteria were healthy term infants between 37 and 42 weeks. Exclusion criteria were birth asphyxia or infant illnesses and congenital defects, and maternal drug exposure or serious illnesses. We calculated that 164 infants from both sites would be required to show a clinically meaningful difference of 2 points in PIPP scores [13], with an α -error of 0.05 and power (1- β error) of 80%.

Treatments

The study device was a standard Empi Select TENS unit (Empi, Inc. St. Paul, Minnesota) that was cleared for this study by the Food and Drug Administration (IDE #G120296). During the study, the TENS unit was silent and covered by the RN research associate to hide settings and maintain blinding. Small electrodes were placed in treatment groups B and C on the baby's legs at specific acupuncture points: ZuSanLi (ST36), SanYinJiao (SP6), KunLun(BL60), and TaiXi (KI3). StimCare electrodes with a gel base were applied; electrodes were wrapped with gauze to ensure that placement remained intact during the heel stick procedure. The TENS unit was turned on and settings were increased very gradually over 60 seconds to avoid startling the infant. A low continuous current of 3.5 mA and frequency of 10 Hz was delivered [9] for 10 $\pm$ 1 minutes prior to the heelstick, with continued stimulation during and for 2 minutes after the heelstick. This paradigm is based on the basic animal research developed by Dr. Han and other research groups [14,15]. Sham stimulation in groups A and D was performed by applying electrodes adjacent to the proposed acupuncture points (ST36, SP6, KI3, BL60) but the TENS unit was not switched on.

Newborns randomized to the sucrose analgesia groups A and C received 1 $\pm$ 0.1 ml of the 24% sucrose solution orally with pacifier at 2 $\pm$ 0.5 minutes prior to the procedure, whereas groups B and D received 1 $\pm$ 0.1 ml of sterile water with pacifier.

Outcome Measurements

Our primary outcome was the validated PIPP score that included assessment of contextual, physiological (vital signs), and behavioral (facial expression) parameters. PIPP scores less than 6 indicate minimal pain or no pain and scores over 12 indicate moderate to severe pain [2]. Table 1 presents a time line for gathering data related to PIPP scores and other outcomes. Facial expressions were assessed by video for the PIPP score. Two research assistants scored all videotapes; if there was not 100% agreement on facial PIPP scores, videotapes were rescored.

Changes in HRV caused by heelstick pain were evaluated using the DL 900 Holter monitor (Braemar, Inc) with 3-channel output with 5 leads for heart rate variability. These changes have been validated for pain studies in preterm and term infants [16].

Salivary cortisol has been validated as a measure of acute pain-related stress in preterm infants [17]. Saliva specimens were obtained before, and at 5 ± 0.5 minutes after the heelstick by gentle insertion of a salivary swab (Salimetrics, Inc) made specifically for infants. The samples were stored at -20 degrees Celsius within 1 hour of collection, analyzed in duplicate using Alpcor Cortisol (saliva) ELISA kits.

Statistical Methods

All statistical analyses were performed in SAS Version 9.3. The HRV and PIPP score responses were modeled using a repeated measures analysis of variance (ANOVA) using the SAS Proc Mixed Procedure. The primary contrasts of interest were the differences between the baseline time point vs. the heelstick and recovery means. *Post hoc* multiple comparisons were performed on 12 contrasts using the Bonferroni adjustment with a 5% family wise error rate. Observed PIPP score means and differences from baseline were reported with standard deviations and Bonferroni adjusted p values. Salivary cortisol was modeled using repeated measures ANOVA and the Bonferroni adjustment.

Results

Figure 1 presents a flow diagram for infants who were enrolled, participated, and completed the study. A total of 162 infants were enrolled from the two sites. Nine infants who were enrolled did not complete the study due to errors or outside events. No infants were withdrawn from the study due to adverse events. The mean gestational age of infants was 39 (± 1.2) weeks and the mean birth weight was 3329 (± 472) grams.

The analysis of group by time interaction of PIPP scores across all phases of the procedure gave a main effect of $F(9,119) = 1.95$, $p = 0.05$. Table 2 outlines posthoc comparisons of observed PIPP score means ($\pm$ SD) across phases of heelstick. The time points evaluated compared baseline PIPP scores before treatment to PIPP scores during (a) initiation of NESAP therapy or sham, (b) heelstick, and (c) recovery phase. PIPP scores did not increase significantly in any of the four groups during initiation of NESAP therapy but before heelstick. As expected, all treatment groups experienced increases in PIPP scores during the heelstick/heel squeeze phase. NESAP therapy had no significant effect on PIPP scores, although PIPP scores from baseline to heelstick phase increased the most in the two groups

(NESAP alone and usual care) that did not receive sucrose ($p<0.01$). Mean PIPP scores remained below 5 during the heelstick in all four groups, indicating minimal or no pain. Mean PIPP scores were higher during the recovery phase compared to baseline in the NESAP group, but differences in recovery PIPP scores among the four treatment groups were not significant.

Heart rate variability (HRV) analyzed with RM-ANOVA showed no significant differences in the LF/HF ratios from baseline to heelstick ($p=0.6315$) or recovery ($p=0.507$) phases among the four treatment groups. Due to difficulties in collecting adequate saliva, salivary cortisol levels were missing in 78 infants (51%). There were no significant changes in salivary cortisol.

Discussion

NESAP therapy using our parameters showed no benefit for acute pain relief. Although not effective for heelstick pain, no crying and no change in PIPP scores occurred during the 10 minutes of NESAP before the heelstick. This indicates that although NESAP therapy was not effective for pain relief, it was safe and did not cause discomfort, consistent with our pilot study determining the safety of TENS in newborns at 3.5mA and 10 Hz [9].

Our findings differed from those of Ecevit et al. who reported lower Neonatal Infant Pain Scale scores and shorter crying times in premature infants ($n=10$) who received acupuncture before heelsticks [18]. This small study used actual acupuncture with needling placed between the eyebrows, in contrast to our study that used NESAP with electrodes placed on the lower leg. In a similar study, acupressure was used in a group of preterm infants ($n=16$) with resulting lower PIPP scores and shorter duration of crying during heelsticks [19].

The use of TENS units for analgesia has a long history in both adults and children, for both acute pain and chronic pain relief [20]. In pediatric dental pain, TENS was superior to a local anesthetic in relieving pain due to simple restorative procedures [21]. TENS application at acupuncture points has increased in recent years, as it is a non-invasive method of stimulating acupuncture points. Ni et al demonstrated that TENS stimulation at the P6 acupoint resulted in a decreased inflammatory response following pediatric cardiac surgery [22], while Kabalak et al showed that TENS application resulted in decreased emesis following tonsillectomy in a pediatric population [23]. Our previous study demonstrated the safety of TENS in neonates, [9] but no other studies have examined the effectiveness of NESAP against heelstick pain in infants.

According to Han, low frequency stimulation at 2–4 Hz activates endomorphins and enkephalins, while high frequency stimulation at 100–200 Hz activates dynorphin A receptors in adults [11]. This process leads to increased descending inhibition, as well as anti-inflammatory effects [24]. Choi concluded that TENS therapy also relieves pain through activation of central pain modulation and the descending pain-inhibitory pathways [12]. Some of these mechanisms may not be fully developed in neonates, may have a blunted response or may serve different developmental functions. [25,26]

It is possible that NESAP was ineffective for reducing heelstick pain in newborns due to the lack of sufficient development of inhibitory pathways at this age or perhaps because of the inability to individualize the TENS intensity in the neonates. It is also possible that different parameters of TENS therapy (eg different frequencies, intensity) may be more effective for acute pain management in neonatal or infant populations. Further research on the differential effects of TENS stimulation at different frequencies as well as different age groups is warranted. Additionally, stimulation of acupoints by other types of interventions such as acupressure, acupuncture or laser stimulation may be warranted.

Our study found that PIPP scores during heelsticks did not change significantly from baseline in the two groups that received sucrose, resulting in a minimal pain response to heelsticks. These results confirm the effectiveness of sucrose to relieve pain during procedures [10]. Based on these results, we agree with Lago et al. (2014) that sucrose administration results in calmer, more relaxed infants and can be recommended before invasive procedures [27].

Among the three methods used, we found that PIPP scoring was the most sensitive method to detect differences in pain levels during heelstick and between the treatment groups. Salivary cortisol has been used as a marker of stress in infants, but results have been variable. We found it difficult to collect an adequate volume of saliva to run salivary cortisol analysis, and this is one limitation of the study. The success rate of obtaining adequate saliva for analysis before and after heelstick was only 46%. Similar to our results, Shibata et al (2013) found significantly increased NIPS scores and heart rates in newborns during heelsticks but no significant changes in salivary chromogranin or salivary amylase. We agree that salivary biomarkers are not a reliable method to assess pain in newborn infants and that emphasis must be placed on multidimensional pain instruments including a combination of behavioral and physiological measures [28].

HRV did not show any significant differences before and after the heelstick among groups, although it has been used in the past as a pain marker for neonates [16]. One consideration when interpreting these results is the brevity of each burst of HRV data, which ranged from 2 to 5 minutes according to phase of data collection (baseline, heelstick, recovery). These brief durations of time may not have been enough to produce significant changes in LF/HF ratio.

We noted that PIPP scores remained low, with mean scores of 5 or less during the heelstick procedure for all treatment groups. A PIPP score of less than 6 indicates minimal or no pain, and these scores are lower than those generally reported for heelstick pain. For ethical reasons, infants in each group received routine care designed to prevent and manage pain, which included facilitated tucking and a pacifier for nonnutritive sucking. Facilitated tucking significantly reduces PIPP scores during venipuncture in preterm infants. [29] We found that the combination of sucrose, facilitated tucking, and pacifier was the most effective, agreeing with Yin and others who also found that the same combination was most effective for heelstick pain in 110 infants. [30]

This study adds to the growing body of evidence that sucrose is effective and can be accepted as standard of care for treating heelstick pain. Future studies, possibly using a non-inferiority design, should compare sucrose rather than placebo with other methods of treatment for heelstick pain, even though this approach would require a larger sample size.

Conclusions

NESAP therapy using 3.5 mA and low frequency (10 HZ) was ineffective against heelstick pain in neonates, but PIPP scores did not change significantly in the two groups that received sucrose, indicating minimal or no pain. Facilitated tucking and pacifier alone may have relieved heelstick pain and resulted in lower PIPP scores in all groups. PIPP scores were the most sensitive method of assessing heelstick pain.

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Key notes

- Neonates undergoing routine heelsticks were randomized to usual care (facilitated tucking and pacifier) or usual care with addition of either NESAP, oral sucrose, or NESAP plus sucrose.
- Premature Infant Pain Profile (PIPP) scores indicated that NESAP was ineffective in reducing procedural pain.
- PIPP scores did not change significantly in the two groups that received sucrose, indicating minimal or no pain when sucrose was administered.

Figure 1.

CONSORT Flow Diagram for study: Does Noninvasive Electrical Stimulation of Acupuncture Points (NESAP) reduce heelstick pain in neonates?

Table 1

Timeline for Treatment and Data Collection

Time Frame	Activities	Data Collection
20–30 minutes before heelstick	Apply pulse oximeter Apply HRV electrodes Apply NESAP electrodes	Obtain baseline heart rate, oxygen saturation level, and blood pressure Collect saliva sample Begin baseline facial videotaping and continue throughout with code markers for phases and start of therapies
15 minutes before heelstick	Position infant with facilitated tucking and maintain position throughout Provide pacifier throughout	Continue monitoring heart rate and oxygen saturation for baseline levels Start HRV monitor
12 minutes before heelstick		First PIPP score given during rest
10 minutes before heelstick	Start NESAP or sham therapy	PIPP scores every 30 seconds for 120 seconds Place marker on HRV monitor
5 minutes before heelstick		Obtain second heart rate, oxygen saturation, and blood pressure
2 minutes before heelstick	Give 1 ml 24% sucrose or sterile water Start heel warmer	
Heelstick	Perform heelstick according to unit protocol for routine newborn heelstick for metabolic screening	PIPP scores every 30 seconds for 120 seconds Place marker on HRV monitor Measure cry duration Measure duration of heelstick
Immediately after heelstick		PIPP scores every 30 seconds for 120 seconds Place marker on HRV monitor
5 minutes after heelstick	Discontinue NESAP Discontinue oxygen saturation monitor Discontinue videotaping Discontinue facilitated tucking	Obtain third heart rate, oxygen saturation, and blood pressure Place marker on HRV monitor Collect second saliva sample

PIPP – Premature Infant Pain Profile

HRV – Heart rate variability

TENS – Transcutaneous Electrical Nerve Stimulation

Table 2Changes in observed PIPP score means ($\pm$ SD) from baseline across phases of heelstick

Treatment Group	Time Epoch			
	PIPP scores before treatment (baseline)	PIPP scores during NESAP (or sham)	PIPP scores during heelstick	PIPP scores during recovery
Group A Sucrose + usual care (n=37)	2.8 ($\pm$ 1.7)	2.6 ($\pm$ 1.5)	4.0 ($\pm$ 1.8)	2.8 ($\pm$ 1.1)
Group B NESAP + usual care (n=37)	1.8 ($\pm$ 1.4)	1.8 ($\pm$ 2)	5.0 ($\pm$ 4.0) *	3.0 ($\pm$ 2.7) *
Group C NESAP +sucrose +usual care (n=40)	2.4 ($\pm$ 2.2)	2.1 ($\pm$ 1.4)	3.6 ($\pm$ 1.2)	2.6 ($\pm$ 1.6)
Group D usual care (n=39)	1.8 ($\pm$ 1.5)	2.1 ($\pm$ 1.3)	4.9 ($\pm$ 4.0) *	2.9 ($\pm$ 1.9)

Note: usual care included facilitated tucking and pacifier

* Bonferroni adjusted p value for increase in PIPP score from baseline <0.01