Effect of a music intervention on anxiety in adult critically ill patients: a multicenter randomized clinical trial

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Abstract

Background: Previous studies show positive effect of music on reducing anxiety, pain, and medication requirement. Anxiety has become a more pertinent issue in the intensive care unit (ICU) since wakefulness is preferred according to recent guidelines. Nevertheless, evidence on the effect of music in ICU patients is scarce. Therefore, we studied the effect of music intervention on anxiety in ICU patients.

Methods: A multicentre randomized clinical trial was conducted between August 2020 and December 2021 in ICU's at an academic medical center and two regional hospitals. Adult critically ill patients were eligible when hemodynamically stable and communicable (Richmond agitation-sedation scale (RASS) of at least -2). Patients in the intervention arm were offered music twice daily during three days for at least 30 minutes per session. Patients in the control group received standard care. The primary outcome was anxiety level assessed with the visual analogue scale for anxiety [VAS-A; range 0-10] twice daily (morning and evening). Secondary outcomes included; 6-item state-trait anxiety inventory (STAI-6), sleep quality, delirium, heart rate, mean arterial pressure pain, RASS, medication, ICU length of stay, patients' memory and experience of ICU stay.

Results: 94 patients were included in the primary analysis. Music did not significantly reduce anxiety (VAS-A in the intervention group; 2.5(IQR 1.0-4.5), 1.8(0.0-3.6), and 2.5(0.0-3.6) on day 1,2, and 3 versus 3.0(0.6-4.0), 1.5(0.0-4.0), and 2.0(0.0-4.0) in the control group; p>0.92). Overall median daily VAS-A scores ranged from 1.5 to 3.0. Fewer patients required opioids (21 vs. 29, p=0.03) and sleep quality was lower in the music group on study day one (5.0(4.0-6.0) vs. 4.5(3.0-5.0), p=0.03). Other outcomes were similar between groups.

Conclusions: Anxiety levels in this ICU population were low, and music did not decrease anxiety. This study indicates that efficacy of music is context and intervention-dependent, given previous evidence showing decreased anxiety.

Trial Registration number:

Netherlands Trial Register: NL8595, Registered, 1 April 2020

ClinicalTrials.gov ID: NCT04796389, Registered retrospectively, 3 April 2021

Background

Anxiety is common in Intensive Care Unit (ICU) patients and occurs in 30 to 80% of patients.(1-3) However, routine assessment of anxiety is variable.(4) Anxiety in the ICU not only reduces patient comfort, but can also have behavioural and physiological consequences, e.g. through elevated stress level.(4-6) Furthermore, anxiety and pain are strongly correlated, and may reinforce each other leading to higher sedative and analgesic requirement. (2, 7) These medications are known to have negative side-effects, such as prolonged mechanical ventilation.(8-13) Furthermore, benzodiazepines are associated

with delirium.(14, 15) Currently, there are limited therapeutic options for anxiety other than analgo-sedation and there are no clear guideline recommendations for non-pharmacologic treatment of anxiety in the ICU.(4) The Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients (PADIS) strongly recommend avoiding sedatives, especially benzodiazepines, whenever possible due to negative side effects. In addition, the tendency to strive for wakefulness in ICU patients may add to the incidence and severity of anxiety.

Music may be a useful treatment to alleviate anxiety. Music as a non-pharmacologic therapy has been widely studied and has shown beneficial effects in other settings, e.g. on perioperative anxiety and pain and neurohormonal stress response.(16, 17) Other studies suggested positive effects of music interventions in the ICU on pain, anxiety, stress, and sedative, and analgesic medication requirement.(6, 18-23) An additional advantages of music is that it is risk-free. A previous randomized controlled trial by Chlan et al.(22) evaluated the effect of patient directed music intervention on anxiety in the ICU and reported a positive effect. However, it is likely that efficacy of the intervention is highly context specific and therefore may not be reproducible in other settings.

Since anxiety may be under-detected but is burdensome for patients, there is a need for effective non-pharmacologic interventions that are widely applicable and effective.(3, 7) Research on the effect of music on anxiety in wakeful ICU patients is scarce.(21) Therefore, we studied the effect of a music intervention on anxiety in critically ill patients.

Methods

Study design

This multicentre, randomized, controlled trial was conducted between August 2020 and December 2021 and took place at the ICU's of one academic and two tertiary referral hospitals in the Netherlands. The study was approved by the Medical Ethics Review Board of Erasmus MC (MEC2020-0212) and the local institutional review boards (Ikazia Hospital: IZ/705/SW2037, Haga Teaching Hospital: T20-080). The trial was registered in the Netherlands Trial Register (www.trialregister.nl, ID: NL8595) and the United States National Library of Medicine (www.clinicaltrials.gov, ID: NCT04796389). The study protocol has been previously published.(24) The study is reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement (Additional file 1).(25)

Study population

ICU patients aged 18 years or older were eligible for inclusion in the study when meeting the following criteria: hemodynamically stable, communicable (Richmond Agitation and Sedation Scale, RASS >-3 in the 24 hours before inclusion (meaning the patient was at least briefly awakened with eye contact to voice) and was considered to be able to provide information regarding anxiety level, had an expected ICU stay upon randomization of at least 48 hours, and a written informed consent was acquired from the

patient or legal representative. Exclusion criteria were: severe hearing impairment, neurological condition (e.g. severe stroke, when deemed to interfere with processing of music), insufficient knowledge of the Dutch or English language, and participation in another study that may possibly intervene with the primary outcome (level of anxiety).

Randomization and masking

Parallel block randomization was used to allocate subjects with an equal allocation ratio in either the intervention or the control group using online web-based randomization program. In order to prevent bias due to non-blinding of the outcome assessors (member of the research team or attending nurse), the patient reported outcomes were accompanied by a clear description of how they should be assessed.

Intervention

Subjects allocated to the intervention arm were offered to listen to music during three days twice per day, in the morning and evening, during at least 30 minutes per session in addition to standard care. Music intervention was provided through over-the-ear headphones connected through Bluetooth with a tablet on which music lists, based on genre, artist etc., were available, from which the patients' preferred music could be chosen. Music preference was assessed by the patients, or legal representative if the patient was not able to do so, family members, or friends at baseline directly after inclusion and randomisation (day before the start of the intervention). We discouraged patients to listen to rock and heavy metal music during the trial, since it is likely that loud and/or rock music may lack the right qualities for this setting.(26) The first session was planned in the morning, between 09.00 and 12.00 AM, the day after inclusion. The evening session was planned before intended sleep, generally between 20.00 and 23.00 PM. In agreement with the direct caregivers, patients were allowed to listen longer to music as requested by the patient or legal representative. Music was only provided when patients were conscious and could reply to the question whether they wanted to listen to music. Additionally, we encouraged nurses to document music being played apart from the music applied with the headphones within the trial protocol, although this was discouraged. Patients in the control group received standard care without structured music intervention.

Outcomes

The primary outcome was level of anxiety as assessed with the visual analogue scale for anxiety (VAS-A). In the intervention group, anxiety was assessed after the music was applied. The VAS-A is a patient reported outcome and ranges from zero to ten, whereas zero is defined as "no feeling of anxiety" and ten as "most anxious ever".(21, 22, 27) The effect of music on anxiety was also assessed using the six item State- Trait Anxiety Inventory (STAI-6, which was added as an additional anxiety assessment since it assesses anxiety dimensions, such as anxiety about an event, or anxiety level as a personal characteristic). The STAI-6 ranges from 20 to 80 and was categorized as low (score of 20-39), moderate (score of 40-59), or high anxiety level (score of 60-80))(28, 29). Furthermore, we assessed sleep quality (with a visual numeric scale ranging from one to seven, in which one indicates "did not/barely sleep" and

seven indicates “slept very well”)(30), pain (using the Critical-Care Pain observation (CPOT) in mechanically ventilated patients and the numeric rating scale (NRS)/VAS for pain in non-ventilated)(4), medication requirement (analgesics, sedatives, and antipsychotics, reported as daily administration [yes/no] and dosages), RASS, delirium (measured with the Intensive Care Delirium Screening Checklist [ICDSC]), complications related to agitation, including auto-removal of lines and tubes, time on mechanical ventilation, ICU LOS, physical parameters (heart rate [HR], and mean arterial pressure [MAP] at the time anxiety assessments, and patients’ ICU memory and experiences. Memory was evaluated with the ICU memory tool (ICUMT)(31), which we adapted and shortened to a seven-item questionnaire to avoid overlap with assessment of anxiety or delirium, and with other tools. The patient experience was evaluated in the music group using a five-item and for the control group a three-item self-made questionnaire.-

Statistical analysis

The baseline characteristics were summarized using means/median (SD/IQR) and number (percentage) for continuous and categorical variables, respectively. A sample size of 52 per group was needed to detect a 1.95 point difference in VAS-A, between the groups with a power of 80%, a two-sided alpha of 0.05, and a dropout rate of 10%, which was based on a previous trial.(22) Data analysis was performed using an intention to treat (ITT) approach for all patients who had at least one VAS-A assessed. The total mean/median of the VAS-A was calculated separately for each study day. A two-sided p-value of <0.05 was considered statistically significant. Our primary outcome, the mean VAS-A, was analyzed for days one to three separately. A multilevel linear regression with random intercepts was used to compare the change in anxiety over the three study days.(32) In the two level linear mixed models design (multilevel linear regression model), study day was set at level one, and subjects at level two. Age and sex were included as independent variables in the model. Secondary, a per-protocol analysis was performed. The secondary outcomes were analyzed using similar statistical strategy as the primary outcome. Opioid dosages were adapted into fentanyl equivalents (fentanyl intravenous (iv) + remifentanil iv(33) + (fentanyl patch/2.4)(34) +(sufentanil iv/10)(35) + (morphine iv/100)(34) + (oxycodone oral/150)(34)) and intermittent sedatives (benzodiazepines) as lorazepam equivalents (lorazepam + (temazepam/10)(36) + (oxazepam/15)(36) + (diazepam/5)(33) + (bromazepam/5)(37) + (zopiclon/3.75)(33)). Also, each STAI-6 item was analyzed separately.

Results

Between August 2020 and October 2021, 1666 patients were assessed for eligibility, of whom 195 met eligibility criteria (Fig. 1). Written informed consent was obtained from 107 patients, of whom 54 were allocated to the intervention group and 53 to the control group. The final analysis compromised 50 patients in the intervention group and 44 patients in the control group. Baseline characteristics are presented in Table 1. No differences were found in baseline characteristics between the two groups. Patients had a mean age of 62.8+/-10.3 years, were predominantly male (66%), and had mean Acute Physiology And Chronic Health Evaluation (APACHE) IV score of 62.9(29.9).

Table 1
Baseline characteristics

Characteristic	N	Control	N	Intervention	P
Age, years, mean (SD)	44	62.9 (9.1)	50	62.6 (11.3)	0.91
Male, %	28	63.6	34	68.0	0.82
Weight, kg, mean (SD)	44	89.5 (26.4)	50	87.1 (20.5)	0.62
Reasons for admission					
Medical	37	84.1	40	80.0	0.95
- COVID-19[a]	15	34.1	18	36.0	
Surgical	6	13.6	9	18.0	
Trauma	1	2.3	1	2.0	
Comorbidities, %					
- Psychiatric[b]	4	9.1	3	6.0	0.86
- Chronic pain[c]	3	6.8	5	10.0	0.86
- Cardiovascular	27	61.4	25	50.0	0.27
- Neurologic (cerebral)	6	13.6	6	12.0	0.81
- Gastro-intestinal	10	22.7	15	30.0	0.43
Hospital admission duration before inclusion, days, median (IQR)	44	17.0 (6.0-33.5)	50	16.5 (7.3–34.0)	0.72
ICU admission duration before inclusion, days	44	11.0 (3.0–28.0)	50	8.0 (3.0-29.3)	0.78
Mechanical ventilation at baseline[d], %	44	77.3	50	72.0	0.73
Pain at baseline, median (IQR)*	33	0.0 (0.0–0.0)	44	0.0 (0.0-0.4)	0.70
ICDSC at baseline, median (IQR)	41	1.0 (0.5–2.5)	46	1.3 (0.4–2.5)	0.89
Delirium at baseline, %	7	15.9	10	20.0	0.81
APACHE IV, mean (SD)	42	61.8 (25.1)	49	64.0 (33.7)	0.72
RASS at baseline, median (IQR)	40	0 (-1–0)	48	0 (-1–0)	0.57
Sleep at baseline, median (IQR)*	43	5.0 (3.0–6.0)	49	4.5 (3.5-6.0)	0.81

Characteristic	N	Control	N	Intervention	P

SD; standard deviation, ICU; Intensive Care Unit, IQR; interquartile range, ICDSC; Intensive Care Delirium Screening Checklist, APACHE; Acute Physiology And Chronic Health Evaluation, RASS; Richmond Agitation-Sedation Scale

[a]No differences in number of covid-19 patients per group (p = 1.0).

[b]Psychiatric history: depression, anxiety, substance abuse.

[c]Chronic pain history: migraine, critical illness neuropathy, plexus brachialis neuritis, hernia nucleus pulposus, problems neck for which specialized pain management is required, carpal tunnel syndrome, Bels paralysis.

[d]Baseline is defined as day 0, the day before the intervention started.

*Pain was assessed with pain (using the Critical-Care Pain observation (CPOT) in mechanically ventilated patients and the NRS/VAS for pain in non-ventilated).

Sleep was assessed with a visual numeric scale ranging from one to seven, in which one indicates “did not/barely sleep” and seven indicates “slept very well.

Primary outcome

On average patients listened 49.2+/-43.1 minutes of music per day (day 1; 64.1+/-81.7 minutes, day 2; 45.7+/-45.8 minutes, day 3; 37.9+/-55.8 minutes) in the intervention group. The median (IQR) VAS-A scores in the intervention group of 2.5 (1.0-4.5), 1.8 (0.0-3.6), and 2.5 (0.0-3.6) on respectively day one, two, and three were similar to the VAS-A scores of 3.0(0.6-4.0), 1.5(0.0–4.0), and 2.0(0.0–4.0) in the control group for both the intention to treat and per protocol analyses (Table 2, Fig. 2). Also, no significant effects were found in the mixed linear regression analysis (Additional file 2/3)

Table 2
Primary outcomes

Outcome	N	Overall Median/IQR	N	Control Median/IQR	N	Intervention Median/IQR	P value
Primary outcomes							
Intention-to-treat analysis							
VAS-A day 1	94	3.0 (1.0-4.5)	44	2.5 (1.0-4.5)	50	3.0 (0.6-4.0)	0.92
VAS-A day 2	85	1.5 (0.0–4.0)	40	1.8 (0.0-3.6)	45	1.5 (0.0–4.0)	0.98
VAS-A day 3	75	2.0 (0.0–4.0)	36	2.5 (0.0-3.6)	39	2.0 (0.0–4.0)	0.94
Per-protocol analysis							
VAS-A day 1	64	2.8 (1.0-4.5)	42	2.8 (1.0-4.5)	22	2.8 (0.6–4.4)	0.77
VAS-A day 2	56	2.0 (0.4–3.5)	37	2.0 (0.0–4.0)	19	1.0 (0.5-3.0)	0.42
VAS-A day 3	52	2.5 (0.4-4.0)	36	2.5 (0.0-3.6)	16	2.8 (0.9–4.5)	0.41
N; number of patients, IQR; interquartile range, VAS-A; visual analogue scale for anxiety							

Secondary outcomes

On the first study day patients in the control group reported a significantly higher quality of sleep than patients in the intervention group (median(IQR); 5.0(4.0–6.0) vs. 4.5(3.0–5.0), p = 0.03, Additional file 4). No other significant differences were found in the secondary outcomes.

Medication requirement

No differences were found between the intervention and control group for continuous intravenous sedatives, intermittent sedatives, and antipsychotic requirement (Additional file 5). Only on the first study day, less patients in the intervention group used opioids (21 vs. 29, p = 0.03). No differences were found between the groups for fentanyl equivalents dosages. Only two patients, one in each group, had required epidural analgesia and s-ketamine, therefore further analysis was not performed for these medications.

Complications related to agitation

Complication rates were similar between the intervention and control groups (Additional file 4).

Follow up: ICU memory and experience

Follow up was done in 64 patients, 32 in each group (Additional file 6); 20 patients died, three patients withdrew consent, six were lost to follow-up, and one patient was still admitted to the ICU at the moment of this analysis. No differences were found in memory and satisfaction regarding the ICU admission. The experience with the music intervention in the intervention group was scored as “very good” by 12.0%,

“good” by 52.0%, and “neutral” by 36.0%. 80.6% of the patients in the intervention group would listen to music during a next hospital admission. Sixty-eight percent of the patients in the control group would listen to music during a next hospital admission. The choice in music varied greatly among patients, but most commonly included pop, Dutch, and classical music.

Discussion

In this multicenter clinical trial a music intervention did not decrease anxiety levels in adult ICU patients. Opioid requirement was lower and sleep quality was worse on the first day of the music intervention, but these findings require further research. There were no effects on other (secondary) outcomes, notably no effects on medication use aimed at anxiety reduction (benzodiazepines) or associated outcomes, such as delirium.

The effect of music in the ICU has been a topic of interest in the past decades.(18, 21) The largest RCTs performed in this context by Chlan et al.(22) showed that patient directed music among ICU patients receiving ventilatory support reduced anxiety. There are several important differences between the study of Chlan et al. and our study. First, the music intervention in Chlan’s study was applied when feeling anxious in contrast to our study that provided the intervention during pre-specified moments. Further, the intervention in our study was aimed to test an immediate result of music on anxiety during three days, whereas in Chlan’s study the duration of the intervention was up to 30 days. Chlan et al. did not describe the timing and frequency of anxiety assessment in their study and tested it only once daily. Delirious patients were not excluded from our study when they seemed communicable at randomisation. These factors might have hampered anxiety assessments in our study. The median daily duration of music intervention in our group was higher, 35.0 (20.8–65.8) vs. 12.0 (0.0-796.0), although the mean durations were longer in Chlan’s trial. Finally, in Chlan’s study a third of the patients dropped out for primary outcome analysis due to less than two VAS assessments. In our study, there was a lower dropout rate of 7% (4/54) in the intervention group and 17.0% (9/53) in the control group (mostly due to ICU discharge before the intervention). Recent reviews by Bradt et al.(18) and Umbrello et al.(21) concluded that positive effects of music on anxiety could be present in respectively mechanically ventilated and ICU patients. However, the RCTs included in these reviews are of low quality. Bradt et al. could perform a meta-analysis for anxiety (VAS and STAI). Pooled analysis (288 patients) resulted in a significant 1.11 lower score in the music group. Quality of the evidence was graded as low and the clinical relevance of 1.11 mean difference is questionable.

In our study, anxiety scores were low, ranging median from 1.5 to 3.0 on the VAS-A difference (compared with a corresponding VAS-A of 5 in Chlan’s trial). The reason for this is unclear since for example sedation levels were not provided in Chlan’s trial. However, in our trial non-ventilated patients could be included who may experience less anxiety. Patients in our study were included after a median of approximately 9.5 days after ICU admission and 16.5 days after hospital admission, which may have caused habituation to the ICU/hospital environment, and thus levels of anxiety may have dropped at the moment they were

included. In the study by Chlan et al. this period was shorter, respectively 6(0–40) and 7(0–33) days for the music and control group.

We found differences between the groups in sleep quality on the first study day. Also, in a recent meta-analysis by our research group, positive effect of music on sleep quality in the ICU population was found.(38) Furthermore, on the first study day a lower amount of patients required opioids in the music group. This finding seems in line with a meta-analysis in the surgical population.(39) Further research is warranted regarding these outcomes.(2, 7) Importantly, no patient had bad experience with the intervention which supports the feasibility of the intervention.

Strengths and limitations

This is the second largest randomized controlled trial studying the effect of music on anxiety in the ICU population following a conventional trial design. However, several limitations should be discussed. This was an un-blinded trial. We chose to not include a control group with headphones without music since the Chlan trial found no difference in effect on anxiety between the headphone only and headphone with patient directed music groups. In addition, people who listen to music on a daily basis may be more willing in participating in music trials, and this a priori preference could not be easily captured, while it could have influenced the effect of the intervention on anxiety. Further we hypothesized that the effect of music intervention would be immediate, but given our results, in contrast to the Chlan trial, it cannot be excluded that a music intervention of longer duration might have been more effective due to the repeated exposure over a longer period. Further, the response rates of the anxiety questionnaires, which is dependent on patients' cognitive ability to score their own anxiety and sleep quality, was challenging since patients admitted to the ICU are often sedated hampering their cognition. Besides, they may experience delirium, and are critically ill which impedes compliance with questionnaires aimed at subjective experiences. Furthermore, the trial started in the middle of the COVID-19 pandemic. This challenged study logistics and might have impeded the quality of the anxiety assessments since adhering to the protocol for this study by nurses was sometimes felt as laborious given the high workload.

Clinical implications and future perspectives

This study shows that the previously reported benefit of music intervention on anxiety may not be reproducible and likely depends on setting, exact application method of music intervention and other factors, such as workload of nurses involved in anxiety assessments and the application of the music intervention. Further, the intervention might have a different effect in delirious patients. Clearly, subjective outcome assessments have limitations in the ICU population, since the medical condition and sedation may alter the patient's responses. We found possible adverse influence of music on sleep quality, which might have been related to the standardized application of the intervention at bedtime rather than being patient directed. Further studies should focus on factors associated with effectiveness of music intervention and this study and a previous trial provide lessons on how to apply music interventions to be effective. Still, since patients in the intervention group had a good experience with the intervention and

music has shown other positive effects in the ICU and other populations,(4, 17, 18, 38, 40) without any side-effects, it may still be considered as a useful addition to alleviate suffering of patients, especially upon patients' request.

Conclusions

In this clinical trial a music intervention did not decrease anxiety levels of adult ICU patients and did not convincingly affect any other predefined outcomes. Further research on effects of music intervention in the critically should take into consideration the methods of application (e.g. regarding timing or patient-incentive in start of the intervention), different outcomes and targets, and selection of patients.

Abbreviations

ICU Intensive Care Unit

PADIS Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients

CONSORT Consolidated Standards of Reporting Trials

RASS Richmond agitation-sedation scale

VAS-A Visual Analogue Scale for Anxiety

STAI-6 State-Trait Anxiety Inventory

CPOT Critical-Care Pain observation

NRS Numeric Rating Scale

ICDSC Intensive Care Delirium Screening Checklist

LOS Length of Stay

HR Heart Rate

MAP Mean Arterial Pressure

ICUMT ICU memory tool

SD Standard Deviation

IQR Interquartile Range

ITT Intention-to-treat

APACHE Acute Physiology And Chronic Health Evaluation

Declarations

Ethics approval and consent to participate

This study will be conducted according to the principles of the Declaration of Helsinki (64th WMA General Assembly, Fortaleza, Brazil, October 2013) and in accordance with the Medical Research Involving Human Subjects Act. The study protocol has received ethical approval from the Medical Ethical Review Committee of the Erasmus Medical Centre in Rotterdam prior to the beginning of the study. Eligible patients and/or their legal representative received an information folder and an informed consent form, and had a maximum of 48 hours to consider their participation. Participation in this study was on voluntary basis.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

None.

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Authors' Contributions

JJ and MJ conceived the study idea. EK coordinated the study. EK, TO, SS, and SW collected the data. EK and MJ interpreted the data and wrote the first draft of the manuscript. JJ, DAMPJG, MJ, TO, SS, SW critically revised the manuscript. EK, DAMPJG and MJ had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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References

1. Tate JA, Devito Dabbs A, Hoffman LA, Milbrandt E, Happ MB. Anxiety and agitation in mechanically ventilated patients. Qual Health Res. 2012;22(2):157–73.
2. Barr J, Fraser GL, Puntillo K, Ely EW, Gelinas C, Dasta JF, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013;41(1):263–306.
3. Castillo MI, Cooke M, Macfarlane B, Aitken LM. Factors associated with anxiety in critically ill patients: A prospective observational cohort study. Int J Nurs Stud. 2016;60:225–33.
4. Devlin JW, Skrobik Y, Gelinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med. 2018;46(9):e825-e73.
5. Cuesta JM, Singer M. The stress response and critical illness: a review. Crit Care Med. 2012;40(12):3283–9.
6. Khan SH, Kitsis M, Golovyan D, Wang S, Chlan LL, Boustani M, et al. Effects of music intervention on inflammatory markers in critically ill and post-operative patients: A systematic review of the literature. Heart Lung. 2018;47(5):489–96.
7. Park S, Na SH, Oh J, Lee JS, Oh ST, Kim JJ, et al. Pain and anxiety and their relationship with medication doses in the intensive care unit. J Crit Care. 2018;47:65–9.
8. Pandharipande P, Ely EW. Sedative and analgesic medications: risk factors for delirium and sleep disturbances in the critically ill. Crit Care Clin. 2006;22(2):313 – 27, vii.
9. Jean R, Shah P, Yudelevich E, Genese F, Gershner K, Levendowski D, et al. Effects of deep sedation on sleep in critically ill medical patients on mechanical ventilation. J Sleep Res. 2019:e12894.
10. Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. Chest. 1998;114(2):541–8.
11. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology. 2006;104(1):21–6.
12. Conti G, Mercurio G, Iacobone E, Auricchio D, Liberati Q. Sedation in the Intensive Care Unit. The basis of the problem. Minerva Anestesiol. 2002;68(4):240–4.
13. Foster J. Complications of Sedation in Critical Illness: An Update. Crit Care Nurs Clin North Am. 2016;28(2):227–39.
14. Ely EW, Gautam S, Margolin R, Francis J, May L, Speroff T, et al. The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med. 2001;27(12):1892–900.
15. American Geriatrics Society Expert Panel on Postoperative Delirium in Older A. American Geriatrics Society abstracted clinical practice guideline for postoperative delirium in older adults. J Am Geriatr Soc. 2015;63(1):142–50.
16. Fu VX, Oomens P, Sneiders D, van den Berg SAA, Feelders RA, Wijnhoven BPL, et al. The Effect of Perioperative Music on the Stress Response to Surgery: A Meta-analysis. J Surg Res. 2019;244:444–

55.
17. Kuhlmann AYR, de Rooij A, Kroese LF, van Dijk M, Hunink MGM, Jeekel J. Meta-analysis evaluating music interventions for anxiety and pain in surgery. Br J Surg. 2018;105(7):773–83.
18. Bradt J, Dileo C. Music interventions for mechanically ventilated patients. Cochrane Database Syst Rev. 2014(12):CD006902.
19. Garcia Guerra G, Almeida L, Zorzela L, King-Jones S, Joffe AR, Hartling L, et al. Efficacy of music on sedation, analgesia and delirium in critically ill patients. A systematic review of randomized controlled trials. J Crit Care. 2019;53:75–80.
20. Thrane SE, Hsieh K, Donahue P, Tan A, Exline MC, Balas MC. Could complementary health approaches improve the symptom experience and outcomes of critically ill adults? A systematic review of randomized controlled trials. Complement Ther Med. 2019;47:102166.
21. 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.
22. 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(22):2335–44.
23. Richard-Lalonde M, Gelinas C, Boitor M, Gosselin E, Feeley N, Cossette S, et al. The effect of music on pain in the adult intensive care unit: A systematic review of randomized controlled trials. J Pain Symptom Manage. 2019.
24. Kakar E, Van Mol M, Jeekel J, Gommers D, van der Jagt M. Study protocol for a multicentre randomised controlled trial studying the effect of a music intervention on anxiety in adult critically ill patients (The RELACS trial). BMJ Open. 2021;11(10):e051473.
25. Consolidated Standards of Reporting Trials (CONSORT) 2010. http://www.consort-statement.org/.
26. Kuhlmann AYR, de Rooij A, Hunink MGM, De Zeeuw CI, Jeekel J. Music Affects Rodents: A Systematic Review of Experimental Research. Front Behav Neurosci. 2018;12:301.
27. Abend R, Dan O, Maoz K, Raz S, Bar-Haim Y. Reliability, validity and sensitivity of a computerized visual analog scale measuring state anxiety. J Behav Ther Exp Psychiatry. 2014;45(4):447–53.
28. Marteau TM, Bekker H. The development of a six-item short-form of the state scale of the Spielberger State-Trait Anxiety Inventory (STAI). Br J Clin Psychol. 1992;31(3):301–6.
29. C.D. S. Manual for the State-Trait Anxiety Inventory (Form Y1 – Y2). Consulting Psychologists Press. 1983.
30. Smit L, Trogrlic Z, Devlin JW, Osse RJ, Ponssen HH, Slooter AJC, et al. Efficacy of halopeRIdol to decrease the burden of Delirium In adult Critically ill patiEnts (EuRIDICE): study protocol for a prospective randomised multi-centre double-blind placebo-controlled clinical trial in the Netherlands. BMJ Open. 2020;10(9):e036735.

31. Jones C, Humphris, G., Griffiths, R. Preliminary validation of the ICUM tool: a tool for assessing memory of the intensive care experience. Clinical Intensive Care. 2000.
32. Chakraborty, H.; Gu, H. A mixed models approach for intent-to-treat analysis in longitudinal clinical trials with missing data. RTI international; Research Trinagle Park, NC: RTI Press publication No. MR-0009-0903; 2009. Retrieved 5/2/12 http://www.rti.org/rtipress.
33. Girard TD, Exline MC, Carson SS, Hough CL, Rock P, Gong MN, et al. Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness. N Engl J Med. 2018;379(26):2506–16.
34. West of Scotland Chronic Pain Education Group. Pain Management. https://paindata.org/calculator.php.
35. Noordzij P.G. KM, Landman J.J. Klinische anesthesiologie. 2017.
36. Howard P, Twycross R, Shuster J, Mihalyo M, Wilcock A. Benzodiazepines. J Pain Symptom Manage. 2014;47(5):955–64.
37. VInkers CH TJ, Luykx JJ, Vis R. Kiezen voor de juiste benzodiazepine: werkingsmechanisme en farmacokinetiek. Ned Tijdschr Geneeskd 1987;131(16):651–655.
38. Kakar E, Venema E, Jeekel J, Klimek M, van der Jagt M. Music intervention for sleep quality in critically ill and surgical patients: a meta-analysis. BMJ Open. 2021;11(5):e042510.
39. Fu VX, Oomens P, Klimek M, Verhofstad MHJ, Jeekel J. The Effect of Perioperative Music on Medication Requirement and Hospital Length of Stay: A Meta-analysis. Ann Surg. 2020;272(6):961–72.
40. Kakar E, Billar RJ, van Rosmalen J, Klimek M, Takkenberg JJM, Jeekel J. Music intervention to relieve anxiety and pain in adults undergoing cardiac surgery: a systematic review and meta-analysis. Open Heart. 2021;8(1).

Figures

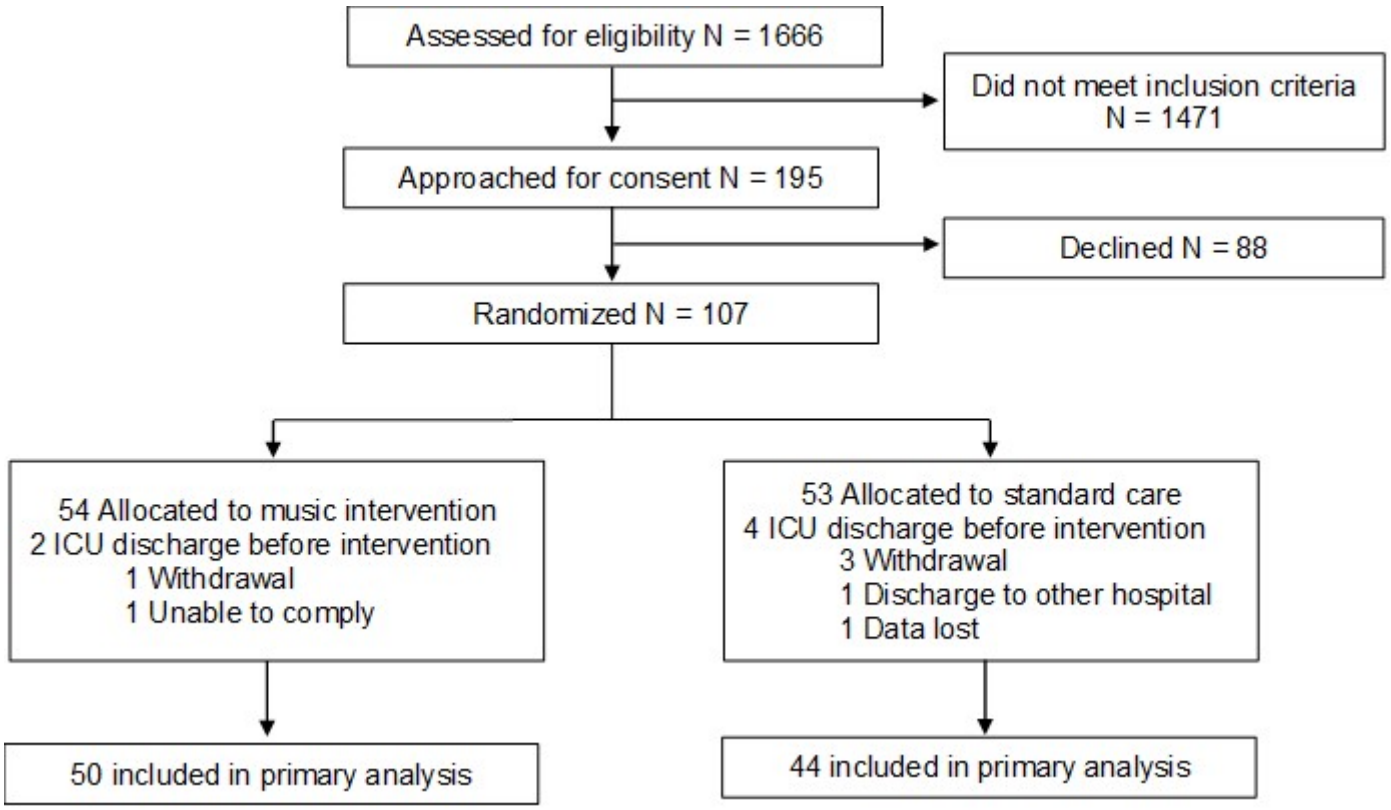

Figure 1

Participant flowchart

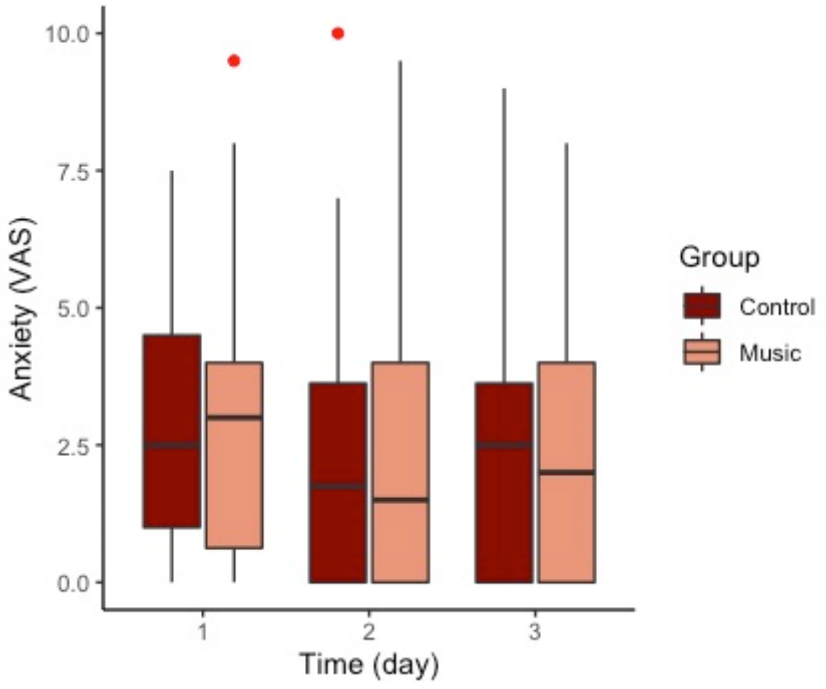

Figure 2

Median (IQR) anxiety scores per group

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