- **Short informative title**

Reduction of Visual and Auditory Stimuli to Reduce Pain During Venipuncture in Premature Infants. Study Protocol for a Randomized Controlled Trial.

- **Short running title**

Stimuli reduction before venipuncture

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Made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data;	MB,MM,LG,MAM,SA
Involved in drafting the manuscript or revising it critically for important intellectual content;	MB,MM,LG,MAM,SA
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Agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.	MB,MM,LG,MAM,SA

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ABSTRACT

Aim: To evaluate the efficacy of the reduction of visual and auditory stimuli on pain during venipuncture in premature newborns of 32-36 weeks of gestation.

Design: Open, randomized, non-blind parallel clinical trial.

Method: Study to take place at the neonatal intensive care unit of a University Hospital in 2019-2021. 56 recently born babies between 32 and 36 weeks of gestation will participate. The dependent variable is the level of pain determined using the Premature Infant Pain Profile instrument. The intervention will be assigned randomly using the random.org software. Data analysis will be carried out using the IBM SPSS v.25 software assuming a level of significance of 5%.

Discussion: The evidence for the efficacy of reducing sensory stimulation and its effect on pain in minor procedures has not been studied in depth. There are no studies that evaluate the reduction of visual and auditory stimuli in a combined way.

Impact: It is easy to incorporate the reduction of visual and auditory stimuli into nursing practice. The results of this study could have a direct impact on clinical practice.

Trial registered at clinicaltrias.gov: NCT04041635.

Keywords: nursing, premature infant, pain, venipuncture, stimuli reduction

INTRODUCTION

The World Health Organization defines premature as a baby born before 37 complete weeks of gestation, based on the fact that newborns of terms of between 37 and 38 weeks are considered to be of low risk, especially in developed countries, where this group behaves like mature newborns and therefore do not need special treatment (Aguila, 2000).

Currently, the term *premature* seems to be insufficient as it covers a very heterogeneous group of babies with very different: gestational ages, birth weights, nutritional status, risks and morbidity and mortality; which has made it necessary to catalogue them into sub-groups. From this arise: very low birth weight (VLBW) newborns, which weigh less than 1500 g; extremely low birth weight (ELBW) newborns; or extremely preterm, which include lower weights than 1000 g or 28 weeks of gestation and fetal newborns, which are those of a weight between 500 and 750 g and which constitute the group of highest risk (Aguila, 2000).

Over time, improved scientific technology has reduced mortality and it has also improved the quality of care provided for premature babies (Horbar, Badger, Lewit, Rogowski, & Shiono, 1997). This fact has not been accompanied by a reduction in long term after effects which are mainly: respiratory, sensory and effects on neurodevelopment (Pérez Villegas, Villalobos Alarcón, Aguayo García, & Guerrero Faquiez, 2006).

Most premature babies must be admitted to a neonatal intensive care unit (NICU). During hospitalization and especially during the first weeks of life, they are exposed to painful procedures (Roofthooft, Simons, Anand, Tibboel, & van Dijk, 2014).

The International Association for the Study of Pain defines pain as "a disagreeable sensory and emotional experience, associated with real or anticipated tissue damage". It can have negative consequences in the posterior development of the newborn as much as in the critical moment. It has been shown that pain produces clinical instability, such as changes in cardiac and respiratory frequencies; in blood pressure and intracranial saturation of oxygen and can cause complications such as interventricular haemorrhages (Madrid, 2007).

Due to the neurological immaturity of premature newborns, they perceive pain in a more intense and diffuse way, due to a lack of auto-regulatory mechanisms (Bhutta, Cleves, Casey, Cradock, & Anand, 2002; Dinerstein & Brundi, 1998).

Background

The most frequent painful procedures in NICU are venal or arterial punctures in the heel with lancets, insertion of venal and arterial catheters, lumbar puncture and vesicle drains (Nallely, Fajardo, Ramírez, & G, 2013; Shah & Ohlsson, 2011). Venipuncture is one of the techniques used most frequently. During the first weeks of hospitalization premature newborns of less than 33 weeks gestation can be exposed to a median of four venipunctures, of which only six out of 10 are successful at the first try (Courtois et al., 2016).

Pain caused by invasive procedures in premature babies admitted to the NICU negatively affects their neurodevelopment and professional nurses should do the maximum possible to avoid or reduce it wherever possible (López Maestro et al., 2013). Some of the non-pharmacological methods that have been used are: postural aids and physical containment, structuring of direct manipulation, promotion of auto-regulatory behaviours, non-nutritive suction, involvement of parents in treating their child and reduction of visual and auditory stimuli, (McAnulty et al., 2010; Sánchez Rodríguez, Quintero Villegas, Rodríguez Carmelo, Nieto-Sanjuanero, & Rodríguez-Balderrama, 2010; Bonnie Stevens, Yamada, Ohlsson, Haliburton, & Shorkey, 2016). The method most used and studied in NICU for the treatment and prevention of pain during invasive procedures is the administration of sucrose. This method, together with physical containment and positional changes are effective in reducing pain in newborns during the collection of blood samples (Bonnie Stevens et al., 2016).

In premature babies of less than 32 weeks of gestation, the reduction of visual and auditory stimuli four hours before a puncture with lancet did not show significant differences in the values for cardiac frequency during the procedure. One of its limitations was that was performed from the combined data of four hospitals. (Aita, Goulet, Oberlander, Snider, & Johnston, 2015).

In another study carried out in premature babies of between 28 and 33 weeks of gestation, a privation of visual stimuli during venipuncture reduced the level of pain of the patient after the intervention by 0.56 points according to the Neonatal Infant Pain Scale (NIPS). During puncture, the differences were not statistically significant (Alemdar & Özdemir, 2017; Lawrence et al., 1993).

The evidence for studies of reduction of visual or auditory stimuli during venipuncture is limited. Procedures, techniques and population are not equal and can't be compared. For this reason, the research team has proposed the design of a study to evaluate the efficacy of incorporating and reduction of visual and auditory stimuli into the routine procedure with

containment and the administration of sucrose on the pain response during venipuncture of premature newborns.

THE STUDY

Aim

The objective of the study was to evaluate the efficacy of the reduction of visual and auditory stimuli on pain during venipuncture in premature newborns of 32-36 weeks of gestation.

Design

The study is designed as an open randomized, non-blind parallel clinical trial

Setting of the study

It will be carried out at the Neonatal Intensive Care Unit (NICU) of a University Hospital in Spain, a tertiary care centre that is the basic hospital for a population of 250,000 inhabitants. The NICU of the centre has 6 intensive care beds and 7 intermediate care and general beds.

Sample/Participant

Research team consider a 3 units difference on Premature Infant Pain Profile (PIPP) scores as a clinically relevant outcome.

Accepting an alpha risk of 0.05 and 80% power in a two-sided test, 26 subjects are needed in the first group and 26 in the second to detect a difference equal to, or superior to 3 units on the PIPP scale. It is assumed that the common standard deviation is 3,23 (Ahn & Jun, 2007). A rate of loss of follow-up of 30% has been estimated. During 2018 a total of 282 recently born babies were admitted.

Inclusion criteria

Premature babies born between 32 and 36 weeks of gestation (both included) that are haemodynamically stable, require venipuncture and whose parents or legal guardians have signed informed consent forms will be included.

Exclusion criteria

Premature babies of gestational age inferior to 32 weeks, treated with intravenous or oral analgesics, sedatives or relaxants, of critical status or haemodynamically unstable, or requiring invasive mechanical ventilation will be excluded.

The participants will be randomly allocated to the intervention and control groups using the randomization grid designed with the *random.org* software.

Intervention

Babies in the control group will receive physical contention with the administration of sucrose two minutes before carrying out the venipuncture procedure (usual care). Venipuncture will be performed with 22G extraction needles or peripheric venous catheter. During the puncture, the eyes will not be covered and monitor alarms and devices will not be silenced.

Babies in the intervention group will receive reduced visual and auditory stimuli in addition to usual care during venipuncture. Phototherapy goggles and earmuffs will be placed 3 minutes before the venipuncture (leaving the patient in resting state after the manipulation) and will be maintained during the procedure. Monitor alarms and devices will be silenced and will remain silenced and noise in the unit will be minimized during the procedure. Three nurses expert in neonatology will carry out the venipuncture: 2 will perform the procedure and one will administer the PIPP scale.

Data collection

To recruit patients the principal investigator (PI) for the study will identify expectant mothers at risk of premature birth from medical records on the maternity ward. They will then be informed of the study verbally and in writing (informative sheet) and they will be given the informed consent forms. The PI will inform the professionals of the candidates who have accepted to participate.

Case report forms will be numbered and classified into the 2 groups according to the randomization grid and will be left in a file in the NICU. At the moment of admission to the unit, the nurse responsible for the patient will verify if they are participating in the study. In the case that they are, the data collection sheet will be added to the patient's file. Data will only be collected during the first puncture carried out on the newborn executed in the period between the first and fifth day of life. The nurse responsible for the baby will complete the PIPP just before carrying out the technique and 30 seconds after the puncture. All data will be transcripted and stored in a secure database allocated in an internal server with access restricted to the research team.

Instruments

The clinical variables will be completed from the electronic medical records. To evaluate pain, the primary outcome measure was the Premature Infant Pain Profile (PIPP). It is a nurse-rated questionnaire of seven items (gestational age, behaviour, increase in cardiac frequency, lowering of oxygen saturation, brow furrowing, eyes tightly closed, naso-labial furrow) evaluated at three different points (basal, 15 and 30 seconds after the painful moment) and each item is scored on a Likert scale of 0-3 points. The evaluation system is based on comparing the basal state of the newborn, the status during the painful intervention and finally, status some seconds after finishing the intervention. For all ages, a value of less than or equal to 6 indicates a minimal presence of pain, or non-existence of pain and values of 12 or more, indicate moderate or intense pain. Regarding the reliability of psychometric properties. The PIPP scale has inter-observer reliability of (0.93-0.96) and intra-observer reliability of (0.94-0.98), convergent validity with the duration of crying (Pearson r=0.492, p<0,03) and internal consistency of 0.78 measured by the Cronbach's alpha. It is translated into 4 languages (Norwegian, Greek, Icelandic and Portuguese) and for the study the original version in English will be used (Ballantyne, Stevens, McAllister, Dionne, & Jack, 1999; Bueno, Costa, Oliveira, Cardoso, & Kimura, 2013; Dionysakopoulou et al., 2018; Jonsdottir & Kristjansdottir, 2005; B Stevens, Johnston, Petryshen, & Taddio, 1996; Bonnie Stevens, Johnston, Taddio, Gibbins, & Yamada, 2010; Vederhus, Eide, & Natvig, 2006).

The PIPP scale is more sensitive than the CRIES and FLACC scales for evaluating the negative effects of painful stimuli on recently born premature babies who receive intensive care. It is also well accepted for evaluating pain in these patients, as it includes gestational age in its items (Ahn & Jun, 2007; Nallely et al., 2013). A unique form will be designed with all the variables and all the items of the PIPP scale.

Ethical considerations

The design of the project of the clinical trial has been evaluated and approved by the Research Ethics Committee in December 2018 (RN: PI-18-208). The trial is registered in clinicaltrials.gov (NCT04041635).

Data analysis

For the univariate analysis of the qualitative variables, measures of central tendency, of dispersion and form will be assessed. The test for normality will be carried out with the Kolmogorov-Smirnov test. The non-normally distributed continuous variables will be expressed as a median and interquartile range. The categorical variables will be expressed as

absolute values and percentages. The relationship between gestational age and pain results will be explored using the Pearson correlation coefficient. To study the relationship between PIPP and the application or not of reduction of visual and aural stimuli the Student t-test or Mann-Whitney U test will be applied according to normality. The IBM SPSS v.25 Software package will be used applying a level of significance of 5%.

Validity and reliability

The demographic and clinic variables were developed by the researcher and validated by six experts in neonatology who works at a University hospital and two university professors from the Faculty of Nursing. The PIPP scale has good reliability. To ensure a better administration all the collaborators of the data collection phase will be trained.

DISCUSSION

At the moment the evidence for the efficacy of reducing sensory stimuli and their relationship with pain in minor procedures is limited. The scarce evidence available provides results for newborns of less than 32 weeks and with lancet heel puncture (Aita et al., 2015) or with reduction of visual stimuli alone for venipuncture (Alemdar & Özdemir, 2017). The effect of reducing visual and auditory stimuli on pain during venipuncture in newborns of more than 32 weeks gestation has not been studied sufficiently.

Limitations

There could be difficulties in recruitment as the acquisition of patients takes place during pregnancy and the child could be born in another centre. The baby could also be born with a different gestational age than that established in the criteria for inclusion, or it may not be admitted to the NICU. The research team will increase the time for fieldwork until they reach the estimated sample size. There could be a different pain response depending on the material used. The type of material will be collected as a variable and the team will consider a statistical analysis for subgroups.

The use of the English version of the PIPP could cause erroneous measurements. To limit this effect the professionals will be instructed on its use in training sessions previous to the start of the fieldwork. The external validity could be limited if the results of the study are not

comparable with other studies due to different factors such as different populations, instruments used to evaluate neonatal pain or centres with different levels of care than ours.

CONCLUSION

The reduction of visual and auditory stimuli is a simple technique to incorporate into the NICU and can be applied in routine procedures such as venipuncture. If the results show a reduction of pain this would imply a direct benefit for patients, improvement in clinical status and reduction of problems of morbidity in the short and long term.

The results of the study could open new lines of research in nursing care based on the evaluation and control of pain with non-pharmacological methods.

Conflict of Interest statement

The authors declare no conflict of interest.

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