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Original Article

Effect of music therapy on short-term psychological and physiological outcomes in mechanically ventilated patients: A randomized clinical pilot study

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ABSTRACT

Background: Elevated anxiety levels are common in patients on mechanical ventilation (MV) and may challenge recovery. Research suggests music-based interventions may reduce anxiety during MV. However, studies investigating specific music therapy techniques, addressing psychological and physiological well-being in patients on MV, are scarce.

Methods: This three-arm randomized clinical pilot study was conducted with MV patients admitted to the intensive care unit (ICU) of Hospital San José in Bogotá, Colombia between March 7, 2022, and July 11, 2022. Patients were divided into three groups: intervention group 1 (IG1), music-assisted relaxation; intervention group 2 (IG2), patient-preferred therapeutic music listening; and control group (CG), standard care. The main outcome measure was the 6-item State-Anxiety Inventory. Secondary outcomes were: pain (measured with a visual analog scale), resilience (measured with the Brief Resilience Scale), agitation/sedation (measured with the Richmond Agitation–Sedation Scale), vital signs (including heart rate, blood pressure, oxygen saturation, and respiratory rate), days of MV, extubation success, and days in the ICU. Additionally, three patients underwent electroencephalography during the interventions.

Results: Data from 23 patients were analyzed in this study. The age range of the patients was 24.0–84.0 years, with a median age of 66.0 years (interquartile range: 57.0–74.0). Of the 23 patients, 19 were female (82.6%). No statistically significant differences between the groups were observed for anxiety (P=0.330), pain (P=0.624), resilience (P=0.916), agitation/sedation (P=0.273), length of ICU stay (P=0.785), or vital signs. A statistically significant difference between the groups was found for days of MV (P=0.019). Electroencephalography measurements showed a trend toward delta and theta band power decrease for two patients and a power increase on both beta frequencies (slow and fast) in the frontal areas of the brain for one patient.

Conclusions: In this pilot study, music therapy did not significantly affect the anxiety levels in patients on MV. However, the interventions were widely accepted by the staff, patients, and caregivers and were safe, considering the critical medical status of the participants. Further large-scale randomized controlled trials are needed to investigate the potential benefits of music therapeutic interventions in this population.

Trial Registration ISRCTN trial registry identifier: ISRCTN16964680

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Introduction

Being hospitalized in an intensive care unit (ICU) can be a traumatic and stressful experience for many patients.[1] In the United States, approximately 20%–38% of the patients admitted to an ICU require mechanical ventilation (MV), and similar figures are reported in European countries.[2,3] MV consists of the entry and exit of air flow toward the lungs via an endotracheal tube driven by a pressure gradient. The primary goals of MV are to improve gas exchange in the lungs and alleviate respiratory distress.[4,5] However, patients undergoing MV frequently experience psychological and physiological challenges, including the presence of the orotracheal tube, medical procedures, pain, noise, fear, or communication problems.[6,7] The most common stressors identified by MV patients are dyspnea, anxiety, fear, and pain.[8] Correlation between anxiety, depression, or insomnia and the perception of pain is widely recognized[9,10] and can negatively affect the recovery of a critically ill patient.

After ICU care, many patients suffer from continuous distress or a worsening of their symptoms, known as the post-ICU syndromes.[11] Recent studies suggest that more than 20% of the ICU patients still suffer from post-traumatic stress symptoms 1 year after discharge and 30% of patients continue to experience high levels of anxiety after their hospitalization.[1,12] This is relevant because MV and increased anxiety are two of the factors associated with post-ICU syndrome.[13,14] Thus, while MV is necessary to support respiratory function and improve survival of critically ill patients, this situation can cause multiple difficulties. Increased anxiety in the ICU is usually treated pharmacologically, but several researchers recommend multimodal and nonpharmacological approaches, including music therapy.[15]

Music therapy and other music-based interventions are being increasingly implemented in medical settings, including the ICUs. Recent reviews report benefits in improving insomnia in adults,[16] promoting motor skills and communication in patients with brain damage,[17] relieving depressive symptoms,[18] and reducing anxiety in various populations, such as presurgical patients,[19] coronary patients,[20] and cancer patients.[21]

For MV patients, a meta-analysis involving 14 studies and 805 patients showed a statistically significant reduction of anxiety levels favoring music *vs.* control groups (CGs) (P=0.0006).[21] Another review highlights less use of sedoanalgesic drugs and improvements in patients' vital signs.[22] Furthermore, an increasing number of individual studies support the role of music-based interventions as a viable non-pharmacological option that can be used adjunctively to manage anxiety and pain in MV patients.[23–35] However, the methodological heterogeneity of these studies is huge and there is almost no research conducted by credentialed music therapists using specific music therapy methods and techniques. Given the lack of studies with MV patients in the Colombian context, this randomized clinical pilot study was performed to describe the effects of two music-therapy techniques—music-assisted relaxation (MAR) and patient-preferred therapeutic music listening (PTML)—on short-term psychological and physiological outcomes in MV patients in the ICU.

Methods

Research design

This randomized clinical pilot study had three parallel arms: (1) intervention group 1 (IG1): standard care + MAR; (2) intervention group 2 (IG2): standard care + PTML; and (3) CG: standard care alone.

The study was conducted in the ICU of Hospital San José in Bogotá, Colombia between March 7, 2022, and July 11, 2022. The study was approved by the Ethics Committee for Research with Human Subjects of the Hospital San Jose-Fundación Universitaria de Ciencias de la Salud on April 20, 2021 (number 0183–2021), and all participants signed an informed consent. Patients were awake and mentally competent. The informed consent was read to the participants and family members and any questions were answered. Patients could communicate via a script board, by nodding or shaking their heads, or by making gestures. The study was performed in accordance with the Declaration of Helsinki and relevant guidelines and regulations. The study protocol was registered at International Standard Randomised Controlled Trial Number (ISRCTN), reference number ISRCTN16964680.

Inclusion and exclusion criteria

The inclusion criteria were: (1) MV patient>18 years old in the ICU; (2) being alert and mentally competent (Richmond Agitation–Sedation Scale [RASS] between −1 and +1); and (3) the expectation of continuing MV for more than 3 days from the moment of signing the informed consent. The exclusion criteria were: (1) confirmed bilateral hearing loss; (2) delirium or disorders of consciousness; (3) known psychiatric disorders; (4) cognitive disabilities; and (5) known addictions to psychoactive substances.

Interventions and procedures

MAR: IG1

MAR is a music therapy technique that includes listening to live music, combined with guided relaxation and/or the use of imagery. MAR is based on the principles of entrainment, which describes the synchronization of two independent rhythms through their interaction.[36,37] In music therapy, entrainment corresponds to the matching and subsequent modification of musical elements in relation to the physiological rhythms or behavioral and emotional states of the patients. MAR has been shown to be effective in palliative care patients,[38] presurgical pediatric patients,[39] and patients with chronic pain,[40] among others.

In this study, the patient was first asked to close his/her eyes or to focus on a fixed point on the ceiling or wall. A verbal introduction was then given, focusing on generating body awareness. In the next step, a mental image was introduced (e.g., sitting on a beach watching the waves of the ocean, imagining a personalized safe and comfortable place). The patient was asked to let himself/herself be guided by the music while concentrating on the imagery. Once the music had finished, the patient was asked to become aware again.

Music therapy sessions for IG1 lasted on average for 26.5 min (range: 18.5–35.0 min). In most cases, patients referred to fields, woods, rivers, or lakes as favorite places for the imagery. Two patients did not refer to any favorite landscape or place. Besides the music therapist's voice, an acoustic guitar (Yamaha C-40) and an ocean drum (a double-skinned drum with small metal pallets inside, imitating the sound of waves) were used as accompanying musical instruments. The music was of slow-to-moderate tempo, repetitive in its structure, and consisted of mostly arpeggiated chord progressions (e.g., II-IV-I, I-V-VI-IV), aiming at creating a safe and calm environment. At times, sus9 chords were used to create a sense of space, and melodies were maintained in the middle register of the guitar or the therapist's voice. The ocean drum was often used to start the intervention (sometimes overlapping with the verbal introduction) or at the end, usually entrained to the patient's breathing rhythm. A staff member was present during the interventions to guarantee adequate patient safety and care at times.

PTML: IG2

The use of prerecorded music is a frequent resource in music therapy and other music-based interventions. In music therapy, listening to music is based on an initial assessment and the patient's preferences and takes place in the context of a therapeutic relationship. In this sense, the music is not only shared between the patient and the music therapist, but it is also guided by the associations the patient has with the music. The music therapist maintains an active listening approach during the session and can verbally intervene to elaborate the emotions, sensations, and thoughts that may arise from the music.

In this study, the patient was first asked to identify music that he/she associated with a state of relaxation and well-being, either via the script board or with yes/no questions. In case the patient could not identify any specific songs or genres, the music therapist used a preselection of music that met the characteristics of anxiolytic music (long and soft tones, no fixed rhythm, simple melodies, consonant harmonies). In the next step, a wireless speaker and a tablet were used to play back the music. The music therapist was present throughout the session and accompanied the patient's continuous selection of music until the session ended.

Music therapy sessions for IG2 lasted on average 27.5 min (range: 16.0–35.0 min). The music selected by the patients was mediated by the region of their origin, religious beliefs, personal tastes, or biographical memories. All but one patient asked for specific artists and songs. Musical genres included vallenato music (artists: Diomedez Diaz, Los Hermanos Zuleta, Jorge Oñate, etc.; songs: Ilusiones, La Plata, etc.), boleros (artists: Los Panchos, songs: Como un rayito de luna, Sin ti, Toda una vida, etc.), religious music (various artists; songs: Ave Maria, Padre Nuestro, En la cruz, Ante tu presencia, etc.), ballads (artists: Leo Dan; songs: Como te extraño, Ella me olvidó, etc.), or rancheras (artists: Vicente Fernández; songs: Estos celos, A mi manera, El rey, etc.). Although the songs had different musical characteristics depending on the genre, a positive association of the patients with the music was common to all song choices. During music-listening, the music therapist regularly checked in with the patient regarding volume, song selection, and if they would like to share some of the memories or feelings produced by the intervention.

Standard care: CG

In the CG, the participants received standard care alone. However, environmental control (avoiding nonemergency medical procedures and keeping the room door closed) was recommended during measurements. The CG interventions lasted on average for 30.5 min (range: 29.0–33.0 min).

Frequency of interventions

A maximum of four interventions (one intervention daily) were conducted from the day of signing the informed consent until the fourth intervention or the first extubation.

Sample size

For this pilot study, the participation of a minimum of 21 participants was determined. This sample size was calculated according to Viechtbauer et al.[41] with a confidence level of 95% and a probability of undesirable events in the study of 50%. The formula used was $n=\ln(1-\gamma)/-\ln(1-\pi)=\ln(1-0.95)/\ln(1-0.50)=4.3\approx 5$, where $\gamma=0.95$ is the confidence level and $\pi=0.50$ is the probability of undesirable events. Estimating a loss to follow-up of 30%, seven participants per arm was determined.

Primary outcome measure

The primary outcome measure was the Spanish version of the 6-item State-Trait Anxiety Inventory (STAI-E6). In its original version, the STAI consists of 40 items rated on a 4-point Likert scale, measuring trait and state anxiety.[42] There are several short versions of the STAI, but only one that has been validated with ventilated patients: in its original version in English by Chlan et al.[43] and in its Spanish version by Perpiñá-Galvañ et al.[44,45] The STAI-E6 has an internal consistency of Cronbach's alpha of 0.79 and adequate results regarding its reliability and validity.[45] The STAI-E6 was applied after signing the informed consent and after each intervention.

Secondary outcome measures

Pain

Pain levels were measured with a visual analog scale (VAS) from 0 to 10; 0 indicates a state without any pain and 10 indicates the most severe pain possible. Each number is distributed on a line 1 cm apart and the patient can mark the subjective pain intensity. The VAS was applied after signing the informed consent and after each intervention.

Resilience

Resilience is defined as the ability to bounce back from a stressful event. The Brief Resilience Scale (BRS) was developed in its original English version by Smith et al.[46] and contains six items rated on a 5-point Likert scale. The Spanish version was validated by Rodríguez-Rey et al.[47] and showed adequate internal consistency with a Cronbach's alpha of 0.80–0.91. The BRS was applied after signing the informed consent and after the second, third, and last interventions.

Agitation/sedation

Agitation/sedation was measured with the RASS, which consists of 10 items with a score of +4 to −5 depending on the behavioral state of the patient. The RASS was published in English by Ely et al.[48] and validated in Colombia by Rojas-Gambasica et al.[49] The RASS was applied after signing the informed consent and after each intervention.

Vital signs

Heart rate (HR), respiratory rate (RR), oxygen saturation, and blood pressure (BP) were collected through routine patient monitoring. Vital signs were recorded before and after each intervention.

Days of MV

Days of mechanical ventilation (MV) can be calculated by subtracting the day of intubation from the day of the first extubation. In the case of re-intubations, the same procedure was followed, adding up all ventilation days during the time in the ICU.

Extubation success

Number of failed extubations and/or necessary re-intubations.

Days in the ICU

The length of stay in the ICU is determined by subtracting the date of admission from the date of discharge.

Exploratory outcome measures

As an exploratory outcome, electroencephalography (EEG) measurements were conducted in three voluntary patients (two from IG1 and one from IG2). One music therapy session was recorded for each patient. EEG recordings were measured for a 5-min baseline resting state with eyes closed and then for approximately 11 min of the music therapy session. EEG recordings were made according to the international 10–20 configuration, but the number of electrodes was reduced to 8, which were FP1, FP2, C3, C4, T3, T4, O1, and O2 (plus one reference electrode in the Cz position and one ground electrode), with the aim of reducing EEG assembly time. All measurements were performed with Micromed LTM64 equipment (Micromed S.P.A., Mogliano Veneto, Italy) with a sampling frequency of 512 Hz.

Randomization and blinding

Randomization was performed on a 1:1:1 basis with randomized numbers in an Excel sheet. Owing to the nature of the intervention, participants were not blinded. However, data collection and statistical analysis were performed by blinded researchers. The procedure was as follows: if randomized to one of the intervention groups, the music therapist entered the ICU and sent a text message at the beginning of the session (e.g., patient 1, start) to the research assistant who was not present in the ICU. After finishing the session, the music therapist sent another text message (e.g., patient 1, finished), after which the research assistant entered the ICU and collected postintervention measurements. If randomized to the CG, the same procedure was performed but no music-therapy sessions took place.

Statistical analysis of the primary and secondary outcome measures

Statistical analysis was performed with Stata 17. For the quantitative outcome measures, descriptive statistics were used. Continuous variables are expressed as medians and interquartile ranges (IQRs), and categorical variables as absolute and relative values. Pre- and post-intervention comparisons in categorical variables were made using Fisher's exact test, and those for quantitative variables used the Mann–Whitney U test. Comparisons that reported $P < 0.05$ were interpreted as statistically significant differences.

EEG analysis

The data were initially filtered between 1 Hz and 30 Hz, and visually inspected noise and artifacts were subsequently removed. An independent component analysis (ICA) algorithm identified and removed one noise-detected component associated with the ventilation machine and blinking.[50] Subsequently, 2.5-min and 5-min central windows were extracted for baseline and music therapy periods, respectively. Five frequency bands were analyzed: Delta (1–4 Hz), Theta (4–8 Hz), Alpha (8–12 Hz), slow Beta (12–18 Hz), and fast Beta (18–30 Hz). The data were segmented into 3-s windows with a 1.5-s overlap. Band power was calculated by integrating power spectral density (PSD) values in each frequency band using Simpson's rule.[51] Next, the power evolutions for each frequency band and channel were z-score normalized to the baseline. Brain connectivity matrices were calculated by Pearson cross-correlation analysis conducted on a 30-s epoch with an 18-s overlap for all electrode combinations. For the brain connectivity matrix the same pair of electrodes was set to 0, while different pairs were assigned a connection strength weight. [52] Electrodes degree and the shortest path of all epoch-connectivity matrices were subsequently calculated. Strength connectivity in each channel was calculated as mean over rows, and then was represented in a topographic form. Results were visualized using the Visbrain Python library.[53] For power-evolution and brain-correlation measures, permutation tests comparing two populations were adopted for statistical analysis.[54] All baseline epochs were analyzed along with the same number of randomly selected music therapy epochs. The null hypothesis assumed equal z-score means for the two periods. With 9999 permutations, the test results were corrected by the false discovery rate (FDR)[55] to address possible type 1 errors, potentially leading to the rejection of the null hypothesis if the corrected *P*-value was less than 0.05.

Results

Over a 5-month period from March 7, 2022, to July 11, 2022, a total of 28 patients were screened for eligibility to participate in this study. Three patients were excluded due to their neurological condition or mental health comorbidities, and 25 patients were invited to participate. One patient declined, leaving 24 patients for randomization. One patient did not receive the allocated intervention because he/she died shortly after randomization, leaving a final sample of 23 participants. The flow diagram of this study is presented in Figure 1.

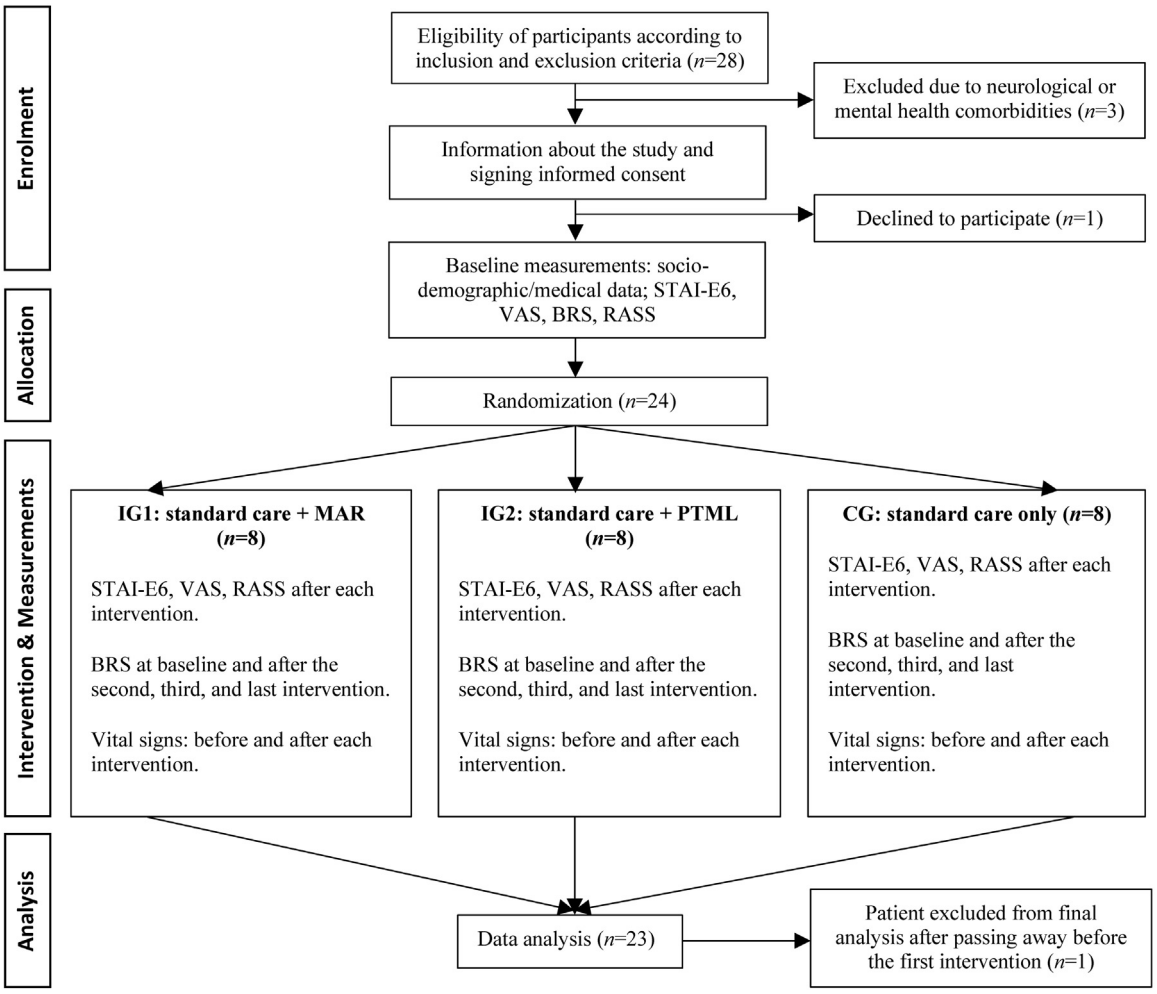

Figure 1. Flow diagram adapted from Schulz et al.[66]
BRS: Brief Resilience Scale; CG: Control group; ICU: Intensive care unit; IG:Intervention group; MAR: Music-assisted relaxation; MV: Mechanical ventilation; PTML: Patient-preferred therapeutic music listening; RASS: Richmond Agitation–Sedation Scale; STAI-E6: 6-item State-Trait Anxiety Inventory; VAS: Visual Analog Scale.

Sociodemographic and medical data

The age range of patients was 24.0–84.0 years, with a median age of 66.0 years (IQR: 57.0–74.0 years). Of the 23 patients, 19 were female (82.6%). The most frequent diagnoses were heart failure, infectious diseases, carcinomas, and post-surgery conditions. The reason for MV was either surgical (n=5; 21.7%) or observation and symptom control (n=18; 78.3%). No statistically significant differences between baseline characteristics of the three groups were found (Table 1).

Main outcome measure

No statistically significant differences for the STAI-E6 were found in within- and between-group analyses. Median scores at baseline were 40.0 (IQR: 36.0–50.0) and fluctuated in the following measurement time points between median values of 31.5 and 53.0. Table 2 shows the results of the STAI-E6 at baseline and interventions 1–4.

Secondary outcome measures

Pain, resilience, and agitation/sedation

No statistically significant differences were detected for pain, resilience, or agitation/sedation within or between groups (Table 3). VAS pain levels fluctuated markedly during the study, with scores ranging between 0 and 8. The BRS scores were stable between 3.0 and 3.2 across groups and measurement time points. The RASS scores did not indicate an occurrence of delirium in any of the three groups (means: −1.0 to 1.0).

Vital signs

Vital signs were measured before and after each intervention. In the IG1 and IG2 groups, a trend toward decreased heart rate and RRs after the interventions was observed, but this was not statistically significant. No definite trend was observed for oxygen saturation and BP. Two statistically significant differences were observed for systolic and mean BP in the CG after intervention 3 (P=0.036 and P=0.015, respectively). Table 4 shows the results for vital signs.

Days of MV

Patients in IG1 were intubated between 1 day and 5 days (median=2.0, IQR: 1.0–3.0), in IG2, between 1 day and 15 days (median=6.0, IQR: 2.0–9.0), and in the CG, between 6 days and 13 days (median=8.0, IQR: 7.8–12.3), resulting in a statistically significant difference between the groups (P=0.019).

Table 1
Patient characteristics at baseline (*n*=23).

Characteristic	IG1 (*n*=8)	IG2 (*n*=7)	CG (*n*=8)	*P*-value
Age (years)	67.0 (58.0–75.5)	64.0 (58.0–69.0)	71.5 (43.5–74.0)	0.869
Female	7 (87.5)	4 (57.1)	8 (100.0)	0.083
Estado civil				0.613
Single	1 (12.5)	1 (14.3)	2 (25.0)	
Married	3 (37.5)	5 (71.4)	4 (50.0)	
Divorced	4 (50.0)	1 (14.3)	1 (12.5)	
Widowed	0	0	1 (12.5)	
Sociodemographic status				
1	0	3 (42.9)	0	0.172
2	2 (25.0)	1 (14.3)	3 (37.5)	
3	6 (75.0)	3 (42.9)	5 (62.5)	
Origin				1.000
Bogotá	4 (50.0)	4 (57.1)	4 (50.0)	
Outside of Bogotá	4 (50.0)	3 (42.9)	4 (50.0)	
Education				0.959
Primary school finished	1 (12.5)	2 (28.6)	2 (25.0)	
Secondary school not finished	1 (12.5)	0	1 (12.5)	
Secondary school finished	2 (25.0)	1 (14.3)	2 (25.0)	
University not finished	3 (37.5)	1 (14.3)	1 (12.5)	
University finished	1 (12.5)	2 (28.6)	2 (25.0)	
Reason for MV				0.837
Surgical	2 (25.0)	2 (28.6)	1 (12.5)	
Symptom control	6 (75.0)	5 (71.4)	7 (87.5)	
ICU days	14.5 (8.0–26.0)	11.0 (10.0–22.0)	15.0 (11.5–24.5)	0.785
MV days	2.0 (1.0–3.0)	6.0 (2.0–9.0)	8.0 (7.5–12.5)	0.019
Patients receiving sedatives	4 (50.0)	6 (85.7)	7 (100)	0.314
Fentanyl	3	5	7	
Fentanyl – Isoflurane	0	1	0	
Fentanyl – Midazolam	1	0	0	
Patients receiving analgesics	4 (50.0)	0	1 (12.5)	0.800
Bupivacaine	1	0	0	
Hydroform	3	0	1	

Data are expressed as median (interquartile range) or *n* (%).
CG: Control group; IG1: Intervention group 1; IG2: Intervention group 2; ICU: Intensive care unit; MV: Mechanical ventilation.

Table 2
Main outcome measure (STAI-E6) in different timepoints.

Outcome measure	Baseline		Intervention 1		Intervention 2		Intervention 3		Intervention 4		*P*-value
	n	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	
CG	8	45.0 (33.0–56.0)	8	38.0 (31.5–41.5)	8	45.0 (38.0–58.0)	7	43.0 (36.0–50.0)	5	36.0 (33.0–43.0)	0.176
IG1	8	40.0 (33.0–44.5)	8	38.0 (31.5–45.0)	4	31.5 (28.0–36.5)	3	36.0 (33 .0–40.0)	2	35.0 (30.0–40.0)	0.654
IG2	7	40.0 (36.0–43.0)	7	33.0 (33.0–40.0	3	46.0 (30.0–60.0)	2	53.0 (46.0–60.0)	2	39.5 (33.0–46.0)	0.179
P-value	0.754		0.834		0.182		0.114		0.670		
Overall	23	40.0 (36.0–50.0)	23	36.0 (33.0–40.0)	15	40.0 (30.0–56.0)	12	41.5 (36.0–48.0)	9	36.0 (33.0–43.0)	0.330

CG: Control group; IG1: Intervention group 1; IG2: Intervention group 2; IQR: Interquartile range; STAI-E6: 6-item State-Trait Anxiety Inventory.

Table 3
Secondary outcome measures (VAS, BRS, and RASS) in different timepoints.

Parameter	Outcome measure	Baseline		Intervention 1		Intervention 2		Intervention 3		Intervention 4		*P*-value
		n	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	*n*	Median (IQR)	
VAS	CG	8	5.0 (0.0–5.0)	8	2.5 (0.0–3.0)	8	6.0 (0.0–8.5)	7	5.0 (0.0–6.0)	5	3.0 (0.0–3.0)	0.571
	IG1	8	2.0 (1.0–2.5)	8	2.0 (0.0–6.5)	4	0.0 (0.0–1.5)	3	3.0 (0.0–7.0)	2	2.0 (0.0–4.0)	0.073
	IG2	7	2.0 (1.0–2.0)	7	3.0 (0.0–3.0)	4	0.0 (0.0–2.5)	2	8.0 (7.0–9.0)	2	5.5 (4.0–7.0)	0.654
	P-value	0.473		0.912		0.143		0.118		0.183		
	Overall	23	2.0 (1.0–3.0)	23	3.0 (0.0–3.0)	16	0.0 (0.0–6.0)	12	5.0 (1.5–6.5)	9	3.0 (0.0–4.0)	0.624
BRS	CG	8	3.2 (2.7–3.5)	NA	NA	8	3.0 (2.7–3.2)	3	3.0 (3.0–4.0)	5	3.0 (3.0–3.0)	0.563
	IG1	8	3.1 (3.0–3.5)	NA	NA	4	3.0 (3.0–3.2)	1	3.2 (3.2–3.2)	2	3.0 (3.0–3.0)	0.563
	IG2	6	3.0 (2.6–3.1)	NA	NA	3	3.0 (1.6–3.1)	NA	NA	2	3.0 (3.0–3.0)	0.248
	P-value	0.645		NA		0.534		0.637		1.000		
	Overall	22	3.1 (2.8–3.5)	NA	NA	15	3.0 (2.8–3.1)	4	3.1 (3.0–3.6)	9	3.0 (3.0–3.0)	0.916
RASS	CG	8	1.0 (0.5–1.0)	8	0.0 (–1.0–0.5)	8	–0.5 (–1.0–1.0)	7	0.0 (–1.0–1.0)	5	–1.0 (–1.0–0.0)	0.287
	IG1	8	0.0 (–1.0–0.0)	8	0.0 (–1.0–0.0)	4	0.0 (–1.0–0.5)	3	0.0 (0.0–0.0)	2	0.0 (0.0–0.0)	1.000
	IG2	7	–1.0 (–1.0–0.0)	7	–1.0 (–1.0–0.0)	4	0.0 (–1.0–0.5)	2	0.0 (–1.0–1.0)	2	–0.5 (–1.0–0.0)	0.654
	P-value	0.003		0.264		0.981		0.938		0.628		
	Overall	23	0.0 (–1.0 –1.0)	23	0 .0 (–1.0–0.0)	16	0.0 (–1.0–0.5)	12	0.0 (–1.0–0.5)	9	0.0 (–1.0–0.0)	0.273

BRS: Brief Resilience Scale; CG: Control group; IG1: Intervention group 1; IG2: Intervention group 2; IQR: Interquartile range; NA: Not available; RASS: Richmond Agitation–Sedation Scale; VAS: Visual Analog Scale.

Table 4
Vital signs in different groups pre- or post-each intervention.

Parameter	Outcome measure	Intervention 1					Intervention 2					Intervention 3					Intervention 4				
		Pre		Post		*P*-value	Pre		Post		*P*-value	Pre		Post		*P*-value	Pre		Post		*P*-value
		n	Median (IQR)	*n*	Median (IQR)		*n*	Median (IQR)	*n*	Median (IQR)		*n*	Median (IQR)	*n*	Median (IQR)		*n*	Median (IQR)	*n*	Median (IQR)	
HR	IG1	8	97.5 (75.5–109.5)	8	93.5 (69.5–103.0)	0.094	4	81.5 (69.0–98.0)	4	81.0 (70.5–98.0)	1.000	2	65.5 (64.0–67.0)	2	64.0 (62.0–66.0)	0.500	2	79.5 (75.0–84.0)	2	77.0 (72.0–82.0)	0.500
	IG2	7	96.0 (77.0–98.0)	7	90.0 (82.0–98.0)	0.402	4	86.5 (82.0–94.5)	4	92.0 (87.5–97.5)	0.375	2	97.5 (84.0–111.0)	2	93.5 (77.0–110.0)	0.500	2	82.5 (78.0–87.0)	2	78.0 (73.0–83.0)	0.500
	CG	8	83.0 (62.0–102.0)	8	85.5 (58.5–109.5)	0.528	8	89.5 (83.0–113.0)	8	84.5 (75.0–111.5)	0.208	7	91.0 (80.0–100.0)	7	88.0 (77.0–104.0)	1.000	5	94.0 (92.0–99.0)	5	96.0 (91.0–99.0)	0.750
RR	IG1	8	15.5 (12.0–20.0)	8	14.5 (11.5–16.0)	0.348	4	13.5 (11.0–18.5)	4	13.0 (12.0–17.0)	1.000	2	14.5 (12.0–17.0)	2	13.5 (11.0–16.0)	0.346	2	19.5 (19.0–20.0)	2	17.0 (15.0–19.0)	1.000
	IG2	7	14.0 (11.0–22.0)	7	14.0 (12.0–20.0)	0.269	4	18.0 (10.0–61.0)	4	12.0 (12.0–58.5)	1.000	2	22.5 (13.0–32.0)	2	21.5 (11.0–32.0)	1.000	2	22.0 (12.0–32.0)	2	17.0 (11.0–23.0)	0.500
	CG	8	20.0 (15.0–25.0)	8	20.0 (15.0–23.5)	0.684	8	21.0 (19.0–33.0)	8	21.5 (15.5–28.5)	0.554	7	26.0 (21.0–31.0)	7	26.0 (16.0–33.0)	0.787	5	24.0 (20.0–25.0)	5	19.0 (16.0–27.0)	1.000
SpO_2	IG1	8	95.0 (93.0–97.0)	8	96.0 (94.0–97.0)	1.000	4	94.0 (93.0–96.0)	4	97.0 (95.5–98.5)	0.181	2	96.5 (95.0–98.0)	2	96.5 (95.0–98.0)	1.000	2	96.0 (95.0–97.0)	2	96.0 (94.0–98.0)	1.000
	IG2	7	96.0 (94.0–97.0)	7	97.0 (93.0–98.0)	0.586	4	95.0 (94.5–97.0)	4	96.5 (95.5–97.0)	0.773	2	94.0 (92.0–96.0)	2	96.5 (95.0–98.0)	0.500	2	93.5 (90.0–97.0)	2	95.0 (92.0–98.0)	0.500
	CG	8	94.0 (91.0–94.5)	8	94.5 (90.5–96.0)	0.500	8	94.0 (92.0–97.0)	8	95.5 (93.0–97.5)	0.670	7	93.0 (90.0–95.0)	7	93.0 (90.0–98.0)	0.461	5	94.0 (92.0–99.0)	5	94.0 (92.0–100.0)	1.000
BP systolic	IG1	8	128.0 (115.0–154.0)	8	128.0 (108.0–151.0)	0.326	4	108.0 (94.0–118.5)	4	115.5 (98.5–127.5)	0.125	2	115.5 (114.0–117.0)	2	119.5 (114.0–125.0)	1.000	2	115.5 (111.0–120.0)	2	113.0 (111.0–115.0)	1.000
	IG2	7	113.0 (95.0–143.0)	7	116.0 (94.0–135.0)	0.551	4	138.0 (126.0–174.0)	4	129.0 (118.0–165.0)	0.269	2	147.5 (131.0–164.0)	2	150.0 (128.0–172.0)	1.000	2	131.5 (114.0–149.0)	2	110.0 (109.0–111.0)	0.500
	CG	8	104.0 (97.0–151.0)	8	110.5 (103.0–122.0)	0.833	8	111.0 (104.5–134.0)	8	116.0 (108.0–130.0)	1.000	7	121.0 (102.0–161.0)	7	104.0 (102.0–155.0)	0.036	5	110.0 (104.0–115.0)	5	113.0 (109.0–128.0)	0.250
BP diastolic	IG1	8	67.0 (50.0–70.0)	8	62.0 (52.0–68.0)	0.261	4	47.0 (44.5–60.0)	4	52.5 (46.0–62.5)	0.789	2	58.5 (51.0–66.0)	2	57.5 (48.0–67.0)	1.000	2	53.0 (46.0–60.0)	2	52.5 (45.0–60.0)	1.000
	IG2	7	64.0 (48.0–77.0)	7	55.0 (50.0–78.0)	0.553	4	78.0 (68.0–81.5)	4	69.0 (58.5–79.0)	0.250	2	82.0 (81.0–83.0)	2	78.5 (74.0–83.0)	1.000	2	77.5 (65.0–90.0)	2	65.5 (65.0–66.0)	1.000
	CG	8	57.0 (53.0–66.0)	8	59.0 (52.0–62.5)	0.397	8	64.0 (47.0–75.0)	8	60.0 (47.0–68.0)	0.310	7	65.0 (51.0–72.0)	7	66.0 (51.0–68.0)	0.073	5	54.0 (50.0–68.0)	5	64.0 (50.0–66.0)	1.000
BP median	IG1	8	87.5 (79.5–99.0)	8	79.0 (73.0–89.0)	0.149	4	66.0 (62.5–78.5)	4	71.0 (63.5–85.5)	0.461	2	80.0 (76.0–84.0)	2	81.5 (77.0–86.0)	0.500	2	74.0 (63.0–85.0)	2	74.0 (66.0–82.0)	1.000
	IG2	7	89.0 (66.0–105.0)	7	81.0 (65.0–104.0)	0.149	4	103.0 (92.0–108.5)	4	96.5 (82.5–100.0)	0.250	2	105.5 (100.0–111.0)	2	105.0 (98.0–112.0)	1.000	2	100.5 (86.0–115.0)	2	81.5 (80.0–83.0)	0.500
	CG	8	74.5 (68.0–99.0)	8	74.0 (70.5–91.0)	0.624	8	81.0 (65.0–93.5)	8	83.0 (69.0–86.5)	0.528	7	82.0 (71.0–104.0)	7	80.0 (67.0–96.0)	0.015	5	79.0 (75.0–81.0)	5	76.0 (76.0–85.0)	1.000

BP: Blood pressure; CG: Control group; HR: Heart rate; IG1: Intervention group 1; IG2: Intervention group 2; IQR: Interquartile range; RR: Respiratory rate; SpO_2: Oxygen saturation.

Extubation success

Only four participants required reintubation after their first extubation; these were two patients in IG1, one in IG2, and one in CG. Thus, no statistical analysis was performed.

Days in the ICU

The time spent in the ICU was between 3 days and 45 days (median=14.5, IQR: 8.5–24.5) for IG1, between 8 days and 30 days (median=1.0, IQR: 10.5–18.0) for IG2, and between 8 and 34 (median=15.0, IQR: 12.8–23.8) for the CG (P=0.786).

EEG measurements

EEG power evolution

Figure 2 shows the power change between baseline and the intervention. Delta band: Conflicting results were observed between patients 1 and 3. While patient 1 showed a significant overall decrease in power density across most electrodes, patient 3 exhibited a significant overall increase. Patient 2 only had a significant decrease in the prefrontal left region. Theta band: a significant decrease for patient 1 and a significant increase for patient 3 were observed. Patient 2 had a significant decrease in both hemispheres in the prefrontal regions and an increase in the left temporal region. Alpha band: non-concordant results between patients were found. Slow beta band: patients 2 and 3 experienced significant increases in power in the central and temporal regions, with patient 2 in the left hemisphere and patient 3 in the right hemisphere. Additionally, patient 2 showed an increase in power in the left prefrontal and right occipital regions. Patient 1 did not exhibit any significant changes. Fast Beta band: the most significant changes were observed in patient 2, with a significant increase in power density in the central, temporal, and occipital regions in both brain hemispheres. Patient 3 exhibited only a power density increase in the left temporal region, while patient 1 did not show any significant changes.

EEG connectivity

Connectivity strength changes between baseline and intervention for each electrode were visualized in topographical plots (Figure 3). Delta band: a significant increase in strength in left and right electrodes was found for patient 3. Patients 1 and 2 had no significant results. Low Beta band: a decrease in strength of connectivity was found for patient 1 in the right central region and for patient 2 in the prefrontal right region. Theta, Alpha, and fast Beta bands did not show any significant results.

Discussion

In this study, no statistically significant differences between the anxiety levels of the patients in the three groups were observed. For secondary outcome measures, the intubation period (days of intubation) was shorter for IG1 (P=0.019), but the small sample size means that correlating an intervention success to this finding is not possible. A more consistent trend was observed with respect to a decrease in the HR and RR in both intervention groups but this needs to be confirmed in future studies with larger sample sizes. In previous pilot studies on the effect of music therapy on patients with MV, Lee et al.[56] reported mixed results, with no significant changes in anxiety levels but

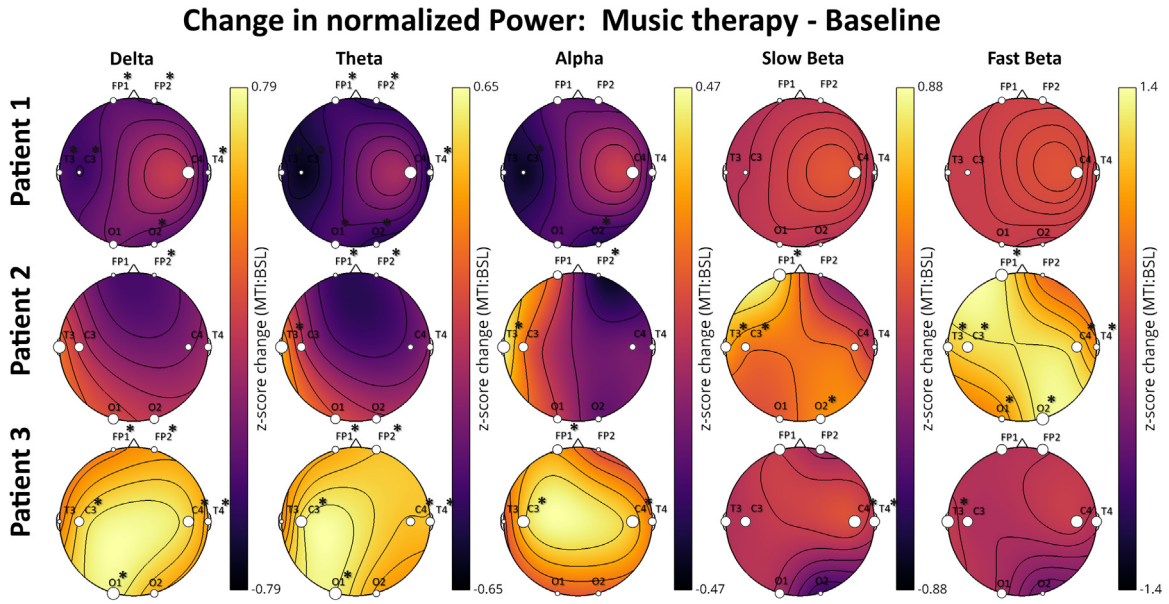

Figure 2. Topographic maps showing the change in power spectral densities averaged over all epochs between baseline and music therapy intervention for three ventilated ICU patients (rows). The different frequency bands—delta, theta, alpha, slow beta, and fast beta—are presented in columns one to five, respectively. The white marker size of the electrode represents the value of the change: the greater the size, the greater the increase. The color bar was adjusted for each frequency band for the three patients, with a perceptually uniform colormap symmetrically centered at zero, where purple represents a decrease and yellow represents an increase in standard deviations of the power evolution of the intervention with respect to the baseline. Electrodes with significant changes (P <0.05 from the permutation test FDR corrected) are marked with an asterisk. Patients 1 and 3 were part of IG1 and patient 2 was part of IG2.
BSL: Baseline; FDR: False discovery rate; ICU: Intensive care unit; IG1: Intervention group 1; IG2: Intervention group 2; MTI: Music therapy intervention.

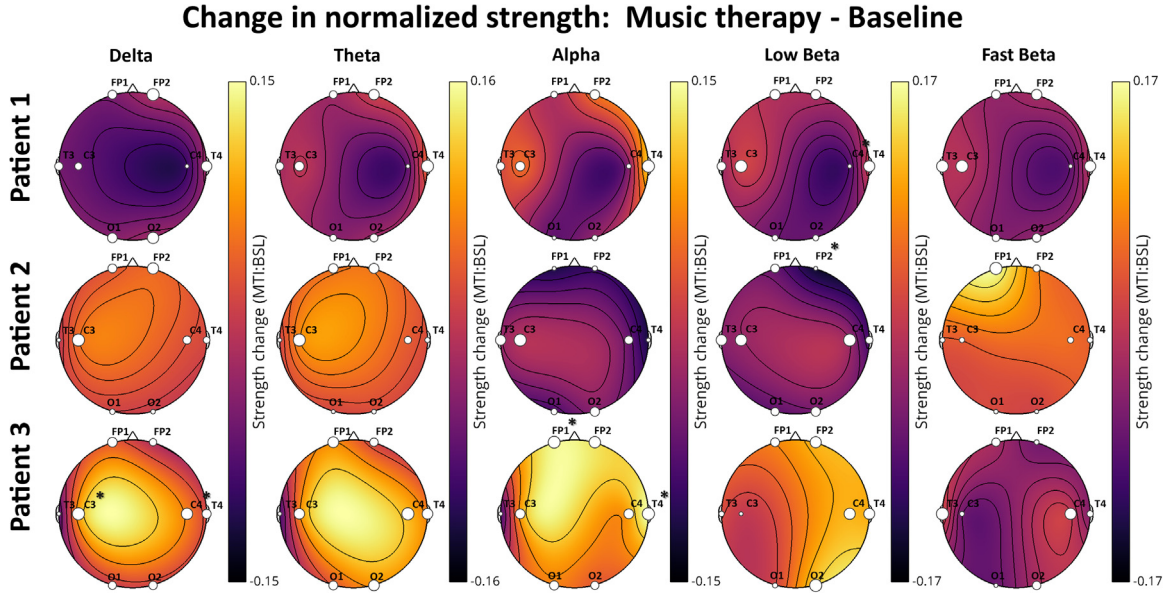

Figure 3. Correlation matrix with channels as nodes and links as the change in the Pearson correlation in PSD evolution between baseline and music therapy intervention between all electrodes for three ventilated ICU patients (rows). The different frequency bands—delta, theta, alpha, slow beta, and fast beta—are presented in columns one to five, respectively (See Methods for the values of the bands). The color bar was adjusted for each frequency band, with a perceptually uniform colormap centered at zero, where purple represents a decrease and yellow represents an increase in the correlation of the power evolution among all electrodes during the intervention relative to the baseline.
BSL: Baseline; ICU: Intensive care unit; MTI: Music therapy intervention; PSD: Power spectral density.

a statistically significant effect on the patients' vital signs. Wong et al.[29] found significant differences in the anxiety state and vital signs and Almerud and Petersson[57] found significant differences for BP, but not for other vital signs. However, drawing comparisons to previous studies is complex, as study designs, cultural and geographic backgrounds of the patients, and the interventions themselves differ. Most notably, live music therapy approaches are still scarce as compared to prerecorded music-listening interventions.

Hunter et al.[35] used live music therapy songwriting or improvisation during weaning from MV trials of 61 patients matched to a historical CG. The results showed a decrease in patient-rated and nurse-rated anxiety levels, a decrease in HR and RR, but no significant differences in days to wean from

MV. More recently, Golino et al.[25] used entrained live music by a certified music therapist with 118 patients, resulting in statistically significant differences in agitation, pain, and HR, but not for RR or oxygen saturation. In this study, two different music therapy methods——MAR and PTML——were used. While live music is the preferred approach as it is more versatile and thus safer, recorded music can be a valuable strategy, especially when based on a previous assessment, in relation to specific clinical goals, and applied within the context of a therapeutic relationship.

For EEG measurements, changes in the PSD for different EEG frequency bands and brain connectivity have been found to be relevant for identifying and understanding brain biomarkers for chronic pain and pain perception.[58–60] Evidence suggests that music can modulate brain activity in structures associated with depression, post-traumatic stress, and anxiety.[61] However, there is lack of information on how music therapy affects brain activity in MV patients. Some of the trends in our EEG measurements (e.g., delta and theta band power decreases in patients 1 and 2) were also reported in a study on music therapy with chronic pain patients.[40] In particular, the theta band has been related to attention processes and to pain processing through the insular cortex.[62] A decrease in this band may be linked to the analgesic effect produced by music therapy, but additional studies are needed to address this finding. For patient 2, we found a power increase on both beta frequencies (slow and fast) in the frontal areas of the brain. This activity has been widely reported as cognitive activity and focused attention.[63] Thus, we hypothesize that listening to patient-preferred music might have activated attention and cognition. Similar findings are reported in the literature; for example, an increase in beta power in frontotemporal areas was observed in unconscious patients during preferred music-listening.[64] We found almost no significant changes in connection strength for the shortest path and degree measures. This is congruent with a study involving 51 participants with varying levels of generalized anxiety and which reported no significant alterations in brain connectivity metrics such as the shortest path.[65] The shortest path is understood as the efficiency of the network for rapid communication of information between distant brain regions.[54] This suggests that even if there are changes in the power of band frequencies, the connectivity networks between nodes may maintain similar levels of efficiency, regardless of changes in stress and anxiety levels. However, the low number of samples and time analyzed for each patient do not allow more definite conclusions to be drawn.

Strengths and limitations

Although the results of our study cannot be generalized owing to the pilot status of the study, we implemented methodological robustness by including a parallel CG, randomization of group allocation, and blinding of data collection and data analysis. For the outcome measures, we used well-validated research tools and added the BRS to detect any mediating role of resilience on anxiety or pain. Our study explores MV patients from a broad perspective, highlighting the importance of emotional and psychological aspects within the dynamics of an ICU hospitalization. This approach was highly appreciated by the staff, patients, and caregivers and music therapy was widely accepted as a viable, safe, and humanizing healthcare intervention with this population.

This study has several limitations. First, the quantitative approach taken in this pilot study does not recognize the lived experiences and meaning that music therapy might have for MV patients. However, most patients transitioned to tracheostomy after extubation, and a significant percentage of patients passed away during hospitalization, which might challenge a qualitative approach with this population. A previous mixed-methods study also reported difficulties in collecting and analyzing qualitative data since patients did not remember much from their ICU stay.[57] The feasibility of a qualitative or mixed-methods approach should be explored in a future study. Second, heterogeneity among the patients was high. Neurological patients face diverse challenges and trajectories within the ICU. Distinguishing between causes of MV (e.g., traumatic brain injury, respiratory diseases, postsurgical conditions) should be considered in a future main trial. Third, although we aimed for a process-based approach across several days, only 9 of the 24 randomized patients (37.5%) finished all four interventions. This is because most stable patients with a RASS of −1.0 to +1.0 are extubated rapidly. Furthermore, seven patients (29.2%) died during the course of their hospitalization, meaning that the attrition rate in this context might be higher than in other settings. Fourth, pain levels fluctuated considerably over the course of the study period. This could be due to various reasons, such as daily scheduled medical procedures, physiotherapy, suctioning of the endotracheal tube, or worsening of clinical symptoms. Thus, in future studies, self-reported and externally rated pain levels should be considered, such as in the study by Golino et al.[25] Fifth, while measuring resilience was an innovative component of this study, many patients did not fully understand the items of the scale. The BRS uses similar items phrased positively and negatively, but this was cognitively too challenging for patients considering the severity of their medical condition. Thus, we found the BRS was an inadequate tool for the specific population of our study. Sixth, maintaining blinding is challenging and resource-intensive in the ICU. As the doors of the ICU rooms are made of glass, the blinded research assistant could not be present at the ICU during the intervention or control conditions. However, the research assistant had to be available quickly after the interventions finished to take the measurements, as patients often have a busy schedule in the ICU and any other procedure or therapy could alter current anxiety and pain levels and vital signs. Finally, the impediment of moving the patient's head due to intubation presented various challenges for the EEG measurements. Using caps with electrodes was not feasible, but a setup with free gold cup electrodes allowed the necessary connections in the most difficult areas of the head to be made more rapidly. Furthermore, the highly dynamic environment of the ICU presented substantial challenges to standardizing the intervention protocol during EEG recording, including potential interruptions, medical emergencies, and the considerable background noise from the hospital environment.

Conclusions

This might be the first study regarding music therapy with MV patients in Colombia. Music therapy is a relatively new field of clinical practice and research in the country, although the ap-

proach is being increasingly implemented in hospital settings. While a larger confirmatory study is needed to determine the effectiveness of live music therapy with this population, the high acceptability by staff, patients, and caregivers is promising. Our study further supports the music therapy profession in Colombia in being recognized as a safe, effective, and humanizing therapy, and positions music therapists as innovative and competent research partners for future studies in medical contexts.

Author Contributions

Mark Ettenberger: Writing – original draft, Supervision, Project administration, Methodology, Conceptualization. **Rosangela Casanova-Libreros:** Writing – review & editing, Methodology, Formal analysis. **Josefina Chávez-Chávez:** Writing – review & editing, Methodology, Formal analysis. **Jose Gabriel Cordoba-Silva:** Writing – review & editing, Formal analysis, Data curation. **William Betancourt-Zapata:** Writing – review & editing, Formal analysis, Data curation. **Rafael Maya:** Writing – review & editing, Investigation, Conceptualization. **Lizeth Alexa Fandiño-Vergara:** Writing – review & editing, Investigation, Data curation. **Mario Valderrama:** Writing – review & editing, Supervision, Formal analysis. **Ingrid Silva-Fajardo:** Writing – review & editing, Project administration, Conceptualization. **Sandra Milena Hernández-Zambrano:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

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Ethics Statement

The study was approved by the Ethics Committee for Research with Human Subjects of the Hospital San Jose-Fundación Universitaria de Ciencias de la Salud on April 20, 2021 (number 0183–2021), and all participants signed an informed consent. Patients were awake and mentally competent. The informed consent was read to the participants and family members and any questions were answered. Patients could communicate via a script board, by nodding or shaking their heads, or by making gestures. The study was performed in accordance with the Declaration of Helsinki and relevant guidelines and regulations. The study protocol was registered at ISRCTN, reference number ISRCTN16964680.

Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

References

[1] Parker AM, Sricharoenchai T, Raparla S, Schneck KW, Bienvenu OJ, Needham DM. Posttraumatic stress disorder in critical illness survivors: a meta analysis. Crit Care Med 2015;43(5):1121–9. doi:10.1097/CCM.0000000000000882.
[2] Cederwall CJ, Naredi S, Olausson S, Rose L, Ringdal M. Prevalence and intensive care bed use in patients on prolonged mechanical ventilation in Swedish intensive care units. Respir Care 2020;66(2):300–6. doi:10.4187/respcare.08117.
[3] Wunsch H, Wagner J, Herlim M, Chong D, Kramer A, Halpern SD. ICU occupancy and mechanical ventilator use in the United States. Crit Care Med 2013;41(12):2712–19. doi:10.1097/CCM.0b013e318298a139.
[4] Silva PL, Rocco PR. The basics of respiratory mechanics: ventilator-derived parameters. Ann Transl Med 2018;6(19). doi:10.21037/atm.2018.06.06.
[5] Pettenuzzo T, Fan E. 2016 year in review: mechanical ventilation. Respir Care 2017;62(5):629–35. doi:10.4187/respcare.05545.
[6] Gil B, Ballester R, Gómez S, Abizanda R. Afectación emocional de los pacientes ingresados en una unidad de cuidados intensivos. Revista de Psicopatología y Psicología Clínica 2013;18(2):129–38. doi:10.5944/rppc.vol.18.num.2.2013.12769.
[7] Lindgren VA, Ames NJ. Caring for patients on mechanical ventilation: what research indicates is best practice. Am J Nurs 2005;105(5):50–60. doi:10.1097/00000446-200505000-00029.
[8] Thomas LA. Clinical management of stressors perceived by patients on mechanical ventilation. AACN Clin Issues 2003;14(1):73–81. doi:10.1097/00044067-200302000-00009.
[9] Sheng J, Liu S, Wang Y, Cui R, Zhang X. The link between depression and chronic pain: neural mechanisms in the brain. Neural Plast 2017;2017:9724371. doi:10.1155/2017/9724371.
[10] Woo AK. Depression and anxiety in pain. Rev pain 2010;4(1):8–12. doi:10.1177/204946371000400103.
[11] Parker AM, Sricharoenchai T, Needham DM. Early rehabilitation in the intensive care unit: preventing impairment of physical and mental health. Curr Phys Med Rehabil Rep 2013;1(4):307–14. doi:10.1007/s40141-013-0027-9.
[12] Nikayin S, Rabiee A, Hashem MD, Huang M, Bienvenu OJ, Turnbull AE, et al. Anxiety symptoms in survivors of critical illness: a systematic review and meta-analysis. Gen Hosp Psychiatry 2016;43:23–9. doi:10.1016/j.genhosppsych.2016.08.005.
[13] Lee M, Kang J, Jeong YJ. Risk factors for post–intensive care syndrome: a systematic review and meta-analysis. Aust Crit Care 2020;33(3):287–94. doi:10.1016/j.aucc.2019.10.004.
[14] Myers EA, Smith DA, Allen SR, Kaplan LJ. Post-ICU syndrome: rescuing the undiagnosed. JAAPA 2016;29(4):34–7. doi:10.1097/01.JAA.0000481401.21841.32.
[15] Urner M, Ferreyro BL, Douflé G, Mehta S. Supportive care of patients on mechanical ventilation. Respir Care 2018;63(12):1567–74. doi:10.4187/respcare.06651.
[16] Jespersen KV, Koenig J, Jennum P, Vuust P. Music for insomnia in adults. Cochrane Database Syst Rev 2015;2015(8):CD010459. doi:10.1002/14651858.CD010459.pub2.
[17] Magee WL, Clark I, Tamplin J, Bradt J. Music interventions for acquired brain injury. Cochrane Database Syst Rev 2017;1(1):CD006787. doi:10.1002/14651858.CD006787.pub3.
[18] Aalbers S, Fusar-Poli L, Freeman RE, Spreen M, Ket JC, Vink AC, et al. Music therapy for depression. Cochrane Database Syst Rev 2017;11(11):CD004517. doi:10.1002/14651858.CD004517.pub3.
[19] Bradt J, Dileo C, Shim M. Interventions with music for preoperative anxiety. Cochrane Database Syst Rev 2013;2013(6):CD006908. doi:10.1002/14651858.CD006908.
[20] Bradt J, Dileo C, Potvin N. Music for stress and anxiety reduction in coronary heart disease patients. Cochrane Database Syst Rev 2013;2013(12):CD006577. doi:10.1002/14651858.CD006577.
[21] Bradt J, Dileo C, Magill L, Teague A. Music interventions for improving psychological and physical outcomes in cancer patients. Cochrane Database of Syst Rev 2016(8):CD006911. doi:10.1002/14651858.CD006911.pub3.
[22] Bradt J, Dileo C. Music interventions for mechanically ventilated patients. Cochrane Database Syst Rev 2014;2014(12):CD006902. doi:10.1002/14651858.CD006902.pub3.
[23] Hetland B, Lindquist R, Chlan L. The influence of music during mechanical ventilation and weaning from mechanical ventilation: a review. Heart Lung 2015;44(5):416–25. doi:10.1016/j.hrtlng.2015.06.010.
[24] Chiu-Hsiang L, Chiung-Ling L, Yi-Hui S, Mei Yu L, Chung-Ying L, Long-Yau L. Comparing effects between music intervention and aromatherapy on anxiety of patients undergoing mechanical ventilation in the intensive care unit: a randomized controlled trial. Qual Life Res 2017;26(7):1819–29. doi:10.1007/s11136-017-1525-5.
[25] Golino AJ, Leone R, Gollenberg A, Christopher C, Stanger D, Davis TM, et al. Impact of an active music therapy intervention on intensive care patients. Am J Crit Care 2019;28(1):48–55. doi:10.4037/ajcc2019792.
[26] Lee CH, Lee CY, Hsu MY, Lai CL, Sung YH, Lin CY, et al. Effects of music intervention on state anxiety and physiological indices in patients undergoing mechanical ventilation in the intensive care unit: a randomized controlled trial. Biol Res Nurs 2017;19(2):137–44. doi:10.1177/1099800416669601.

[27] Umbrello M, Sorrenti T, Mistraletti G, Formenti P, Chiumello D, Terzoni S. Music therapy reduces stress and anxiety in critically ill patients: a systematic review of randomized clinical trials. Minerva Anestesiol 2019;85(8):886–98. doi:10.23736/S0375-9393.19.13526-2.
[28] Mofredj A, Alaya S, Tassaioust K, Bahloul H, Mrabet A. Music therapy, a review of the potential therapeutic benefits for the critically ill. J Crit Care 2016;35:195–9. doi:10.1016/j.jcrc.2016.05.021.
[29] Wong H, Lopez-Nahas V, Molassiotis A. Effects of music therapy on anxiety in ventilator-dependent patients. Heart Lung 2001;30:376–87. doi:10.1067/mhl.2001.118302.
[30] Chlan LL, Engeland WC, Savik K. Does music influence stress in mechanically ventilated patients? Intensive Crit Care Nurs 2013;29:121–7. doi:10.1016/j.iccn.2012.11.001.
[31] Chlan LL, Weinert CR, Heiderscheit A, Tracy MF, Skaar DJ, Guttormson JL, et al. Effects of patient-directed music intervention on anxiety and sedative exposure in critically ill patients receiving mechanical ventilatory support: a randomized clinical trial. JAMA 2013;309:2335–44. doi:10.1001/jama.2013.5670.
[32] Tam WWS, Wong ELY, Twinn SF. Effect of music on procedure time and sedation during colonoscopy: a meta-analysis. World J Gastroenterol 2008;14:5336–43. doi:10.3748/wjg.14.5336.
[33] Dijkstra B, Gamel C, der Bijl JV, Bots M, Kesecioglu J. The effects of music on physiological responses and sedation scores in sedated, mechanically ventilated patients. J Clin Nurs 2010;19:1030–9. doi:10.1111/j.1365-2702.2009.02968.x.
[34] Beaulieu-Boire G, Bourque S, Chagnon F, Chouinard L, Gallo-Payet N, Lesur O. Music and biological stress dampening in mechanically ventilated patients at the intensive care unit ward – a prospective interventional randomized crossover trial. J Crit Care 2013;28:442–50. doi:10.1016/j.jcrc.2013.01.007.
[35] Hunter BC, Oliva R, Sahler LJZ, Gaisser D, Salipante DM, Arezina CH. Music therapy as an adjunctive treatment in the management of stress for patients being weaned from mechanical ventilation. J Music Ther 2010;47:198–219. doi:10.1093/jmt/47.3.198.
[36] Trost WJ, Labbé C, Grandjean D. Rhythmic entrainment as a musical affect induction mechanism. Neuropsychologia 2017;96:96–110. doi:10.1016/j.neuropsychologia.2017.01.004.
[37] Clayton M, Sager R, Will U. In time with the music: the concept of entrainment and its significance for ethnomusicology. In: European meetings in ethnomusicology. Romanian Society for Ethnomusicology; 2005. p. 1–82. Vol. 11.
[38] Dimaio L. Music therapy entrainment: a humanistic music therapist's perspective of using music therapy entrainment with hospice clients experiencing pain. Music Ther Perspect 2010;28(2):106–15. doi:10.1093/mtp/28.2.106.
[39] van der Heijden MJ, Araghi SO, Van Dijk M, Jeekel J, Hunink MM. The effects of perioperative music interventions in pediatric surgery: a systematic review and meta-analysis of randomized controlled trials. PLoS One 2015;10(8):e0133608. doi:10.1371/journal.pone.0133608.
[40] Hauck M, Metzner S, Rohlffs F, Lorenz J, Engel AK. The influence of music and music therapy on pain-induced neuronal oscillations measured by magnetencephalography. Pain 2013;154(4):539–47. doi:10.1016/j.pain.2012.12.016.
[41] Viechtbauer W, Smits L, Kotz D, Budé L, Spigt M, Serroyen J, et al. A simple formula for the calculation of sample size in pilot studies. J Clin Epidemiol 2015;68(11):1375–9. doi:10.1016/j.jclinepi.2015.04.014.
[42] Spielberger CD, Gorsuch RL, Lushene PR. Cuestionario de ansiedad estado-rasgo. California: Adaptación Española: Consulting Psychologists Press, Inc; 1994.
[43] Chlan L, Savik K, Weinert C. Development of a shortened state anxiety scale from the Spielberger state-trait anxiety inventory (STAI) for patients receiving mechanical ventilatory support. J Nurs Meas 2003;11:283–93. doi:10.1891/jnum.11.3.283.61269.
[44] Perpiñá-Galvañ J, Richart-Martínez M, Cabañero-Martínez MJ, Martínez-Durá I. Validez de contenido de versión corta de la subescala del Cuestionario State-Trait Anxiety Inventory (STAI). Rev Lat Am Enfermagem 2011;19(4):882–7. doi:10.1590/S0104-11692011000400005.
[45] Perpiñá-Galvañ J, Cabañero-Martínez MJ, Richart-Martínez M. Reliability and validity of shortened state trait anxiety inventory in Spanish patients receiving mechanical ventilation. Am J Crit Care 2013;22(1):46–52. doi:10.4037/ajcc2013282.
[46] Smith BW, Dalen J, Wiggins K, Tooley E, Christopher P, Bernard J. The brief resilience scale: assessing the ability to bounce back. Int J Behav Med 2008;15(3):194–200. doi:10.1080/10705500802222972.
[47] Rodríguez-Rey R, Alonso-Tapia J, Hernansaiz-Garrido H. Reliability and validity of the brief resilience scale (BRS) Spanish version. Psychol Assess 2016;28(5):e101. doi:10.1037/pas0000191.
[48] Ely EW, Truman B, Shintani A, Thomason JW, Wheeler AP, Gordon S, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). JAMA 2003;289:2983–91. doi:10.1001/jama.289.22.2983.
[49] Rojas-Gambasica JA, Valencia-Moreno A, Nieto-Estrada VH, Méndez-Osorio P, Molano-Franco D, Jiménez-Quimbaya ÁT, et al. Transcultural and linguistic adaptation of the richmond agitation-sedation scale to Spanish. Colomb J Anesthesiol 2016;44(3):216–21. doi:10.1016/j.rcae.2016.04.005.
[50] Pion-Tonachini L, Kreutz-Delgado K, Makeig S. ICLABEL: an automated electroencephalographic independent component classifier, dataset, and website. Neuroimage 2019;198:181–97. doi:10.1016/j.neuroimage.2019.05.026.
[51] Welch P. The use of fast fourier transform for the estimation of power spectra: a method based on time averaging over short, modified periodograms. IEEE Trans Audio Electroacous 1967;15(2):70–3. doi:10.1109/TAU.1967.1161901.
[52] Rubinov M, Sporns O. Complex network measures of brain connectivity: uses and interpretations. Neuroimage 2010;52(3):1059–69. doi:10.1016/j.neuroimage.2009.10.003.
[53] Combrisson E, Vallat R, O'Reilly C, Jas M, Pascarella A, Saive AL, et al. Visbrain: a multi-purpose GPU-accelerated open-source suite for Multimodal brain data visualization. Front Neuroinform 2019:13. doi:10.3389/fninf.2019.00014.
[54] Butar F, Park JW. Permutation tests for comparing two populations. J Math Sci Math Ed 2008;3(2):19–30.
[55] Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J Royal Stat Soc: Ser B (Methodol) 1995;57(1):289–300. doi:10.1111/j.2517-6161.1995.tb02031.x.
[56] Lee OK, Chung YF, Chan MF, Chan WM. Music and its effect on the physiological responses and anxiety levels of patients receiving mechanical ventilation: a pilot study. J Clin Nurs 2005;14(5):609–20. doi:10.1111/j.1365-2702.2004.01103.x.
[57] Almerud S, Petersson K. Music therapy – a complementary treatment for mechanically ventilated intensive care patients. Intensive Crit Care Nurs 2003;19(1):21–30. doi:10.1016/S0964-3397(02)00118-0.
[58] Al-Ezzi A, Kamel N, Faye I, Gunaseli E. Review of EEG, ERP, and brain connectivity estimators as predictive biomarkers of social anxiety disorder. Front Psychol 2020;11:730. doi:10.3389/fpsyg.2020.00730.
[59] Zis P, Liampas A, Artemiadis A, Tsalamandris G, Neophytou P, Unwin Z, et al. EEG recordings as biomarkers of pain perception: where do we stand and where to go? Pain and Ther 2022;11(2):369–80. doi:10.1007/s40122-022-00372-2.
[60] Mussigmann T, Bardel B, Lefaucheur JP. Resting-state electroencephalography (EEG) biomarkers of chronic neuropathic pain. A systematic review. Neuroimage 2022;258:119351. doi:10.1016/j.neuroimage.2022.119351.
[61] Koelsch S. Brain correlates of music-evoked emotions. Nat Rev Neurosci 2014;15(3):170–80. doi:10.1038/nrn3666.
[62] Taesler P, Rose M. Prestimulus theta oscillations and connectivity modulate pain perception. J Neurosci 2016;36(18):5026–33. doi:10.1523/JNEUROSCI.3325-15.2016.
[63] Engel AK, Fries P. Beta-band oscillations – signalling the status quo? Curr Opin Neurobiol 2010;20(2):156–65. doi:10.1016/j.conb.2010.02.015.
[64] O'Kelly J, James L, Palaniappan R, Fachner J, Taborin J, Magee WL. Neurophysiological and behavioral responses to music therapy in vegetative and minimally conscious states. Front Hum Neurosci 2013;7:884. doi:10.3389/fnhum.2013.00884.
[65] Qi X, Fang J, Sun Y, Xu W, Li G. Altered functional brain network structure between patients with high and low generalized anxiety disorder. Diagnostics 2023;13(7):1292. doi:10.3390/diagnostics13071292.
[66] Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomized trials. Ann Intern Med 2010;152:726–32. doi:10.7326/0003-4819-152-11-201006010-00232.