Study Protocol

Official Title: Effects of a Musical Intervention on Hormonal and Inflammatory Biomarkers in Mechanically Ventilated Critically Ill Patients

NCT Number: NCT06120660

Sponsor: University of Oviedo

Principal Investigator: Alba Maestro-González, PhD

Site: Hospital Universitario Central de Asturias (HUCA), Oviedo, Spain

Protocol Version/Date: v1.0 — 10 march 2023

Statistical Analysis Plan (SAP): Included in Section 3.8

3.1. Study Type

Randomized, controlled, parallel-group clinical trial with blinded participants, care providers, and outcomes assessors. Patients were under continuous sedation, which ensured participant blinding. The investigator placing the headphones was not blinded due to the nature of the intervention.

3.2. Study Setting

The study was conducted in the General (Polivalent) Intensive Care Unit (ICU) of the Hospital Universitario Central de Asturias (HUCA), a major tertiary public hospital in Oviedo, Spain. HUCA is a modern, highly specialized center with advanced technological infrastructure, extensive ICU capacity, and multidisciplinary teams experienced in managing severe, complex critical illness. The polivalent ICU includes 44 beds distributed across general critical care and neuro-trauma units and provides comprehensive monitoring and life support for patients with multiorgan failure, high-risk postoperative complications, severe trauma, and complex infectious and medical conditions.

3.3. Population and Sample

3.3.1. Study Subjects

Inclusion Criteria:

- Adults aged 18 years or older.
- Admission to HUCA's polivalent ICU for at least 24 hours.
- Intubated and receiving invasive mechanical ventilation.
- Presence of an arterial catheter and/or central venous catheter.
- Sedation level between BIS 40–60 or an equivalent level on the RASS scale (−3 to −4).
- Absence of pain at baseline and during the intervention, defined as a CPOT score of 0.
- No prior exposure to music therapy or similar interventions during the current hospital stay.
- Informed consent obtained from the patient's legally authorized representative within 72 hours of presentation.

Exclusion Criteria:

- Severe neurological disease or injury incompatible with study participation.
- Severe psychiatric illness such as psychosis or schizophrenia.
- Suspected or confirmed drug or alcohol intoxication, overdose, withdrawal, or abstinence.
- Hearing impairment that limits perception of the auditory intervention.
- Cranial injuries preventing safe placement of headphones.
- Limitation of therapeutic effort, expected death within 24 hours, or confirmed brain death.
- Current treatment with systemic corticosteroids.
- Requirement for vasoactive drugs above 0.1 mcg/kg/min.
- Refusal by the responsible attending physician.

Sample Size:

Using a pilot sample of 40 patients, a between-group difference of 1.32 units in serum cortisol and standard deviations of 2.86 (control) and 1.59 (intervention) were assumed. With 80% power and alpha = 0.05, 50 subjects per group were required. After adjusting for a potential 20% loss rate, the final sample size required was 63 patients per group (126 total).

3.4. Study Timeline

Data collection occurred from 1 October 2023 to 28 June 2025.

3.5. Instruments

A study-specific case report form (CRF) was created to collect all relevant variables.

3.5.1. Musical Piece

A licensed music therapist composed a 30-minute audio piece intended to promote mental and physical relaxation in sedated ICU patients. The piece was reproduced twice consecutively, for a total session duration of 60 minutes. It was characterized by a soft musical dynamic (“piano”), slow tempo, two coordinated melodic lines

(piano, synthesizer, ocean drum, acoustic guitar, soft vocals), and background nature sounds such as ocean waves, birds, fire crackling, and rain. The composition was based on a stable harmonic structure in C major, with predictable modulations to A minor, F, G, and occasional D minor. A diatonic scale was used to reinforce calmness and reduce cognitive load.

3.5.2. Headphones

The auditory intervention used Sony WH-1000XM4 noise-cancelling headphones with 40-mm diaphragms, extended frequency response (~40 kHz), integrated digital-to-analog converter with amplifier, and real-time processing to cancel ambient noise using external microphones and phase-inversion. This provided stable and high-quality sound despite the ICU environment.

3.6. Variables

Physiological variables were recorded every 10 minutes during the intervention.

Demographic and Clinical Variables:

- Age, sex, primary diagnosis at ICU admission.
- APACHE II severity score.
- Days on invasive mechanical ventilation at the time of intervention.
- Ventilatory mode and parameters, including FiO2.
- Sedatives, analgesics, and neuromuscular blockers, with dose and infusion rate.

Physiological Parameters:

- Systolic and diastolic arterial blood pressure measured via arterial catheter.
- Heart rate via continuous ECG monitoring.
- Respiratory rate from the ventilator.
- Oxygen saturation (SpO2).
- Level of sedation measured by BIS or RASS.

Biomarkers:

- Serum cortisol (primary biomarker), measured immediately before and after the intervention via arterial line.

- Serum prolactin and interleukin-6 (IL-6), measured at the same time points.

3.7. Procedures

Approvals were obtained from the Ethics Committee of the Principality of Asturias and HUCA administration. ICU clinical staff were informed about study procedures. Patient screening involved review of clinical records and bedside nurse consultation. Legally authorized representatives received written and verbal explanation, and informed consent was obtained prior to enrollment.

A coded identification number was assigned to each participant for confidentiality.

3.7.1. Randomization and Allocation

Participants were randomized to the music intervention group or the control group (quiet rest without headphones) using a computer-generated randomization list. The principal investigator remained unaware of allocation until consent was obtained.
Blinding included participants (sedated), bedside care providers, and laboratory personnel analyzing biomarker samples.

3.7.2. Intervention

The process consisted of three stages:

1. Pre-intervention (baseline).
2. Intervention: 60-minute session of music intervention (intervention group) or quiet rest (control group).
3. Post-intervention (return to usual care).

Pain was verified using CPOT = 0 before beginning. BIS monitoring was applied when necessary; patients outside target sedation levels (BIS 40–60 or RASS −3 to −4) were excluded. Sessions occurred between 16:00 and 17:00 to align with nursing workflows and circadian cortisol patterns.

Baseline arterial blood samples for cortisol, prolactin, and IL-6 were taken at 15:55. Physiological parameters and sedative infusion data were recorded. Headphones were placed. The investigator remained silently at bedside during the session. Any agitation or discomfort led to termination of the session and documentation. Post-intervention arterial blood sampling was then performed, and physiological variables were recorded every 10 minutes during the entire session.

3.8. Statistical Analysis

Analyses followed an intention-to-treat approach, with per-protocol sensitivity analyses. Continuous variables were summarized using mean ± SD or median [IQR]; categorical variables using frequency and percentage.

Baseline differences were analyzed using Student's t-test or Mann–Whitney U test for continuous variables and chi-square or Fisher's exact test for categorical variables.

Primary analysis focused on the change in serum cortisol using linear mixed-effects models with fixed effects for group, time, and group × time interaction, and random intercepts for subjects. Prolactin and IL-6 were analyzed similarly as key secondary outcomes. Non-parametric tests, including the Friedman test and Dunn post-hoc tests, were applied where model assumptions were violated.

Physiological trajectories were analyzed using repeated-measures mixed models incorporating the 10-minute time intervals.

Correlations were assessed using Pearson or Spearman coefficients. Multiple comparisons for secondary outcomes were controlled using the false discovery rate when necessary.

The significance threshold was 0.05. Analyses were performed using R version 4.4.3.

3.9. Ethical Considerations and Funding

The study adhered to the Declaration of Helsinki, the Belmont Report, CIOMS Guidelines, and Spanish Organic Law 3/2018 on data protection. Ethics approval was obtained from the Ethics Committee of the Principality of Asturias (code 2022.537). The trial was registered at ClinicalTrials.gov (NCT06120660). Written informed consent was obtained from each legally authorized representative prior to participation. Confidentiality was ensured through coded identifiers and restricted data access.

Funding:
This study received no institutional funding from the University of Oviedo. Financial support was provided exclusively by the Spanish Society of Intensive and Coronary Care Nursing (SEEIUC) through the "SEEIUC Investiga" Grant 2023 (5th Edition), with a total amount of €4,000, awarded to the project "Efectos de la intervención musical en el estrés del paciente crítico."