The Effect of Music Therapy as an Adjuvant in Stabilizing the Vital Signs of the Neonate: A Randomized Controlled Clinical Trial Protocol

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Background

Partial fetal hearing maturity is reached between 24 and 27 weeks of gestational age. At this stage of fetal development, the fetus is able to perceive the acoustic parameters of speech, such as melody, rhythm, prosody, phonemes, and different tones (1). It is also able to hear the sounds produced by the placenta, adjacent organs, and the maternal heartbeat, which are rhythmic, low in volume, and low in frequency. The fetus is in a protective environment because, in addition, the amniotic fluid and the tissues of the adjacent maternal organs act as filters for high-frequency external sounds (1,2).

However, exposure of a newborn to the extrauterine environment, and especially those who require hospitalization in a neonatal intensive care unit (NICU), involves a series of events that affect not only the newborn, but also their parents and/or caregivers (3). In addition, the reasons for hospitalization include a long hospital stay, which increases the exposure of patients and caregivers to stressful situations. For example, neonates are constantly exposed to unfamiliar stimuli such as sounds from infusion monitors and pumps (auditory), lights (visual), and contact with external elements, as well as painful procedures such as intubation and venipuncture (tactile) (1,3,4).

As a result, during hospitalization, neonates are immersed in an adverse environment compared to the intrauterine environment, which triggers a physiological response to stress that increases oxygen consumption and caloric expenditure during development (5). In addition, the multiple procedures to which they are subjected generate greater stress, which translates into alterations in the sleep-wake cycle and anxiety. The latter may be manifested by the activation of the sympathetic nervous system, causing an increase in the variability of vital signs such as heart rate, respiratory rate, and blood pressure (5).

In preterm infants, these effects are even more pronounced. Prematurity itself is associated with an increased risk of complications and, in addition to overstimulation, leads to adverse effects on growth and neurodevelopment, including changes in brain structure and function (2). The sounds present in NICUs, which are unpredictable and have frequencies reaching peaks of 120 decibels, result in short-term adverse effects on the cardiovascular and respiratory systems (6). For example, an increased susceptibility to episodes of apnea and hypoxemia has been described (2,6).

Similarly, caregivers are also exposed to environmental stressors, and observing invasive and noninvasive procedures performed on their children and other patients increases this exposure. An example of these stressors is the early separation of the binomial and the perception of not being able to fully care for the newborn, which leads to a lack of autonomy in the role of primary caregiver of the newborn (4). So much so that such an

event can increase the risk of depression and anxiety disorders. It has even been found that the postpartum stress experienced by mothers during the hospital stay is negatively associated with nutrition, growth and development, and the success of attachment of the binomial (3).

One of the most popular strategies in recent years is music therapy. This is defined as the clinical use of music as a therapeutic intervention to achieve individualized goals in patients (7). It is an evidence-based, non-pharmacological, non-invasive, dynamic, safe, enjoyable, and cost-effective strategy (1-9). In addition, it is a measure that promotes socio-cultural activities in health care institutions and reduces financial costs due to its ability to minimize pharmacological or invasive interventions to promote the well-being of the newborn.

Studies, including randomized clinical trials, systematic reviews, and meta-analyses, have shown beneficial effects on length of hospital stay, neurodevelopment, and normalization of vital signs (1,3,7,10-13). It has also been shown to be effective in reducing anxiety in mothers of hospitalized neonates (1-3,5,6,12,13,14,16). However, there is heterogeneity in the selection of variables studied and small population samples. In addition, it is necessary to know if there is a significant difference between the use of live music therapy and pre-recorded music that affects neonates, which is why the present study is necessary. In addition, this study will allow us to evaluate how music therapy is a non-invasive complementary strategy for the stabilization of physiological variables of newborns.

Research question

¿What is the effect of an intervention such as music therapy, through an electronic device and live, on vital variables in newborns over 32 weeks hospitalized in the Neonatal Intensive Care Unit of the Clinica Universitaria Colombia?

1.1. Proyect rationale

Prematurity is a public health problem, requiring special high-risk perinatal care provided by trained professionals, which implies a high socioeconomic cost (1). About 15 million children are born preterm each year, corresponding to a rate of more than 1 preterm birth for every 10 live births. This pathology is on the rise and is directly linked to a higher presence of morbidity and mortality and associated complications, and therefore to a higher rate of hospitalizations in NICUs (12,15). Thanks to advances in health systems, the survival rate has improved. However, the short-, medium- and long-term effects linked to prematurity, such as neurodevelopment, are still present (4,14).

Multiple efforts have been made to identify and develop strategies to counteract the negative effects of the environment in NICUs and improve the well-being of the pair. This is where the concepts of Developmental Care and Family-Centered Neonatal Care arise, both examples of the methods used to promote the humanization of health services. The first is defined as the use of medical and basic care interventions, in order to reduce the stress of neonates in NICUs (8). This consists of restructuring the environment, modifying elements such as the intensity of the lights and the reduction of sounds. It also includes improved neonatal posture, decreased body manipulation, and pain management. The second is an approach that promotes parental involvement in caring for the child's emotional, social, and developmental needs. In the latter, communication between the family and health personnel is encouraged, as well as the improvement of elements in the environment such as individualized spaces and the attitude of NICU professionals (9).

One of these strategies is music therapy, a health profession dedicated to humanized care based on the use of both live and recorded music, in order to positively impact health in the field of neonatology and the well-being of caregivers(12,16). This study will allow us to evaluate how music therapy is a non-invasive complementary strategy for the stabilization of the physiological variables of newborns. This then implies a possible reformulation of institutional and public health policies, promoting the realization of socio-cultural activities in the different organizations of the Keralty group.

Primary Objective:

To determine the effect of live and pre-recorded music therapy on vital variables in newborns older than 32 weeks hospitalized in the Neonatal Intensive Care Unit of the Clinica Universitaria Colombia (CUC).

Secondary objectives

- To describe the demographic and clinical characteristics of study participants.
- To analyze the effect of live and pre-recorded music therapy on the vital signs (heart rate, respiratory rate, and oxygen saturation) of study participants.
- To categorize the stressful events, present in neonatal intensive care units according to their origin, namely auditory, tactile, and visual.

Methodology

Study Design

A prospective analytical, pragmatic clinical trial-type study will be conducted to provide evidence on the benefits of health interventions in real-world settings (in routine clinical practice). The study will be conducted at the Neonatal Intensive Care Unit of the CUC in Bogotá D.C. during the period from May 1st to June 30th, 2024.

Study Population

The study will include newborns who are older than 32 weeks gestational age at birth and who are hospitalized in the Neonatal Intensive Care Unit of the CUC.

Inclusion criteria

All newborns who meet the following inclusion criteria will be included:

- Gestational age at birth greater than or equal to 32 weeks.
- Birth weight greater than or equal to 1500 grams.
- Be at least 72 hours of postnatal age.

Exclusion criteria

All newborns who meet at least one of the following criteria will be excluded:

- Respiratory disturbances in the last 48 hours such as:
    - Apnea or Brief Resolved Unexplained Events (BRUE).
    - Need for invasive mechanical ventilation.
- Hemodynamic alterations in the last 48 hours such as:
    - Hypotension (systolic, diastolic, or mean BP < P5) or hypertension (systolic, diastolic, or mean BP > P95).
    - Bradycardia (HR < 100/min).
    - Shock of any etiology
    - Requirement for volume expanders, infusion of inotropic, vasodilators and/or prostaglandin E1
- Neurological alterations such as:
    - Perinatal asphyxia at birth manifested by the need for resuscitation, APGAR < 3 at 5 minutes and/or ≤ 5 at 10 minutes, and metabolic acidosis in cord gases with pH < 7 and BE < -12.
    - Hypoxic-ischemic encephalopathy.
    - Seizure syndrome for up to 48 hours after the last clinical event or alteration of the brain pattern.
    - Interventricular hemorrhage in preterm infants in the first week of diagnosis.
- Management with Extracorporeal membrane oxygenation (ECMO) and/or nitric oxide.
- Temperature less than 36.5 C or greater than 37.5 C.
- Patient under pharmacological sedation or use of beta-blockers.

- Congenital heart disease, operated on or not.
- Congenital malformations.
- Surgical emergencies or recovery from a surgical procedure performed within the last 48 hours.

Sample size

The sample size was determined using the G*Power 3.1.9.7 program, with a confidence level of 95%, statistical power of 90%, mean difference in heart rate between the live music therapy group (140 bpm), prerecorded music therapy group (127 bpm), and the control group (147 bpm). A total sample size of 45 was calculated, with a ratio of 1:1:1 between groups. This equates to 15 participants in each group.

Sample Selection

Stratified random sampling will be used, with two strata according to gestational age defined as follows: stratum 1 neonates <37 weeks and stratum 2 neonates ≥37 weeks. Blocked randomization (block of size 3) will be used for each stratum and for the allocation of participants to each of the intervention and control groups (1:1:1). The allocation sequence will be generated by Microsoft Excel®.

The random assignment will be concealed through the use of opaque envelopes, which will be sealed and numbered sequentially. These envelopes will be carried out by the operational coordinator of the project. The carbon paper inside the envelope will transfer the details of the random number and the group to which it will be assigned (A, B or C). This will ensure that the envelope is not permeable to intense light. The envelopes will be sealed with tamper-evident security tape and will be opened sequentially only after the participant, meeting the eligibility criteria, has received the envelope. The envelopes will be kept in a folder that will be kept on a locked shelf within each unit, which will be in the custody of the project's operational coordinator.

Blinding

It is not possible to blind the participants or the music therapist from randomization due to the nature of the intervention.

Variable Matrix

Variable name	Operational Definition	Nature and Scale of Measurement.	Unit of measurement
Date of birth	Time in which he was born.	Quantitative – Discrete	Day/Month/Year

Sex	Biological characteristics that determine whether it is female or male.	Qualitative – Nominal – Dichotomous	1: Female 2: Male
Gestational age at birth	Number of weeks gestation at the time of birth.	Quantitative – Continuous	Weeks and days of gestational age
Postnatal age at study entry	Age in hours or days since birth.	Quantitative – Discrete	Hours or days
Birth weight	Weight determined by a calibrated neonatal scale.	Quantitative – Continuous	Grams
Classification according to birth weight	Birth weight classification.	Qualitative – Nominal – Polytomic	1: Extreme low birth weight newborn (< 1000 grams) 2: Very low birth weight newborn (< 1500 grams) 3: Low birth weight newborn (< 2500 grams)
Birth Weight Percentile	Relationship between age, height, head circumference and weight.	Quantitative – Discrete	Percentile Value
Clustered Birth Weight Percentile	Comparison of the weight of the newborn with the rest of the same age and sex.	Quantitative – Discrete	1: Birth weight below the 10th percentile 2: Birth weight between the 10th and 90th percentile 3: Birth weight above the 90th percentile
Weight-for-gestational-age classification	Classification of weight in relation to gestational age at birth.	Qualitative – Ordinal – Polytomic	1: Small for gestational age 2: Suitable for gestational age 3: Great for Gestational Age
APGAR Score	A clinical visual examination performed on the newborn one minute and 5 minutes after birth to assess physiological adaptation to the extrauterine environment.	Quantitative – Discrete	Score from 0 to 10

APGAR Rating	Classification of neonatal adaptation to the extrauterine environment, given by the score in the APGAR criteria.	Qualitative – Nominal – Polytomic	1: Normal (7-10 points) 2: Moderate depression (4-6 points) 3: Severe depression (0-3 points)
Presence of comorbidities in the neonate	Presence or absence of associated diseases.	Qualitative – Nominal – Dichotomous	1: Yes 2: No
Name of the associated pathology	The medical term referring to the disease that the individual presents.	Qualitative – Nominal	Name of the disease
Perinatal history	Presence of important events during pregnancy.	Qualitative – Nominal	Background Name
Number of visits	Number of Parent Visits During the Day	Quantitative - discrete	Number
Singing	Emission of sounds or musical compositions by parents or legal guardian up to 30 minutes prior to the intervention.	Qualitative – Nominal – Dichotomous	1: Yes 2: No
Heart rate	Number of heartbeats measured at minute 0, from minute 0 to 30 minutes after the procedure continuously and 30 minutes after the intervention.	Quantitative – Discrete	Beats per minute (bpm)
Respiratory rate	Number of breaths measured at minute 0, from minute 0 to 30 minutes after the intervention continuously and at 30 minutes after the intervention.	Quantitative – Discrete	Breaths Per Minute (rpm)
Oxygen saturation	Measurement of the percentage of oxygen availability in the blood, measured at minute 0, from minute 0 to 30 minutes after the intervention continuously and at 30 minutes after the intervention.	Quantitative – Discrete	Percentage of SaO2 (SaO2%)

Description of interventions

Music therapy is a non-pharmacological therapeutic intervention that will be implemented through two modalities: live and pre-recorded music. Group A will be comprised of patients who have been exposed to live music, which will be carried out by a music therapist using the guitar as the only musical instrument. Instrumental lullabies will be used, which will be selected by the patients' legal guardians. Group B corresponds to patients who will be exposed to pre-recorded music, of the genre of lullabies, instrumental type, using a speaker that will be placed inside the patient's incubator. Group C will be those patients in whom no musical intervention will be performed.

The patient will be placed in an incubator, monitored with a vital sign monitor and pulse oximetry, and under the supervision of a research assistant. The research assistant will be responsible for recording the variables at minute 0, from minute 0 to minute 10, and 30 minutes after the completion of music therapy or non-intervention. The volume will be controlled in the three groups by means of a decibel regulator, with a maximum volume of 70 dB.

During the intervention and for a period of 30 minutes following its conclusion, singing will be prohibited by the music therapist or, in the case of groups A and B, by the parents. This prohibition will be implemented in the same manner in group C, which will be devoid of any form of music exposure in order to prevent the introduction of confounding variables. Both live and pre-recorded music will be instrumental in nature, lacking any lyrics. In accordance with the protocol for admission to the neonatal unit, the use of electronic devices is restricted. Consequently, patients will not be exposed to auditory stimuli of this nature.

Sources of information

The source of information will be primary. Demographic and clinical data will be obtained from the medical record. The vital signs data such as heart rate, respiratory rate and oxygen saturation will be obtained from the records of the monitors of the intensive care units, at the established times, which are: at minute 0, from minute 0 to minute 10 continuously and at 30 minutes after the intervention.

Standardization of measurements

For the standardization of measurements of the different physiological variables, several elements will be considered. First, the trademark of the medical equipment manufacturer of each of the tools that will be used (vital sign monitor and pulse oximeter) will be verified, verifying that they correspond to the same commercial brand since they are different brands, there may be variability between the standard calibration measurements considered within the critical range. Second, it will be verified that each medical tool used has been calibrated in the last 6 months, recording the date of last calibration so that the device can be used during the study.

Subsequently, the professional in charge of the music company will verify that the guitar to be used during the live music is in tune and suitable for use. A decibel regulator will be used during the implementation of the pre-recorded and live music, which will adjust the volume of the sound emitted. to ensure the same decibels per research subject, with a maximum allowable of 70 dB. Vital variables will be recorded at minute 0, from minute 0 to minute 10 and at 30 minutes after the intervention.

Primary Outcome

The primary outcome of this study is the heart rate (HR), which will be measured through pulse oximetry every minute, beginning at minute 0 (prior to the intervention), then from minute 0 to minute 30 (during the intervention), and finally at 30 minutes after the intervention.

Secondary Outcomes

- Respiratory rate (RR) will be measured through pulse oximetry every minute, beginning at minute 0 (prior to the intervention), then from minute 0 to minute 30 (during the intervention), and finally at 30 minutes after the intervention.
- Oxygen saturation (SO) will be measured through pulse oximetry every minute, beginning at minute 0 (prior to the intervention), then from minute 0 to minute 30 (during the intervention), and finally at 30 minutes after the intervention.

Analysis of information

A descriptive analysis of the variables will be performed using absolute and relative frequencies for the qualitative variables, as well as measures of central tendency and dispersion for the quantitative variables according to their normal distribution evaluated through the Kolmogorov-Smirnov test. To compare the data between the groups, one-way ANOVA or Kruskal-Wallis and chi-square ANOVA will be used. To determine the effect of music therapy on vital signs, repeated measures ANOVA or the Friedman test, if applicable, will be used. Assumptions of normality, homoscedasticity and residual distribution will be evaluated. Post-hoc comparisons are performed to determine significant differences between groups using the Student t-test. The level of significance for statistical tests will be $p=<0.05$.

A multivariate logistic regression will be performed to evaluate the effect of music therapy on respiratory rate, heart rate and pulse oximetry, considering confounding variables such as the number of visits, parental singing prior to the intervention, admission diagnosis, gestational age, comorbidities and gender.

Ethical Considerations

This research will adhere to the ethical guidelines developed by the CIOM and the WHO, as well as the stipulations of the Declaration of Helsinki for research involving human subjects. This will ensure the respect and protection of human rights, as well as the protection of the life, health, privacy, and dignity of the study subjects (24). Furthermore, this research is founded upon the tenets of bioethics, with the objective of promoting and ensuring justice, beneficence, non-maleficence, and patient autonomy, as outlined in the Belmont report from 1979 (25). Additionally, this research will have a social and scientific value, as its findings could potentially enhance the health of subjects and transform the manner in which care is delivered through the generation of reliable and valid results derived from a clinical trial. The researchers are highly qualified for the development of this research due to their expertise in pediatric and neonatal medicine, as well as epidemiology. For the administration of the interventions, a company with a high trajectory and experience in these interventions will be hired.

In accordance with the provisions of Resolution 8430 of 1993 (26) of Colombia, as the population of this study is minors, who in this case are newborns who, due to their neurocognitive development, cannot exercise the principle of autonomy per se, this will be delegated to their guardian or legal representative through the completion of informed consent. The objectives and methodology of the research will be clearly explained to the legal representative of the neonate, including the type of music to be used, the daily duration of each session, the time of exposure, and the data to be collected. Conversely, the legally appointed representative will be permitted to observe the child's participation in the study as it progresses, provided that this does not result in any direct alteration of the results through manipulation or direct contact with the patient. This is to ensure that the principle of autonomy is not violated. Furthermore, the legal representative of the newborn will have the option to withdraw from the study at any time, without affecting the medical care of the newborn. This study is classified as a research study with a higher than minimum risk because the intervention can modify the physiological variables of the newborn. However, based on previous studies conducted nationally and internationally, it can be determined that the use of music therapy is at least as safe and advantageous, in light of the foreseeable risks and benefits, as any other established effective alternative.

In order to guarantee the privacy and confidentiality of the information of the subjects involved in the study, the provisions of the Habeas Data Law (Law 1581 of 2012) and Resolution 1995 of 1999 will be taken into account. An alphanumeric code will be used to identify the study subjects. Only the researchers will have access to the databases, and the data will be safeguarded for up to one year after the publication of the results. No sensitive information will be disclosed in the publication or in other

documents drafted during the investigation. The results of this research will only be used to provide new knowledge and encourage new studies.

This research project will be presented to the research committee and the research ethics committee of the Fundación Universitaria Sanitas, where full compliance with ethical principles and quality standards will be taken into account for approval. Currently, there are no conflicts of interest declared by the principal investigator, the co-investigators, or the methodological advisor for the development of the research.

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