Effect of glucose and non-nutritive sucking on puncture pain in premature infants: a crossover clinical trial*

ABSTRACT

Objective: To compare the effect of non-nutritive sucking, 25% oral glucose and 25% oral glucose combined with non-nutritive sucking in pain relief in premature infants submitted to heel puncture for blood glucose monitoring. Method: This is a randomized crossover clinical trial with 34 preterm infants who randomly received interventions: non-nutritive sucking, 25% oral glucose and the two interventions combined for three consecutive days in heel puncture for blood glucose monitoring. Assessment by the Premature Infant Pain Profile for 30 seconds before the intervention, called the baseline period and for 5 minutes after puncture. Results: The combination of interventions made the premature infants return to baseline, with 1 minute and 30 seconds after heel puncture, promoting a 2.2% percentage reduction in the scale. Conclusion: Comparing the effect of isolated and combined interventions showed that, when offered in combination, preterm infants were able to return to baseline parameters more quickly. Brazilian Clinical Trials Registry: RBR-3gm6w5.

DESCRIPTORS

Pain; Infant, Premature; Punctures; Sucking Behavior; Glucose; Neonatal Nursing.


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INTRODUCTION

Pain in premature infants (PTIF) in Neonatal Intensive Care Units (NICU) is a focus of concern and control due to the hemodynamic fluctuations it causes, leading to short and long term sequelae(1), such as physiological instability, changes in brain development, systemic stress response and abnormal patterns in neurodevelopment(2). Among the frequent causes of pain, heel puncture regularity can be highlighted, due to the need for blood glucose monitoring(1,3). In a study that observed 562 infants for 14 days while admitted to NICU, 8,995 heel punctures were identified, among which 7,922 were performed for blood glucose monitoring. Thus, each infant was subjected to a mean of 2.1 punctures per day, with a range from 0 to 20(3).

Pain assessment should be performed with measurement instruments validated continuously so that professionals can be guided to promote their relief effectively. Among the recommended scales, the Premature Infant Pain Profile (PIPP) includes, in addition to physiological measures and behavioral responses to pain, the contextual factors gestational age and behavioral state(2). These contextual factors consider aspects of neurological development directly related to gestational age and the ability to respond to pain, as well as the state of sleep and activity, that are influenced by painful stimulus, expanding the reflection on the definition of pain for infants(4).

Pain relief for procedures should be planned as a priority and performed with non-pharmacological interventions initially(2-3), among which sweet solutions and non-nutritive sucking (NNS) are well-established and recommended strategies(1-3). Glucose in the concentration between 20 and 30% is considered effective, safe and with limited side effects in pain relief; however, there is no consensus on the ideal dose(2-3). In Brazil, 25% glucose has been used more in clinical practice, as it is easily found in the form of an ampoule manufactured and marketed to hospital units.

NNS is considered an intervention that promotes self-regulation and physiological stability in PTIF(5). When combined with the sweetened solution, it shows an additive effect that has a direct impact on the reduction of behavioral and physiological responses of PTIF as well as on the pain score assessed by scales(3). On the other hand, it does not differ from the use of glucose alone in reducing the risks of bradycardia, tachycardia and incidence of desaturation(5).

Commonly, studies that address the use of non-pharmacological interventions in pain relief are aimed at a specific time and procedure. Thus, in this study, it was established as a hypothesis that the combination of 25% glucose with NNS is superior to their use separately for relieving the pain in PTIF submitted to heel puncture for monitoring blood glucose, for three consecutive days.

The objective was to compare the effect of NNS, 25% oral glucose and 25% oral glucose combined with NNS in PTIF pain relief submitted to heel puncture, for blood glucose monitoring.

METHOD

TYPE OF STUDY

This is a randomized crossover clinical trial, developed at the NICU of the Maternity School of Universidade Federal do Rio de Janeiro, from March 2014 to May 2015.

POPULATION

The population consisted of 94 PTIF admitted to a NICU with gestational age at birth between 29 and 36 complete weeks and a medical prescription for capillary blood glucose monitoring. After applying the selection criteria, a sample of 34 PTIF was constituted.

SELECTION CRITERIA

PTIF with Apgar ≥ 7 in the fifth minute of life, postnatal age ≥ 6 hours of life, clinical stability with heart rate and oxygen saturation within the parameters of normality and enteral diet initiated were included. Those diagnosed with grade III or IV intraventricular hemorrhage, leukomalacia, chromosomal abnormalities, central nervous system malformations, congenital heart disease, necrotizing enterocolitis, hyperglycemia, ventilatory assistance, use of drugs that interfered with the nociception response to pain, mothers using illicit drugs, trauma resulting from childbirth and contact precautions were excluded. As a criterion for discontinuity and loss, the suspension of blood glucose monitoring for a period of less than three days was adopted.

INTERVENTION, AND DATA COLLECTION

Each participant received the three proposed interventions, 1- NNS, 2- 25% glucose and 3- 25% glucose + NNS, one for each day when the heel puncture was performed to monitor blood glucose. All collection was carried out in the afternoon after checking the medical prescription for the day.

NNS was offered with a gloved little finger (vinyl glove without latex) two minutes before and during puncture, and a frequency of ≥ 32 suctions per minute should be maintained. Thus, 25% glucose was offered in a 1ml volume directly on the anterior part of the tongue with a 1 ml syringe without a needle, two minutes before puncture. Moreover, 25% glucose + NNS was offered two minutes before puncture, with glucose being offered first and then NNS, according to the terms previously described.

To outline the PTIF profile and hospitalization, sex, birth weight, Apgar in the fifth minute of life, childbirth type, gestational age at birth, birth assistance, hospitalization diagnosis, time of entry into the study and procedures performed in the period 24 hours before heel puncture on each collection day were the variables.
investigated using medical records. Twenty-five procedures were considered to be painful and painless (stressful), the number of times they were repeated and the pain relief measure used were listed. All procedures listed were based on the study instrument called Epidemiology of Painful Procedures in Neonates (EPIPPAIN), duly authorized by the author(7).

The second part of the instrument was obtained at the time of collection on each day, with the assessment date identification, corrected gestational age, current weight, non-pharmacological measure used, adverse events occurred, conduct and blood glucose value. Pain was assessed using PIPP, which is the primary outcome.

PIPP, translated and adapted to Brazilian Portuguese and widely used in clinical research(8), is divided into two moments: observation of infants for 15 seconds in which the current gestational age is considered as an indicator and behavioral state. The lower the gestational age, the higher the score on the scale. The behavioral state to be observed is whether active or quiet, awake or asleep, eyes closed or open and facial movements present or absent. This first moment must be performed before the procedure is conducted, in order to register infants’ behavioral state before a painful stimulus.

The second moment refers to observation of infants for 30 seconds, considering the physiological indicators heart rate and oxygen saturation and three behavioral indicators: protruding eyebrow, squeezed eyes and nasolabial fold. The total score of the scale is 21 points, in which values less than or equal to six indicate minimal or absent pain; between 7 and 11, pain present; greater than or equal to 12, moderate to severe pain. In this second moment, the permanence time of each of the behavioral indicators and fluctuations of physiological indicators after painful stimulus are checked. The longer the behavioral indicator remains and the more intense the change in the physiological indicator, the higher the score. The instrument’s score in the baseline period was used as a parameter.

To obtain the PIPP score, each PTIF was observed for 30 seconds before the application of the intervention considered as the baseline period and for five minutes from the moment of heel puncture for blood collection. The score was obtained for each 30-second chunk. The first minute was called immediate recovery (IR), and the time after, late recovery (LR). The times corresponding to the established chunks were IR30, IR60, LR90, LR120, LR150, LR180, LR210, LR240, LR270 and LR300.

Two digital video cameras were used, one fixed and directed to the pulse oximeter monitor and the other directly to the participant’s face, handled by the main researcher at the time of collection. A Polar RS800X frequency meter was connected to two cardiac electrodes in the chest region of PTIF to check heart rate; subsequently, it was transferred to a digital spreadsheet of the equipment to verify the fluctuation of results. The Magix Movie Edit Pro 15 Plus software was used to perform facial movement second-by-second coding (protruding eyebrows, squeezed eyes and nasolabial fold), recording in a spreadsheet the time that each movement was maintained within the established intervals of the period, baseline and five minutes after heel puncture. Oxygen saturation was also checked and recorded on a separate sheet.

During collection, some participants had conditions with the potential to confuse the response to pain, such as use of caffeine and the frequency of insufficient sucks. To control such conditions, an intention-to-treat analysis was carried out using hierarchical regression model under a Bayesian approach. All variables identified as potentially influential in the PTIF response on each assessment day were controlled, such as weight, frequency of sucking, caffeine use, non-pharmacological intervention used, corrected gestational age, number of painful procedures and number of stressful procedures.

**Sample definition**

In order to calculate the sample size, it was considered that all interventions would be effective, as indicated in the literature. Thus, for the alternative hypothesis to be answered, a difference in the scale score that should be obtained between the use of isolated and combined interventions was defined. The magnitude of effect of the isolated and combined interventions was considered with a three-point reduction margin in the total of PIPP so that the combination of 25% glucose with NNS was more effective than the isolated interventions, according to previous studies(9-10). A significance level of 5% and a test power of 80% were parameters adopted, with a total of 34 participants. Considering the probability of losses during the experiment, a 20% increase was made to the size of the initial sample, totaling 40 PTIF.

Randomization was performed using a simple technique through the website www.randomization.com. The generated individual plan could obey the following sequences: 1, 2 and 3 or 1, 3 and 2 or 2, 3 and 1 or 3, 2 and 1 or 3, 1 and 2. Each individual plan was inserted in an opaque envelope, sealed and numbered consecutively, being used according to infants’ entry into the study. For each participant who entered the study, the number corresponding to the sealed envelope was assigned and the randomized intervention was offered for the corresponding collection day, totaling three collections.

The randomization plan was carried out by a research assistant who was not involved in the collection. A second research assistant was responsible for offering non-pharmacological interventions prior to the procedure according to the sequence in the envelope corresponding to the participants. All heel punctures for blood collection were performed by nursing technicians from the unit itself. Blinding was not possible due to the use of NNS before and during heel puncture. (Figure 1)
**DATA ANALYSIS AND TREATMENT**

All data collected were subjected to double entry by independent researchers; subsequently, its consistency was tested, with the database preparation in a spreadsheet in Microsoft Office Excel, version 2007. To obtain interobserver reliability, the facial movements of 10% of the sample were coded by two nurses who were previously trained and blinded to the objectives of the study, with KAPPA of 90% for protruding eyebrows and 100% for squeezed eyes and nasolabial fold.

At first, descriptive statistics with measures of central tendency and dispersion were applied to characterize the sample. For the initial comparison of the total score obtained by PIPP with the use of 25% glucose, NNS or 25% glucose + NNS interventions, Student’s t test and non-parametric Wilcoxon test were performed in order to obtain a p value. Comparison tests with a p value < 0.05 indicated that there was no return to the baseline period, considering that, according to the literature, all non-pharmacological interventions used in this study would be effective.

From heel puncture, a PIPP score was obtained in each 30-second chunk, considering the variations of a mean value attributed to each assessment day for each PTIF, from the effect of the time from the moment of such painful procedure until its conclusion, besides the condition of PTIF being small for gestational age or not.

To perform the calculations related to the quantitative analysis, the OpenBUGS software, version 3.2.3 Rev, 1012, available from http://www.openbugs.net was used.

The hierarchical model used is presented below. Y represents the PIPP score of infants (i) submitted to the intervention (j) in the moment (time) (k). “Alpha” coefficients represent the numerical effect of the corresponding variable. (Figure 2)

\[
Y_{i,j,k} \sim N(\mu_{i,j,k}, \sigma^2) \\
\mu_{i,j,k} \sim N(\mu_{i,j} + \alpha_{\text{weigt}} \times \text{weight}_{i,j} + \alpha_{\text{suction}} \times \text{suction}_{i,j} + G\alpha_{i,j} \times \text{caffeine}_{i,j} + \alpha_{\text{med1}} \times \text{med1}_{i} + \alpha_{\text{med2}} \times \text{med2}_{i} + \alpha_{\text{med3}} \times \text{med3}_{i} + \alpha_{\text{med4}} \times \text{med4}_{i} + \alpha_{\text{med5}} \times \text{med5}_{i} + \alpha_{\text{med6}} \times \text{med6}_{i}) \\
\theta_{i,j} \sim N(\mu_{i,j} + \alpha_{\text{time}} \times \text{time}_{i} + \alpha_{\text{timek}} \times \text{timek}_{i}, \sigma^2) \\
\mu_{i,j} \sim N(1.8, 0.1)
\]

*Figure 2 – Equations for the Bayesian hierarchical model.*
ETHICAL ASPECTS

Those responsible authorized participation of PTIF by signing an Informed Consent Form (ICF). The project was approved by the Ethics Committees in October and December 2013 by the host and co-participant institutions, under opinions 439.157 and 492.643, respectively. The RBR-3gm6w5 record was obtained by the Brazilian Clinical Trials Registry (ReBEC – Registro Brasileiro de Ensaios Clínicos).

RESULTS

Table 1’s data show the profile of infants and hospitalization while in NICU. There was no predominance of sex; PTIF were born, on average, with 33 weeks and 5 days of gestational age and low weight due to cesarean section; most did not need oxygen support in the delivery room. The predominant hospitalization diagnosis was prematurity, associated with respiratory discomfort, and the time of entry into the study was 10 hours of life to six days.

On the first collection day, PTIF were, on average, 34 weeks old and 1 day old; on the second day, 34 weeks and 1 day; on the third day, 34 weeks and 3 days, maintaining low weight every day. There were ten episodes of adverse events described in Table 1, six episodes in the administration of 25% glucose, three after administration of 25% glucose combined with NNS and one episode while offering NNS. In all episodes, there was spontaneous recovery after a pause in the provision of interventions.

With regard to painful procedures performed in the 24 hours preceding blood glucose collections, a mean of 13.6 procedures was identified per PTIF on the first collection day. On the 2nd and 3rd days of collection, there was a mean of 9 painful procedures per PTIF per day. Among the painful procedures identified, heel puncture was the most frequent, being performed 150 times on the first collection day, with a mean of 4.4 punctures per PTIF, 155 times on the second collection day, with a mean of 4.0 per PTIF and 127 times on the 3rd collection day, with a mean of 3.7 per PTIF. Of the stressful procedures, diaper changing was the most frequent, being performed 259 times on the first day, with a mean of 7.6 times per PTIF, 287 times on the second day, with a mean of 8.4 times/PTIF and 279 on the third day, with a mean of 8.2 times per PTIF.

The use of interventions for pain relief when installing a peripherally inserted central catheter (PICC) and venipuncture for blood collection was identified in the medical records of four PTIF. In the PICC insertion procedure, two PTIF received fentanyl in the 24 hours preceding the 2nd collection day, in addition to one of these also receiving the winding. In the venipuncture procedure for blood collection, one PTIF received 25% glucose + NNS in the 24 hours prior to the 1st collection day, and one PTIF, on the 3rd collection day.

Table 2 analyzes the PIPP score for each intervention offered at each established time. Moreover, the results of hypothesis tests that compare the mean or median of the PIPP score of each time with baseline time are presented. In the case of NNS and 25% glucose, there is evidence that the means for all times have a significant difference from the baseline time mean (p value < 0.05); in other words, the isolated interventions were not able to return PTIF to the same parameters identified in the baseline period, before the painful procedure was performed, when they did not present pain. For the two combined interventions, there is no evidence of differences between the means from the LR 90 time with that of the baseline period (p value > 0.05). Therefore, they are more effective because they cause PTIF to return to baseline after one minute and thirty seconds of puncture.
Regarding the confounding variables, which were controlled by the regression model under a Bayesian approach, what was observed was a tendency to reduce pain through the PIPP score, when under the influence of caffeine use (2% reduction in PIPP), the number of stressful procedures (6% reduction in PIPP), weight (1% reduction in PIPP the greater the weight), procedure observation time (1% reduction in PIPP the longer the elapsed time after the painful procedure), being small for gestational age (16% reduction in PIPP) and insufficient suction (15% increase in PIPP). There was a tendency to increase pain with the isolated use of 25% glucose (increase of 15.4% in PIPP), isolated use of NNS (2.2% reduction in PIPP). There was a tendency to increase pain with the isolated use of 25% glucose (increase of 15.4% in PIPP), isolated use of NNS (2.2% reduction in PIPP) and the combined use of 25% oral glucose with NNS (2.2% reduction in PIPP). There was a tendency to increase pain with the isolated use of 25% glucose (increase of 15.4% in PIPP), isolated use of NNS (increase of 12.4% in PIPP), number of painful procedures (increase of 0.5% in PIPP) and insufficient suction (15% increase in PIPP).

The expected mean value for PIPP was estimated on the first collection day of PTIF 27, which was 6.1. The estimated calculation was for the last assessment chunk (LR300), in which data were lost due to the conclusion of the study with four minutes and thirty seconds instead of five minutes. The credibility gap points to a large margin of uncertainty.

### DISCUSSION

In the present study, what was observed is that the use of 25% oral glucose combined with the NNS was the intervention that made PTIF return to the PIPP score at the same value as that obtained in the baseline period, one minute and thirty seconds after heel puncture. Whereas, when NNS and 25% oral glucose isolated were used, there was no matching of the PIPP score with that of the baseline until the conclusion of observation, which was five minutes. This means that the combination of 25% oral glucose with the NNS used for pain relief in the heel puncture procedure favors the return to baseline faster.

However, the difference in the expected PIPP score for the superiority of the intervention to be confirmed has not been statistically verified. Furthermore, the use of 25% glucose and NNS in isolation showed an increase of 15.4% and 12.4% in the total PIPP score, respectively, contrary to the literature.

Some reasons why the results of the statistical model did not have the expected impact may be related to the lack of a control group, in which the conditions to perform the procedure to be adopted were that of the unit’s routine, allowing comparisons beyond the baseline parameter. Another factor that limited the study was the amount of PTIF that did not suck effectively and that one chose not to exclude from the study. A number of participants in ideal conditions like the one predicted by the sample calculation could show better results in data analysis; however, one chose to portray the individual reality of PTIF in the three days that were assessed and offer, throughout the text, options to relieve pain, having the baseline period as a parameter, used as a reference for later assessments.

Studies that indicate and assess pain using scales\(^1\)\(^{-}^{10}\) consider the baseline period as a parameter so that multidimensional changes are verified. Systematic observation assists in the analysis of the time spent so that the same parameters were achieved, with the use of pain relief interventions in the face of the applied stimulus. Thus, for an intervention to be considered effective, the time counted from the end of the stimulus to self-regulation must be as short as possible, reflected in the scale's score.

Similar results were found in a clinical trial\(^\text{11}\) conducted with 86 PTIF, with a mean gestational age of 31.7 weeks. The efficacy and safety of NNS and sucrose were assessed in three non-consecutive heel punctures, for monitoring blood glucose, as a treatment routine. PTIF who used the combined interventions did not feel pain, and those who used the isolated substances felt mild pain\(^\text{11}\). Despite the results, all options described for pain relief are safe\(^2\)\(^{-}^{6,11}\), recommended\(^1\)\(^{-}^{6}\) and can be offered through prior planning of actions by professionals and the establishment of institutional protocols, assessing the situation of each PTIF\(^2\).

Therapeutic and clinical procedures performed during the hospitalization of PTIF need to be previously assessed.
as to the real need, since studies recommend[2–3] that painful procedures be avoided, that the use of non-invasive monitoring is recommended, as well as anticipating the need for future studies. Regarding the need to perform the painful procedure, the use of non-pharmacological intervention should be planned.

In a study[12] that reviewed treatments with non-pharmacological interventions frequently used in painful procedures that involve breaking the skin, it was shown that the additive effect of sweetened solutions with NNS is effective for mild and moderate pain. However, the more painful procedures performed, the stronger painkillers were used, strengthening the need to control the number of painful procedures in order to provide parameters for professionals. An alternative to control the number of procedures is the daily and individualized record of painful and stressful procedures performed, as well as the attempts made until completion.

Although the recommendations are clear with regard to reducing the number of procedures and the use of pain relief measures for PTIF, the actions are still underdeveloped. In a retrospective cross-sectional study[13] of medical records, it was found that, in the first seven days of admission to NICU, the 150 PTIF were subjected to 4,765 invasive procedures, with a mean of 6.6 per infant per day. The most frequent procedure was heel puncture, performed 1,702 times, with no records of the use of previous non-pharmacological pain relief measures, as well as pharmacological ones, being found by the majority. When the pain scale was applied, 3,884 records were identified, of which 96.8% corresponded to the absence of pain and 17.1% to the presence of pain; however, pain relief interventions have not been verified in most.

Studies[14] that used non-invasive methods of imaging brain activity in order to assess the effectiveness of non-pharmacological and pharmacological interventions in relieving pain showed that they are useful tools capable of verifying that brain activity can be observed, even in the absence of pain indicators, being influenced by contextual factors, such as age, sex, previous pain, stress level and disease. In this study, factors such as diaper change, weight, caffeine use and being small for gestational age reflected in a reduction in the PIPP score, which could be better explored in studies with a multimodal approach.

As well as contextual factors, others[10] must be considered in pain assessment in PTIF, such as the development of the nervous system, which configures the location of pain according to gestational age. Duration of pain, which can be considered as acute or chronic, and side effects of tissue injuries, defined as hyperalgesia and allodynia, demonstrating the complexity of non-verbal responses issued and the factors that may be involved. However, regardless of the type of pain identified, the strategy for its relief must be used, which can be mediated by the construction of an institutional protocol for pain management based on scientific evidence and in the daily life of each unit.

CONCLUSION

The comparison between the effect of 25% oral glucose, NNS and the two combined interventions showed that, when the interventions are offered in combination, PTIF is able to return to its baseline state more quickly. Therefore, it is recommended to adopt this practice in care protocols in neonatal units. The importance of pain assessment at the bedside should be emphasized as a systematic activity through instruments capable of providing accurate information regarding the intensity of pain and the effectiveness of interventions used to relieve it in the light of the baseline period, employed as an assessment parameter before and after the painful procedure.

RESUMO
Objetivo: Comparar o efeito da sucção não nutritiva, glicose oral 25% e glicose oral 25% combinada com a sucção não nutritiva no alívio da dor de recém-nascidos prematuros submetidos à punção do calcanhar para monitorização da glicemia. Método: Ensaio clínico randomizado crossover, com 34 prematuros que, randomicamente, receberam as intervenções: sucção não nutritiva, glicose oral 25% e as duas intervenções combinadas durante três dias consecutivos na punção do calcanhar para monitorização da glicemia. Avaliação pelo Premature Infant Pain Profile por 30 segundos antes da intervenção, denominado período basal e por 5 minutos após a punção. Resultados: A combinação das intervenções fez com que os prematuros retornassem ao período basal, com 1 minuto e 30 segundos após a punção do calcanhar, promovendo uma redução percentual de 2,2% na escala. Conclusão: A comparação do efeito das intervenções isoladas e combinadas mostrou que, quando oferecidas de forma combinada, os prematuros conseguiram retornar aos parâmetros do período basal mais rapidamente. Registro Brasileiro de Ensaios Clínicos: RBR-3gm6w5.

DESCRIPTORES
Dor; Recém-Nascido Prematuro; Puncões; Comportamento de Sucção; Glicose; Enfermagem Neonatal.

RESUMEN
Objetivo: Comparar el efecto de la succión no nutritiva, glucosa oral 25% y glucosa oral 25% combinada con succion no nutritiva para aliviar el dolor en recién nacidos prematuros sometidos a punición del talón para monitorización de glucosa en sangre. Método: Ensayo clínico cruzado aleatorizado, con 34 prematuros que recibieron aleatoriamente las intervenciones: succión no nutritiva, glucosa oral 25% y las dos intervenciones combinadas durante tres días consecutivos en la punición del talón para monitorizar la glucemia. La evaluación por el Premature Infant Pain Profile se realizó durante 30 segundos antes de la intervención, llamado periodo de línea base y durante 5 minutos después de la punción. Resultados: La combinación de intervenciones hizo que los prematuros volvieran a la basal, 1 minuto y 30 segundos después de la punición del talón, promoviendo una reducción porcentual de la escala del 2,2%. Conclusión: La comparación del efecto de las intervenciones aisladas y combinadas mostró que, cuando se ofrecían en combinación, los recién nacidos prematuros podían volver a los parámetros iniciales más rápidamente. Registro Brasileño de Ensayos Clínicos: RBR-3gm6w5.

DESCRIPTORES
Dolor; Recien Nacido Prematuro; Punciones; Conducta en la Lactancia; Glucosa; Enfermería Neonatal.
REFERENCES


