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Non-Pharmacological Measures in Control of Pain and Stress in Critical Preterm Newborn: Systematic Review Protocol and Network Meta-analysis

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Abstract:

Background: *Preterm Infants in the Neonatal Intensive Care Unit (NICU) undergo many procedures that cause pain and stress, which require the use of large amounts of analgesics and sedatives. Drugs, although important, can have adverse effects, are not always available, due to their high cost, and can increase the length of stay at the NICU. As a result, the adoption of non-pharmacological measures to control stress has increased in this population, despite little evidence of their efficacy. The main objective of this study will be to identify which non-pharmacological measures are more effective to control pain and stress in preterm infants.*

Methods: *Systematic review and network meta-analysis protocol of clinical trials searched in MedLine databases via PubMed, Latin American and Caribbean Literature in Health Sciences (LILACS), Excerpta Medica dataBASE (Embase), The Cochrane Central Register of Controlled Trials (CENTRAL), and Physiotherapy Evidence Database (PEDro). Descriptors to be used: premature, pain management, therapeutic touch, facilitated folding, sucking behavior, kangaroo method, analgesics, sedatives, pain, stress, weight gain, facial expression, crying, sleep, and wakefulness. The detailed study protocol was registered in the International Prospective Registry of Systematic Reviews (PROSPERO - CRD42020196891).*

Discussion: *Elimination of pain in premature infants in NICU may be difficult, but it should be a daily goal, as well as the stabilization of other clinical variables. Non-pharmacological measures can be helpful to reduce the amount and intensity of pain. Knowledge of the efficacy of non-pharmacological measures to control pain and stress in NICU premature infants is essential. It may reduce complications, the length of stay at the NICU and minimize the use of analgesics.*

Keywords: *Infant; premature; pain management; NICU.*

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INTRODUCTION

Worldwide, around 15 million premature infants are born with less than 37 completed weeks of gestation annually (WHO, 2019). About a million of them die each year from complications of prematurity (WHO, 2019). Therefore, prematurity is considered a global public health problem and the main cause of death for children under five years of age (WHO, 2018). These numbers are even higher in low- and middle-income countries (WHO, 2018).

In order to survive, preterm infants usually need continuous monitoring and specialized assistance at the Neonatal Intensive Care Unit (NICU) (Duerden et al., 2018). In the NICU, they undergo many painful and stressful procedures (Valeri et al., 2015). They are able to feel pain more intensely than a full-term newborn or a child (Vinall & Grunau, 2014). The explanation relies on their immature sensory system, which presents an imbalance between excitatory versus inhibitory processes, leading to increased nociceptive signaling in the central nervous system (Duerden et al., 2018). In premature infants, pain and stress can cause physiological and behavioral changes, weight loss, and motor and cognitive development impairment (Barker & Rutter, 1995; Field, 2017; Valeri et al., 2015; Witt et al., 2016). They can also result in increased respiratory rate, heart rate, blood pressure, metabolic rate, hypoglycemia, decreased peripheral oxygen saturation, and behavioral changes, such as facial mimicry, crying, and abnormal pattern of sleep and wakefulness (Field, 2017; Witt et al., 2016).

Thus, monitoring and controlling pain and stress in preterm infants in the NICU has clinical relevance and can be considered vital (Field, 2017). This control is often accomplished pharmacologically. However, analgesics and sedatives can have adverse effects and increase the length of stay at the NICU (Puia-Dumitrescu et al., 2021). A recent study with newborns showed that the prolonged use of opioids and benzodiazepines or both was associated with a longer hospital staying and a greater chance of developing necrotizing enterocolitis and bronchopulmonary dysplasia. Long-term use of these drugs was also associated with lower cognitive, motor, and language scores in these children when they are two years old (Puia-Dumitrescu et al., 2021).

In order to address this issue, intensivists have implemented measures to reduce pain and stress in critically premature infants, as part of the humanization of care. These measures include the presence of the family, a more welcoming environment, noise and light control, rationalization of handling and grouping invasive measures at the same time, if possible, blood sampling, therapeutic touch, functional positioning, non-nutritive suction with sucrose during a painful procedure and ofurotherapy, among others (Carbajal et al., 2003; Lacina et al., 2015; Nimbalkar et al., 2013; Rebelato & Stumm, 2019).

There is little evidence on the effectiveness of non-pharmacological measures in controlling pain and stress in critically ill neonates. Furthermore, it is not known which non-pharmacological measure has the greatest efficacy. The hypothesis of this study is that in some situations, non-pharmacological measures can be effective in controlling pain and stress in critically premature infants. Based on this context, the guiding question of the study is: Which non-pharmacological measures are more effective to control pain and stress in preterm infants?

METHODS

Study Design

This is a systematic review and network meta-analysis study protocol for randomized clinical trials.

Research Question

The acronym PICO (population, intervention, comparator, outcome) was used to describe all components related to the identified problem and to structure the research question: "Which non-pharmacological measures are more effective to control pain and stress in preterm infants?" Table 1 presents the description of the components of the PICO strategy used to build the research question.

Acronym	Definition	Description
P	Population	Critical preterm newborn
I	Intervention	Non-pharmacological measures to control pain and stress
C	Comparator	Sedative analgesic or no intervention
O	Outcome	Decrease in pain and stress, weight gain or improvement in Behavioral parameters (facial expression, crying and sleep and wake patterns)

Table 1. PICO strategy for formulating the research question

Participants

Inclusion Criteria

Randomized clinical trials published in English, Portuguese or Spanish, focused in premature infants in NICU, comparing pharmacological and non-pharmacological measures to control pain and stress, including studies comparing non-pharmacological measures to analgesics or no intervention to manage pain and stress, comparing non-pharmacological measures to each other, with combined non-pharmacological measures, or whose primary measured outcomes were pain and stress or the secondary outcome was weight gain, decreased need for analgesics and sedatives, and improvement in behavioral parameters (facial expression, crying and sleep and wake patterns).

Exclusion Criteria

Studies carried out in animals, without a control group, evaluating non-pharmacological measures associated with pharmacological measures, not assessing the outcome with specific scales, or not assessing outcomes before and during or after the painful procedure.

Search strategy and information sources

Searching process will be conducted in MedLine databases via PubMed, LILACS, Embase, Cochrane Library and PEDro through descriptors and correlates found in the Medical Subject Heading (MeSH) and descriptors in Health Sciences (DeCS): Infant; Premature; Pain Management; Therapeutic Touch; Facilitated Tucking or Containment; Sucking Behavior; Kangaroo-Mother Care Method; Analgesics; Hypnotic and Sedatives; Pain; Psychological Distress; Body Weight; Facial Expression; Crying; Sleep; Wakefulness and its synonyms, combined with each other using the Boolean operator "AND" and "OR", according to the search strategy of PubMed, LILACS, in Embase, Cochrane Library and PEDro. The entire search process will be performed in ultra-sensitive search. Whenever possible, the following filters will be used: language: English, Portuguese, and Spanish; type of studies: only in humans; and methodological design: Randomized clinical trials. Detailed search data for the identified studies, as well as the demonstration of information for each phase, will be presented in a flowchart according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Page et al., 2021), as shown in Figure 1.

Studies identification and data extraction

The study selection process will be carried out by two reviewers independently, and segmented into four phases: Identification, Screening, Eligibility, and Selection. Phase 1 (Identification) will consist of database searching using descriptors and filters. After the identification of the studies, duplicates will be removed. Phase 2 (Screening) will consist of the selection of studies after reading the titles and abstracts. Phase 3 (Eligibility) will consist of selecting studies after the complete reading of the texts, based on the inclusion/exclusion criteria. Excluded articles will be presented together with the reasons for exclusion. Phase 4 (Selection) will consist of the final selection of studies for analysis. If there is disagreement among reviewers as to whether to include a research article, a third reviewer will be assigned to evaluate and make a decision on the issue. Reviewers are health professionals, master's students, and the senior researcher is a health professional, doctor, specialist in intensive care. Phase 5 (Recommendations) will establish practical recommendations based on scientific evidence based on the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) method (Guyatt et al., 2008). Rayyan software from the Qatar Computing Research Institute (QCRI) will be used to remove duplicates during data analysis (Ouzzani et al., 2016).

Identification of variables

Neonatal pain and stress

Pain can be defined, according to the International Association for the Study of Pain (IASP), as an unpleasant subjective emotional and sensory experience associated with actual or potential tissue damage, or described in terms of such damage (IAPS, 2017).

Stress is an organism response triggered by several situations that overload the homeostasis selective response mechanisms (Castral et al., 2011). Some authors report that the intense reaction of premature infants to stress is harmful to several physiological,

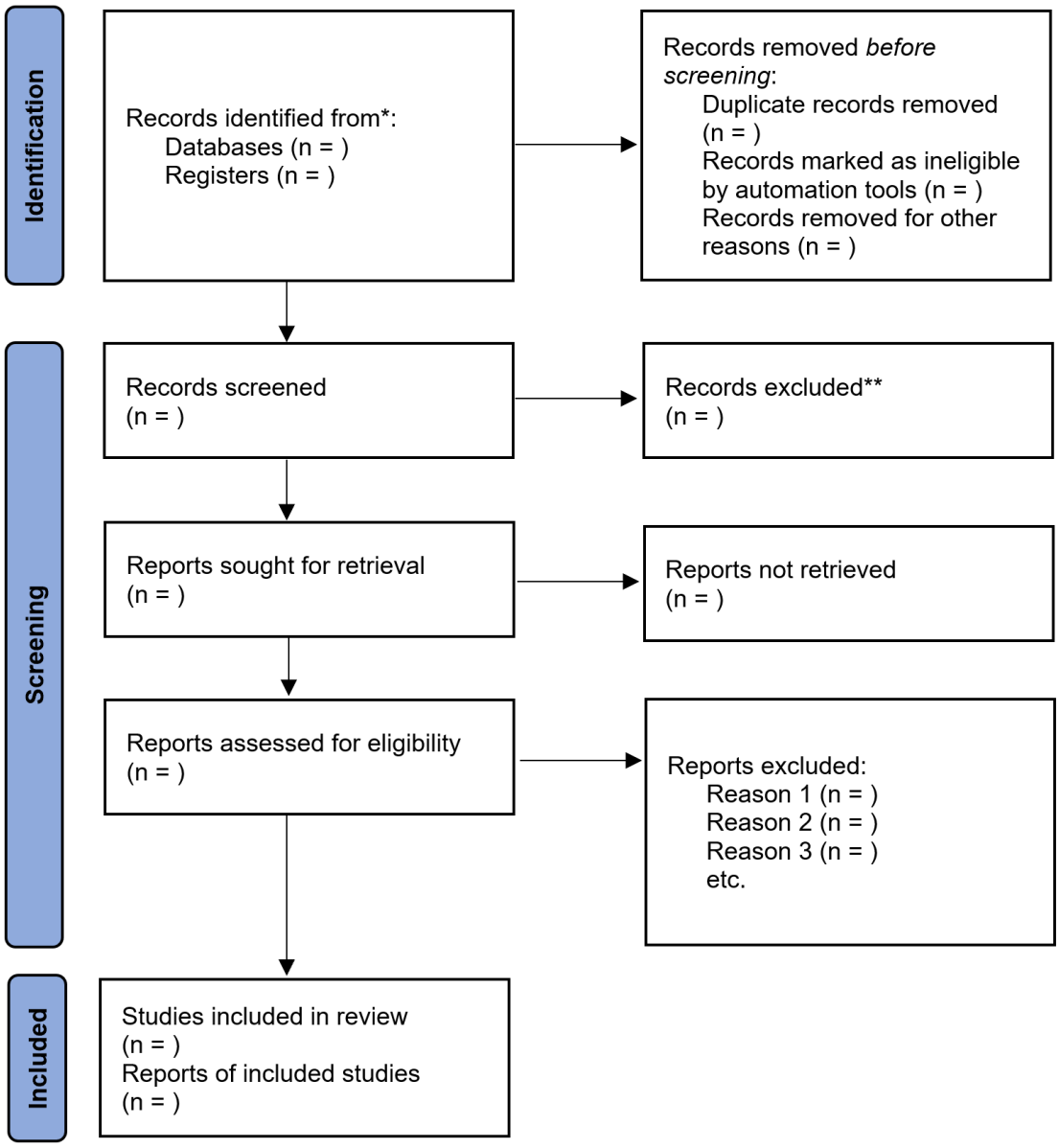

Figure 1. Systematic review flowchart.

functional and structural systems both in the short and long terms (Rebelato & Stumm, 2019).

Weight gain

Daily weight gain of critical preterm infants is associated with lower readmission rates, cerebral palsy and neurodevelopmental deficits. In order to promote weight gain in preterm infants in the NICU, reducing the occurrence of health complications, several low-tech and low-cost methods have been introduced in NICUs, such as the kangaroo position (Baley, 2015).

Behavioral state

Behavioral state of preterm infants will be analyzed through the pattern of sleep and wakefulness, presence of crying and facial expression. In a NICU environment, premature infants are exposed to various sound and painful stimuli, leading to sleep deprivation, which causes fatigue, agitation, crying and irritability, with possible intracranial pressure increasing (Casavant et al., 2017). Sleep and wakefulness in newborns, especially in preterm infants, are fundamental processes for adequate development and are presented

as the main behavioral states during the neonatal period (Lacina et al., 2015). During sleep, the brain, as well as the structures of the hippocampus, midbrain and brainstem, mature. Sleep is also related to motor development, interaction capacity and stress-response in preterm infants (Allen, 2012).

Most used non-pharmacological measures in critical neonates

The most used non-pharmacological intervention measures, compared with each other or with no intervention, identified in previous studies were: Facilitated tucking, non-nutritive sucking with sucrose or glucose, nesting, kangaroo position, recording with the mother's voice, speech and touch, gentle touch, therapeutic touch, sensory saturation (which included olfactory, visual and tactile stimuli), breast milk and care package (environmental modifications, positioning and containment, oxygen supplementation, interaction and approach, and individual care based on suggestions).

Primary and secondary outcomes

Salivary cortisol and some scales based on physiological and behavioral variables, and a mixture of the two, are used to measure pain and stress in critically ill neonates. The most used scales are the Neonatal Infant Pain Scale (NIPS), the Premature Pain Profile (PIPP), and the Douleur Aiguë du Nouveau-né (DAN) (Witt et al., 2016). For this review, pain intensity will be analysed as a primary outcome. The gain of or improvement in behavioral parameters (facial expressions, crying, and sleep and wake patterns) will be analysed as secondary outcomes.

Risk of bias and methodological quality analysis

Two reviewers will independently carry out quality analyses of the selected studies. Quality critical analysis data will be registered for evaluation in a specific form, the Revised tool for Risk of Bias in randomized trials (RoB 2.0 tool) (Sterne et al., 2019). The domains included in RoB2 cover the types of biases that currently affect the results of randomized trials, which are: Risk of bias due to the randomization process, risk of bias due to deviations from the intended interventions, risk of bias due to lack of data from the outcome, risk of bias in outcome measurement, and risk of bias in the selection of reported outcome.

Statistical analysis

Included studies results will be pooled in a network meta-analysis which includes direct and indirect comparisons of all available treatments in a single model. A common heterogeneity parameter will be assumed for all comparisons. A consistency model will be built for each result, and the relative effect sizes of the treatments will be calculated as mean difference (MD) and reported with a 95% confidence interval. To increase the precision of estimating the relative effect sizes of the comparisons and to properly account for correlations between the multi-arm trials, classification probabilities, including all treatments, will be established for each result. Consistency, defined as the difference between direct and indirect evidence pooled for a particular comparison, will be assessed using split-node analysis. Classification probabilities for all treatments will be performed by analyzing the Surface Under the Cumulative Classification Curve (SUCRA) (Harrer, M, Cuijpers, P, Furukawa, TA, Ebert, 2021). All analysis will be performed using the softwares Review Manager (RevMan 5.4) (Deeks, J., & Higgins, 2020) and RStudio 4.1.1 with the R dmetar function (RStudio, 2020).

Protocol Registration

The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) under the number CRD42020196891.

DISCUSSION

Systematic reviews compile scientific evidence that addresses a straightforward research question, using systematic and explicit methods to identify, select, and critically analyse relevant research data, representing a main strategy to support decision-making. For NICU premature infants' pain and stress control, there is little helping evidence. However, this is critical to control this population pain, which can cause physiological changes, behavioral changes, and complications. Several non-pharmacological interventions, which are low operational cost and do not present adverse reactions, aim to reduce the amount and intensity of pain and stress in this population. Knowing their effectiveness is essential.

Study Limitations

We considered the study population limited to studies found in MedLine databases via PubMed, Latin American and Caribbean Literature in Health Sciences (LILACS), Excerpta Medica dataBASE (Embase), The Cochrane Central Register of Controlled Trials (CENTRAL), and Physiotherapy Evidence Database (PEDro). We do not include gray literature. It is possible that the results may not correspond to a generalizable sample.

CONCLUSION

Knowing the most effective non-pharmacological measures to control pain and stress in NICU premature infants is essential. It can reduce complications, the length of stay in the NICU and minimize analgesic use.

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Conflict of interest

None.

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