Journal of Critical Care 53 (2019) 75–80

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.journals.elsevier.com/journal-of-critical-care

Efficacy of music on sedation, analgesia and delirium in critically ill patients. A systematic review of randomized controlled trials

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ARTICLE INFO

Keywords:
Systematic review
Music
Sedation
Analgesia
Delirium

ABSTRACT

Purpose: To systematically synthesize randomized controlled trial data on the efficacy of music to provide sedation and analgesia, and reduce incidence of delirium, in critically ill patients.
Material and methods: Relevant databases (Medline, PubMed, Embase, CINAHL, Cochrane, Alt Healthwatch, LILACS, PsycINFO, CAIRSS, RILM) were searched from inception to April 26, 2018. We also searched the reference lists of included publications and for ongoing trials. The selection of relevant articles was conducted by two researchers at two levels of screening.
Data collection followed the recommendations from the Cochrane Systematic Reviews Handbook. We used the Cochrane Collaboration's tool for assessing risk of bias. Quality of the evidence was rated according to GRADE.
Results: The review identified six adult studies and no neonatal or pediatric studies. A descriptive analysis of study results was performed. Meta-analysis was not feasible due to heterogeneity. One study reported a reduction in sedation requirements with the use of music while the other five did not find any significant differences across groups.
Conclusions: This systematic review revealed limited evidence to support or refute the use of music to reduce sedation/analgesia requirements, or to reduce delirium in critically ill adults, and no evidence in pediatric and neonatal critically ill patients.

1. Background

Stress induced by pain and anxiety is common in patients in Intensive Care Units (ICUs) and can impede delivery of care and recovery [1-3]. Pharmacologic sedation and analgesia in ICUs is usually achieved with narcotics and sedatives. These drugs have significant side effects, putting patients at risk for hemodynamic and respiratory instability, prolonged mechanical ventilation, nosocomial infections, critical illness neuromyopathy, delirium, tolerance, and withdrawal symptoms [4]. These negative consequences can lead to prolonged hospital length of stay and increased health care costs [5].

Non-pharmacologic comfort measures, such as music, can be used to provide anxiolysis and relaxation [4,6-8]. Music is believed to provided sedation/analgesia by distraction, sympathetic nervous system suppression, limbic system stimulation and the release of endogenous endorphins [9,10]. However, the use of music for critically ill patients has not been well studied. A few studies have shown lower levels of anxiety, improved vital signs and lower sedatives/analgesics requirements with the use of music [11,12]. Studies in neonatal ICUs have shown that music helps stabilize vital signs and improves feeding tolerance, suggesting a relaxing effect [13]. However, evidence supporting the use of music to reduce need for sedation and/or analgesia medications in critically ill patients, including children, has not been recently synthesized [10].

We conducted a systematic review (SR) to synthesize the evidence available from randomized controlled trials (RCT) on the efficacy of music to provide sedation and analgesia, and reduce the incidence of delirium, in critically ill patients.

2. Methods

We conducted a SR to obtain a comprehensive and objective summary of the best available evidence on the effects of music for sedation

Abbreviation: CAIRSS, Computer-assisted Information retrieval service system for music; GRADE, Grading of recommendations assessment, development and evaluation; ICUs, Intensive care units; LILACS, Latin american & caribbean health sciences literature; RCT, Randomized controlled trials; RILM, Repertoire international de litterature musicale; SR, Systematic review.

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https://doi.org/10.1016/j.jcrc.2019.06.006
0883-9441/

and analgesia in ICU. The review process followed methodological standards for conducting and reporting SRs, and was registered with the PROSPERO International Register of Systematic Reviews (CRD42017082749) [14-17]. The review included all RCTs evaluating the use of music vs. routine care or placebo in critically ill patients receiving sedative and analgesic drugs. Critically ill was defined as admitted to an ICU (neonatal, pediatric or adult) and included specialized ICUs. Studies conducted in simulated environments or outside the ICU, and those in which all patients received a co-intervention were excluded. A music intervention was defined as the administration of live or recorded music in the ICU setting, regardless of how the music was selected and delivered. All types of music were included. We considered control to be those patients who received routine care (no music) or a placebo (sham) intervention such as headphones without music. Outcomes of this SR were the efficacy of music to provide sedation and analgesia in critically ill patients, and the efficacy of music to reduce the incidence of delirium. Since sedatives and narcotics are usually titrated to achieve specific sedation and/or analgesia scores, we did not include studies that did not report drug requirements.

2.1. Outcomes measures

The primary outcome of this SR was the efficacy of music to provide sedation and analgesia in critically ill patients. Sedation was defined as the administration of opioids, benzodiazepines, hypnotics or any other drug with the intention to reduce the level of consciousness and/or anxiety. Analgesia was defined as the administration of opioids, anesthetics or any other drug with the intention to reduce pain. The efficacy of music was assessed by the sedation and analgesia drug requirements. These requirements were assessed by 3 pre-specified measures of exposure: number of drugs used, frequency of intermittent doses (PRNs), and intensity (mg/kg and/or sedation intensity scores). Our secondary outcome was the efficacy of music to reduce the incidence of ICU delirium [18,19]. Delirium presence or absence was determined by clinical examination or validated scores/tools. Possible adverse effects related to the music intervention, as reported in the included trials, was also included.

2.2. Literature search

The full search strategy is outlined in Supplemental Digital Content I. Comprehensive search strategies were developed using subject headings and keywords with the assistance of a research librarian. The search was conducted in the following sources from the date of the database inception until April 26, 2018: Medline, PubMed, Embase, CINAHL, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Alt Healthwatch, LILACS (Latin-American & Caribbean Health Sciences Literature), and PsycINFO. Hand searches were conducted for Google Scholar, CAIRSS (Computer-Assisted Information Retrieval Service System for Music), RILM (Repertoire International de Litterature Musicale) Abstracts of Music Literature, and from the references list of each included study. We searched for ongoing trials in Current Controlled Trials, ClinicalTrials.Gov, and the National Research Register. No language or publication-type restrictions were applied.

2.3. Selection of relevant articles and data extraction

The selection of relevant articles was conducted at two levels of screening. Level 1 included titles and abstracts and Level 2 included full text articles. The review for relevant articles was performed independently by two researchers (LA and GGG). Those articles in which there was a disagreement were discussed between both researchers. If no consensus was reached, a third reviewer (SV) was involved. The inclusion of articles was determined using a *Relevance Assessment Form* (Supplemental Digital Content II). The final list of included publications was agreed upon by all authors. A data collection tool (Supplemental Digital Content III) was developed prior to the literature search and agreed by all authors. Data collection followed the recommendations from the Cochrane Systematic Reviews Handbook [15].

2.4. Analysis

We used the Cochrane Collaboration's tool for assessing risk of bias [15]. Two reviewers independently assessed risk of bias for each included study and the overall biases were graphed using Review Manager 5.3 (Copenhagen, Denmark). The quality of the evidence was rated according to Grading of Recommendations Assessment, Development and Evaluation (GRADE) [20].

We performed a descriptive analysis of the results reported in the included studies. We originally planned to perform a meta-analysis, and subgroup analysis based on three age groups. The limited number of studies and their heterogeneity (i.e., variability in design and outcomes measured) precluded this approach.

3. Results

The search identified 588 titles and abstracts, of which 66 were potentially relevant. The full texts of these articles were reviewed and the inclusion and exclusion criteria were applied, 45 publications were selected for possible inclusion (Fig. 1). Only 6 adult studies included sedation and/or analgesia requirements as an outcome [11,21-25], of which one also assessed ICU delirium [24]. Studies characteristics can be seen in Tables 1 and 2. Four studies included patients in a stable weaning phase of mechanical ventilation [11,21,23,24], and one study did not specify this condition [22]. The music intervention differed across studies. Only Chlan et al. used patient-selected music [11]; the other studies used music selected by the researchers. All used headphones to deliver the music. While Chlan et al. and Ames et al. used relaxing music [11,25], the other studies used classical music [21-24]. No music intervention included vocals. Timing, duration, and frequency

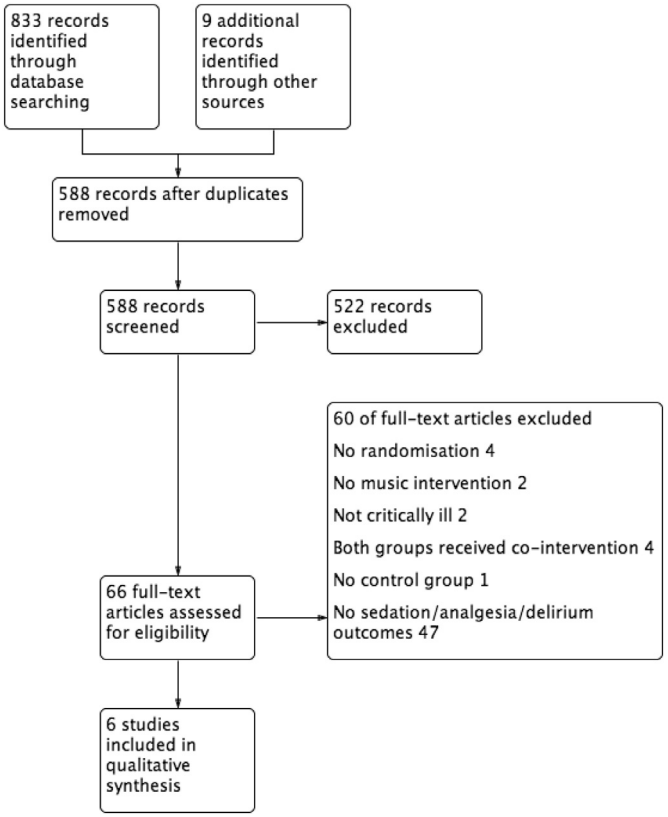

Fig. 1. Study flow diagram.

Table 1
Study design characteristics of included studies.

Publication	RCT design	Control	3rd Arm	Total n	Blinding	Allocation Concealment	Intention to treat analysis	Outcomes
Chlan et al, [9]	Parallel	Standard of care	Noise cancellation headphones	373	No	Yes	Yes	VAS-A, Sedation Intensity Score, Sedation frequency, Urine cortisol levels
Beaulieu-Boire et al, [20]	Cross-over	Headphones with no-music	–	49	Yes	Yes	Not specified	HR, RR, BP, Sedation as daily requirements, IL-6, prolactin, cortisol, ACTH, leptin, MET-enkephalin
To et al, [21]	Parallel	Headphones with no music (not noise cancellation)	–	50	Yes	Yes	Not specified	HR, RR, SBP, Ramsay Score, Success of sedation vacation.
Blankfield et al, [22]	Parallel	Standard of care	Taped therapeutic suggestions	95	No	Not specified	Not specified	Sedation and analgesia used, Anxiety, ICU length of stay.
Iblher et al, [23]	Parallel	Standard of care	Late music (after stopping sedation)	126	Not specified	Not specified	Not specified	HR, SBP, O_2Sat, inotropes, sedation, AMT, ANP, BSKE, CAM.
Ames et al, [24]	Parallel	Standard of care	–	41	No	Yes	Not specified	NRS, Pain VAS, ET-A, ER-D

AMT, Abbreviated Mental Test; ANP, Anesthesiological Questionnaire for patients after anesthesia; BSKE, Condition-scaling using classes and adjectives; ET-A, Emotional Thermometer Anxiety; ET-D, Emotional Thermometer Distress; HR, Heart rate; ICU LOS, Intensive care unit length of stay; NRS, Numerical Rating Scale; O_2Sat, Oxygen saturation; RR, Respiratory rate; SBP, Systolic blood pressure; VAS, Visual Analogue Scale; VAS-A, Visual Analogue Scale for Anxiety.

of the music intervention differed among studies. While Chlan et al. and Ames et al. allowed patients to decide when and for how long they used the intervention, others used a fixed time [11,25]. Outcomes were also different across studies. Hence, we provide a narrative description of the results of the different studies.

3.1. Risk of bias in included studies

The summary risk of bias is presented in Fig. 2 while the risk of bias for each individual trial is shown in Fig. 3. Half the studies clearly described their randomization technique and used allocation concealment [11,21,25]. Due to the nature of the intervention, patients could not be blinded; however, personnel and outcome assessment were blinded to group allocation in only two studies [21,22]. No study specifically reported deviations from the intended intervention. While other treatments between study groups seemed balanced in all of the studies, few details were available except in the Chlan et al. study, which was also the only study to specify that analysis was conducted as intention to treat [11]. Half of the studies (n = 3) were at high risk for attrition bias since they excluded enrolled patients from final analysis post-hoc. Blankfield et al. excluded 5/100 (5%) patients who died in the ICU or stayed >14 days [23]. Chlan et al. excluded 98/373 (26%) patients who remained in the study for <48 h [11]. In Iblher et al.'s study, 34/160 (21%) patients dropped out, 10 because of post-operative complications and 24 due to organizational problems [24]. Three studies were at high risk for selective reporting. Beaulieu-Boire et al. only reported a p-value for the statistical analysis of fentanyl requirements but not for benzodiazepine and hypnotic use; 95%CI for differences were not reported [21]. Iblher et al. did not report propofol use although it was part of their sedation protocol, nor did they report the evaluation of ICU delirium despite being a pre-planned outcome [24]. Similarly, Ames et al. did not report the use of benzodiazepines, and 95% CI and p-values were not reported for any outcomes [25]. To et al. reported the success rate of sedation vacations but did not provide any statistical analysis [22]. The risk of bias for each individual study is shown in Fig. 3. We were unsuccessful in contacting four authors and there was no further data available from the study by To [21-25]. Overall the quality of the evidence is low according to the GRADE method. (Table 3).

3.2. Sedation and analgesia requirements

The main results of the included studies are presented in Table 3. Blankfield et al. compared the use of music, therapeutic suggestions, and standard of care, and reported no significant difference in opioid requirements between the music and control groups [23]. Iblher et al. reported analgesia requirements by use of pethidine and piritramide separately but did not report sedation data [24]. Results of this study involved a complex 5 group comparison in which the authors did not find any statistically significant differences between groups. To et al. described the success rate of sedation holidays in patients sedated with midazolam and/or propofol [22]. Despite a higher rate of success in the music group, the difference was not statistically significant. In

Table 2
Music intervention characteristics.

Publication	Population	Mechanical ventilation	Music Intervention					
			Type of music	Selection	Time	Duration	Frequency	Days
Chlan et al, [9]	Adult mixed ICU, awake and stable	Yes	Relaxing	Patient	Day and night	As per patient	As per patient	Max.30 days
Beaulieu-Boire et al, [20]	Adults mixed ICU, stable	Yes	Classical	Music therapist	Day	60 min	2/day	2 days
To et al, [21]	Adult mixed ICU	Yes	Classical	Researcher	Day	240 min	1/day	1 day
Blankfield et al, [22]	Adult cardiac ICU post CABG/valvular surgery	Not specified	New Age Relaxing	Researcher	Day	30 min	2/day	During whole admission
Iblher et al, [23]	Adult cardiac ICU	Yes	Classical Baroque	Researcher	Day	60 min	1/day	1 day
Ames et al, [24]	Adult mixed ICU Post-surgery	No	Relaxing	Researcher	Day and night	50 min	3–6/day	2 days

CABG, coronary artery bypass grafting; ICU, Intensive care unit.

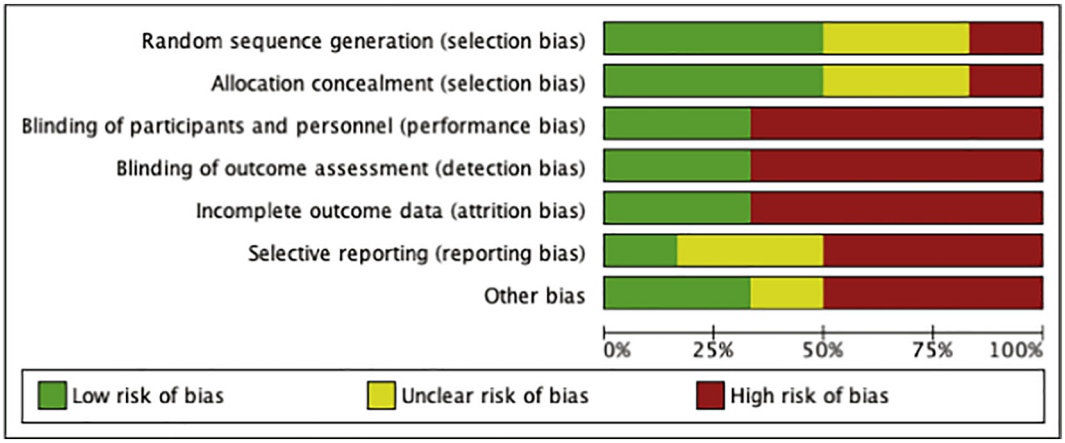

Fig. 2. Risk of bias graph (n = 6 studies).

Chlan et al.'s study, sedation exposure was reported as sedation intensity score (SIS) and sedation frequency. Only in an adjusted analysis, patients who received the music intervention had lower SIS than the control group and lower sedation frequency [11]. Beaulieu-Boire et al. evaluated daily requirements for narcotics and sedatives in a two day crossover design [21] and found no statistically significant differences in the pre/post music intervention analysis. In Ames et al.'s trial of post-operative patients, no statistically significant difference was found in intravenous opioid use nor in epidural fentanyl requirements when they compared the use of music vs. standard of care [25]. (Supplemental Digital Content IV).

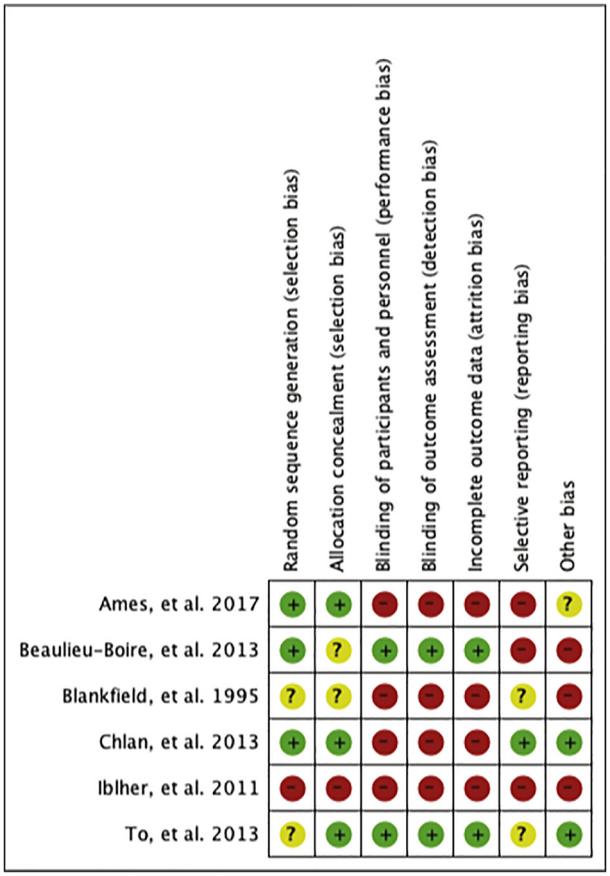

Fig. 3. Risk of bias summary.

3.3. Delirium

Only one adult study investigated the effect of music on ICU delirium. Iblher et al. assessed delirium using the Confusion Assessment Method pre-operatively and on day 3 after cardiovascular surgery [3]. The authors found no statistically significant difference between music and control groups but they did not report the p-values. Since the majority of their patients stayed in ICU for only one day, both assessments were conducted outside the ICU.

3.4. Adverse effects

No study specifically reported adverse effects of the music intervention. However, in Blankfield et al.'s study, 12% (n = 8) of the participants received the intervention (music or therapeutic suggestions) only once and refused to continue for undocumented reasons (22). On the other hand, Ilbher et al. noted that pain at the surgical site was more common in patients who received music vs no music (effect size for immediate post-operative pain −0.42; $P < 0.05$) (24). Nevertheless, when they compared patients who received music early in their admission with those who received it late (once sedation was discontinued), early music was associated with less pain at the surgical site and less discomfort (effect size 0.55; $P < 0.01$). Ames et al. conducted interviews at the end of the study and reported that patients generally had positive responses about music although they would modify the type of music and timing. Of note, 5 out of 41 patients in this study asked for music to be discontinued as it affected communication or induced them to sleep and therefore to miss analgesics.

4. Discussion

Our SR of the use of music in critically ill patients found limited evidence of its efficacy. Only six studies, all involving adult ICU patients, reported the effects of music on sedation and/or analgesia requirements, and only one of these included delirium as an outcome. We did not find any neonatal or pediatric studies meeting our inclusion criteria.

The included studies do not provide adequate evidence on the efficacy of music to provide sedation and analgesia in ICU patients, nor on the use of music to reduce the incidence of delirium. The quality of this evidence is low due to inconsistency and imprecision. Only one study demonstrated that music was statistically associated with less sedation requirements [11]. Some studies had significant methodological issues and were at risk of different types of bias. Four of six trials were either underpowered or no power calculation was provided [21-23,25].

While we were not able to perform a meta-analysis, this SR provides important information to inform future trials. The included studies had

Table 3
Summary of findings table.

Summary of findings			
Music compared to standard of care for sedation and/or analgesia in critically ill patients **Patient or population:** sedation and/or analgesia in critically ill patients **Setting:** Critically ill patients receiving sedation and/or analgesia drugs **Intervention:** Music **Comparison:** standard of care			
Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Sedation and Analgesia requirements follow up: range 1 days to 30 days	Studies showed inconsistent results with the largest study reporting a reduction in Sedation Intensity and Sedation frequency with the use of music. However, the other studies showed no benefit.	623 (6 RCTs)	⊕⊕◯◯ LOW [a,b,c]

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval
GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
[a] Only two studies clearly described the randomization technique and use concealment of allocation. Personnel and outcome assessment were only blinded in two studies. Three studies were at high risk for attrition bias and for selective reporting.
[b] Timing and length of the intervention was variable, and the majority only delivered a few music interventions. It is possible that patients were "undertreated". None of the studies evaluated sedated patients in the acute phase of their illness; and the included patients were on narcotics and sedatives for some time, with variability in the ICU length of stay at the time of study entry.
[c] Only one study reported 95%CI and they are not very wide. The other studies did not report 95%CI and the sample size for the majority of the studies was relatively small. The overall number of participants across the 6 studies is only 623, which does not meet criteria for optimal information size.

several characteristics in common. First, half used classical music [20,21,23] while the rest used "relaxing" music [11,22,25]. Although music has been used for years in healthcare, the exact mechanisms by which it may reduce pain and anxiety are not well understood. It is known that music can modify emotional status by releasing anti-stress hormones and by activating the limbic system of the brain [26]. According to the gate control theory of pain, music can block certain neural pathways and diminish the amount of perceived pain [9,11,26-28]. Stress-reducing music usually has a slow tempo (60–80 beats per minute) without significant variations in intensity [29-31]. Second, none of the included studies used vocals and all of them used headphones to deliver the music. Although there is very limited evidence that a recognizable voice can be beneficial, the logistics of applying such intervention in a large RCT would be complex [32]. The use of headphones may allow blinding of the intervention and prevent confounding by noise, which is common in the ICU setting [33]. Third, timing and length of the intervention was variable in the included studies. The majority of the included studies delivered the music intervention 1 to 2 times/day for a total of 1 to 2 days. In Chlan et al.'s study, frequency and duration were determined by patients, but long interventions in patients who are unable to control duration, may be potentially detrimental [11,26,34]. Since the "optimal dose" of music is unknown, it is possible that patients were "undertreated" and hence no effect was noted [8,11,21-25]. Fourth, it is important to note that patients in the included studies were relatively stable and the majority were in a weaning phase from their mechanical ventilation. This has two significant implications. None of the studies evaluated heavily sedated patients in the acute phase of their illness; and the included patients would have been on narcotics and sedatives for some time, with variability in the ICU length of stay at the time of study entry.

This SR has the following strengths. First, we did not limit studies by age or language. Second, only RCTs were included, in order to provide the highest level of evidence. Third, different from previous reviews, our is focus on sedation/analgesia requirements as current guidelines have suggested the use of music to reduce excessive use of these drugs [10].

The SR also has limitations. It is possible that we missed studies that were presented in conferences but not published. Sedatives and narcotics are usually titrated to achieve specific sedation/analgesia scores [6]. Hence, we did not include studies reporting sedation and/or analgesia scores unless they also report drug requirements. An association between music and better sedation/analgesia scores cannot be assumed to be beneficial unless it is also demonstrated that sedation/analgesia drug requirements are similar or lower in those who received music. We are aware of three ongoing studies (one adult, two pediatric) investigating the effect of music on sedation, and an adult pilot trial exploring the effects on delirium, but none of these are yet completed/published for potential inclusion in our review.

5. Conclusion

This SR of the efficacy of music in critically ill patients revealed limited evidence in adult critical care to support or refute the use of music to reduce sedation and analgesia requirements, or to reduce delirium. We found no evidence on the effects of music on sedation, analgesia and/or delirium in pediatric and neonatal critically ill patients. Further research is needed to determine the role of music in the ICU setting.

Authors contribution

AJ, LH, JH, SV, LA, LZ, SK and GGG participated in the design, analysis and interpretation of the results and drafted the manuscript. SK conducted the initial literature search. LA and GGG conducted the review of the literature and included studies according to the eligibility, and performed the data collection. All the authors reviewed the manuscript and approved the final version.

Financial support

Dr. Hartling is supported by a New Investigator Salary Award from the Canadian Institutes of Health Research.

Conflicts of interest

The authors have no conflict of interests to declare.

Acknowledgments

We would like to thank Orla Smith, RN PhD and Jennifer Tsang MD PhD for their review on behalf of the CCCTG.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2019.06.006.

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