Music for Sedation in Critically ill Children

by

Gonzalo Garcia Guerra

A thesis submitted in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

Medical Sciences - Paediatrics

University of Alberta

Abstract

Stress induced by pain and anxiety is common in pediatric intensive care unit (PICU) patients and can impede the delivery of critical care to children as well as their recovery. Sedation and analgesia in PICU is usually achieved through the use of various analgesics and sedatives, often narcotics and benzodiazepines. Excessive use of these drugs can put patients at risk for hemodynamic and respiratory instability, prolonged mechanical ventilation, withdrawal symptoms, nosocomial infection, delirium and critical illness polyneuromyopathy. These negative consequences lead to prolonged PICU stay and increase health care costs. Non-pharmacologic measures for analgesia and anxiolysis are those interventions that do not involve drugs, and thus may reduce the total medication requirement and their side effects. The use of non-pharmacologic interventions has been recommended by sedation guidelines for critically ill patients. Despite this, there is little evidence on which interventions should be implemented or how. The use of non-pharmacologic measures in PICU, including music, has been inadequately studied.

Available evidence has demonstrated an association between the use of music and reduced need for analgesics and anesthetics as well as lower anxiety in patients. Studies conducted in critically ill adults suggest that music reduces anxiety, sedation requirements, and may help to promote sleep in the ICU. In pediatrics, music has been studied mainly in awake children undergoing invasive or surgical procedures and has shown beneficial effects by reducing pain, stress and anxiety. However, information about the use of music in the pediatric

critical care setting is scarce. Several neonatal studies have investigated the effects of music on vital signs, pain, growth and sleep, but the majority of these studies involve stable premature infants who are not sedated or mechanically ventilated.

The use of music in critically ill children has only been explored in the recent years. Only a few small studies have used music in the PICU environment, but these studies have not clearly addressed the relationship between the use of music and sedation and analgesia requirements. Several questions about the feasibility and effectiveness of a music intervention that attempts to reduce the use of sedation and analgesia drugs in critically ill children during the acute phase of their illness remain unanswered. To answer some of these questions, this thesis includes four research studies that contribute to the current knowledge about the use of music in PICU. The study in Chapter 2 sets the stage and addresses current practice around sedation/analgesia in Canadian PICUs. Moreover, it establishes that pediatric intensivists are interested to formally investigate the use of music in PICU and suggest the most appropriate outcome for research on this topic. Chapter 3 presents evidence for the association between sound levels and sedation requirements in critically ill children. This information was needed in order to plan a study involving music and headphones, as noise is a potential confounder. In order to synthesize the available evidence on the efficacy of music on sedation, analgesia and delirium in critically ill patients, we conducted a systematic review that is presented in Chapter 4. This review revealed limited evidence to support or refute the use of music to reduce sedation/analgesia requirements, or to prevent delirium in critically ill adults, and no evidence in pediatric and neonatal critically ill patients. Hence, the first 3 studies of this thesis demonstrate: interest from the pediatric critical

care community to address the issue of whether music can be used to reduce sedation/analgesia requirements in PICU; that noise is associated with sedation/analgesia requirements and needs to be treated as a confounder; and that there is no available evidence to support or refute the use of music to reduce sedation/analgesia requirements, or to prevent delirium, in in pediatric critically ill patients. This information led to the pilot study presented in Chapter 5. In this pilot randomized controlled trial we demonstrate that a music intervention in critically ill children is feasible, and we collected the necessary information to plan a larger trial.

In summary, the four research projects presented in this thesis address important knowledge gaps around the use of music as a non-pharmacologic intervention to reduce the use of sedation/analgesia drugs in critically ill children.

Preface

This thesis is an original work by Gonzalo Garcia Guerra.

Chapter 2 of this thesis has been published as Garcia Guerra G, Joffe AR, Cave D, Duff J, Duncan S, Sheppard C, Tawfik G, Hartling L, Jou H, Vohra S; Sedation Withdrawal and Analgesia Team, and the Canadian Critical Care Trials Group. "Survey of Sedation and Analgesia Practice Among Canadian Pediatric Critical Care Physicians", Pediatr Crit Care Med. 2016 Sep;17(9):823-30. This research project received research ethics approval from the University of Alberta Health Ethics Research Board, Project Name "Survey of Sedation and Analgesia Practice among Canadian Pediatric Critical Care Physicians", No. 00048017, 05 February 2015.

Chapter 3 of this thesis has been published as Garcia Guerra G, Joffe AR, Sheppard C, Pugh J, Moez EK, Dinu IA, Jou H, Hartling L, Vohra S, Sedation Withdrawal and Analgesia Team (SWAT); Canadian Critical Care Trials Group (CCCTG). "Prospective cohort study on noise levels in a pediatric cardiac intensive care unit" J Crit Care. 2018 Apr;44:318-322. This research project received research ethics approval from the University of Alberta Health Research Ethics Board, Project Name "Noise levels in pediatric intensive care units: should we keep it down?", No. 00055313, 07 May 2015.

Chapter 4 of this thesis has been published as Garcia Guerra G, Almeida L, Zorzela L, King-Jones S, Joffe AR, Hartling L, Jou H, Vohra S; Canadian Critical Care Trials Group. "Efficacy of music on sedation, analgesia and delirium in critically ill patients. A systematic review of

randomized controlled trials" J Crit Care. 2019 Oct;53:75-80. This research project did not require approval from the University of Alberta Health Research Ethics Board.

Chapter 5 of this thesis has been submitted for publication as Garcia Guerra G, Joffe AR, Sheppard C, Hewson K, Dinu IA, Hajihosseini M, DeCaen A, Jou H, Hartling L, Vohra S; Canadian Critical Care Trials Group (CCCTG). "Music use for sedation in critically ill children (MUSiCC trial): a pilot randomized controlled trial" This research received research ethics approval from the University of Alberta Health Research Ethics Board, Project Name "MUSiCC: Pilot randomized controlled trial on Music Use for Sedation In Critically ill Children", No. 00073775, 07 December 2017.

Appendix VI of this thesis includes the protocol for the MUSiCC trial presented in chapter 5 and has been accepted for publication as Garcia Guerra G, Ari Joffe AR, Sheppard C, Hewson K, Dinu IA, deCaen A, Jou H, Hartling L, Sunita V, and the Canadian Critical Care Trials Group. "Music Use for Sedation in Critically ill Children (MUSiCC trial): study protocol for a pilot randomized controlled trial". Pilot Feasibility Stud. 2019

For all the studies presented in this thesis I was responsible for the design, analysis, interpretation as well as the manuscript composition. C Sheppard assisted in the organization and data collection for the studies in Chapter 2, 3 and 5. J Pugh assisted in the organization and data collection for the study in Chapter 3. D Cave, J Duff, S Duncan and G Tawfik were involved in the concept formation and manuscript composition for the study in Chapter 2. IA Dinu assisted with the analysis of the studies presented in Chapters 3 and 5 of this thesis. EK Moez assisted

with the analysis of the study presented in Chapters 3 of this thesis. M Hajihosseini assisted with the analysis of the studies presented in Chapters 5 of this thesis. S King-Jones, L Almeida and L Zorzela contributed with the concept formation, study design, data collection and manuscript review for the study in Chapter 4. K Hewson assisted with the concept and design for the study in Chapter 5. A DeCaen was involved in the study design and manuscript composition for the study in Chapter 5. The Sedation Withdrawal and Analgesia Team assisted with concept formation and manuscript reviews for the studies presented in Chapters 2 and 3 of this thesis. The Canadian Critical Care Trials Group assisted with concept formation and manuscript reviews for the studies presented in this thesis. A Joffe, H Jou and L Hartling were part of my thesis committee and were involved with the concept formation, interpretation and manuscript composition of all the studies within this thesis. S Vohra was the supervisory author and was involved with concept formation and manuscript composition of all the studies within this thesis.

Dedication

To God, who has given me the gift of a wonderful family and a good education.

To my parents, who have given me the love, support and education to become what I am today.

To my grandparents, who were for me an example of perseverance and hard work.

To my wife Maria, she has supported me through high school, university, residency, fellowship, a Master degree and a PhD; almost 30 years! She deserves a PhD in companionship.

To my children Pedro, Andres, Juan, Mateo, Belen, Felipe, Maria and Tomas. Each of them have contributed to my success and have made lots of sacrifices.

To my patients and their families, who have inspired me to find answers to their problems so they can have a more comfortable journey during their illness.

To all the nurses and health care workers that have helped me to conduct my research. A special thanks to our research coordinator Cathy Sheppard; I could have not done all these studies without her.

To my supervisor, Sunita Vohra, and my thesis committee members, Lisa Hartling and Hsing Jou. Their support was key in my success.

Finally, to my mentor Ari Joffe who believed in me since the day I arrived in Canada. Also, to my colleagues in PICU and PCICU who have also given me their support during all these years.

Acknowledgments

I hereby express my gratitude to my supervisory committee, Dr. Sunita Vohra, Dr. Ari R. Joffe, Dr. Hsing Jou, and Dr. Lisa Hartling. The majority of the work done as part of this thesis was funded by the Women and Children's Health Research Institute. The study presented in Chapter 4 was funded by HARD Manufacturing and the World Federation of Pediatric Intensive and Critical Care Societies. Also, I would like to thank the Canadian Critical Care Trials Group for their support.

Table of Contents

List of Table

List of Figures

List of abbreviations

Abbreviation	Definition
AMT	Abbreviated mental test
ARMA	Autoregressive Moving Average
ARIMA	Autoregressive Integrated Moving Average
ANP	Anesthesiological Questionnaire for patients after anesthesia
BSKE	Condition-scaling using classes and adjectives
CABG	Coronary Artery Bypass Grafting
CAM	Confusion Assessment Method
CAPD	Cornell Assessment of Pediatric Delirium
CCCTG	Canadian Critical Care Trials Group
CI	Confidence Interval
CRF	Case Report Form
DBP	Diastolic Blood Pressure
ECLS	Extra Corporeal Life Support
ECMO	Extra Corporeal Membrane Oxygenation
EPICORE	Epidemiology Coordinating and Research Centre
eCRF	Electronic Case Report Form
ET-A	Emotional Thermometer Anxiety
ET-D	Emotional Thermometer Distress
FLACC	Face Legs Activity Cry Consolability Scale
GRADE	Grading of Recommendations Assessment Development and Evaluation
HR	Heart Rate
ICU	Intensive Care Unit
IQR	Interquartile Range
ITT	Intention to Treat
LOS	Length of Stay
MCID	Minimally Clinical Important Difference
MODS	Multiple Organ Dysfunction Syndrome
MUSiCC	Music Use for Sedation In Critically ill Children
NICU	Neonatal Intensive Care Unit
NRS	Numeral Rating Scale
NSAIDs	Non-steroidal Anti-Inflammatory Drugs
RCT	Randomized Controlled Trial
OBWS	Opioid and Benzodiazepine Withdrawal Score
OR	Operating Room
PAED	Pediatric Anesthesia Emergence Delirium Scale
PCICU	Pediatric Cardiac Intensive Care Unit
pCAM	Pediatric Confusion Assessment Method

PELOD	Pediatric Logistic Organ Dysfunction
PICU	Pediatric Intensive Care Unit
PRISM	Pediatric Risk of Mortality Score
PRN	As needed
RASS	Richmond Agitation Sedation Scale
RR	Respiratory Rate
SAE	Serious Adverse Events
SBP	Systolic Blood pressure
SBS	State Behavioral Scale
SD	Standard Deviation
SIS	Sedation Intensity Score
SOS	Sophia Observation Withdrawal Symptoms Scale
SR	Systematic Review
STATA	Software for Statistics and Data Science
SWAT	Sedation Withdrawal and Analgesia Team
VAS	Visual Analogue Scale
VAS-A	Visual Analogue Scale-Anxiety
WAT	Withdrawal Assessment Tool
WFPICCS	World Federation of Pediatric Intensive and Critical Care Societies

Chapter 1: Introduction

1.1 Background and rationale

Stress induced by pain and anxiety is common in pediatric intensive care unit (PICU) patients and can impede the delivery of critical care to children as well as their recovery. [1] Children in PICUs experience pain and anxiety for a wide variety of reasons including current illness, separation from parents, intubation and mechanical ventilation, tubes and vascular access, post-operative pain, and invasive procedures. [2] In PICU, sedation and analgesia are not important just for comfort but also for safety. Children with inadequate sedation/analgesia are at risk for loss of vascular access, unplanned extubation, self-injury, post-traumatic stress and impaired neurodevelopment. [3] Sedation and analgesia in PICU are usually achieved through the use of various parenteral analgesics and sedatives, often narcotics and benzodiazepines. Excessive use of these drugs can put patients at risk for hemodynamic and respiratory instability, prolonged mechanical ventilation, withdrawal symptoms, nosocomial infection, delirium and critical illness polyneuromyopathy. [3] [4]These negative consequences lead to prolonged PICU stay and increase health care costs. [2] [3] [4] [5] Non-pharmacologic measures for analgesia and anxiolysis are those interventions that do not involve drugs, and thus may reduce the total medication requirement and their side effects. [5] The use of non-pharmacologic interventions has been recommended in sedation guidelines for critically ill patients. [6] [7] Despite this, there are no directions on which measures should be implemented and how. The use of non-pharmacologic measures in PICU, including music, has been inadequately studied. [5] [8] [9]

1.1.2 Music and medicine, mechanism of action

The concept of music as an intervention that can promote healing has been present in many cultures for hundreds of years. However, music has only been assessed by science in the

last century. [10] Music has been used to relieve pain and distress for patients with different illnesses. In general, music interventions in the health care setting are delivered in two main ways. [11] The use of pre-recorded music, sometimes referred to as “music medicine”, and the use of live music delivered by a specialized music therapist. The latter involves a relationship between the patient and a trained music therapist and is referred as “music therapy”. Music therapy, in turn, can be “passive” with no direct patient involvement or “active” when the patient joins the music therapist playing music. Several studies have shown that music can help to reduce pain and distress in different clinical settings. [11] Also, available evidence has demonstrated an association between the use of music and reduced need for analgesics, anesthetics, and lower vital signs (heart rate, blood pressure and respiratory rate) suggesting a relaxing effect. [11] In Lee’s meta-analysis, including 97 studies and 9,184 adult and pediatric patients in heterogeneous situations, there were no significant differences between the use of music therapy vs. music medicine. [11]

Although music has been used for many years in the healthcare setting, the exact mechanisms by which it can reduce pain and anxiety are not well understood. Part of the effects of music in the human brain can be explained by the simple process of sound. However, the perception of music is more than just the sum of its basic acoustic characteristics and involves cognitive, motor and emotional areas of the brain. [12] It is well known that music can modify emotional status. [9] According to the gate control theory of pain, activated pain receptors send signals to the brain; distracters such as music can block certain neural pathways and diminish the amount of perceived pain. [13] [14] It seems that by capturing the brain’s attention with pleasant auditory stimuli, music can block the input of noxious stimuli. [15] [16] [17] Available evidence suggests that music also alleviates pain and anxiety by releasing anti-stress hormones and by

activating the limbic system of the brain. [9] The latter mechanism is similar to other pleasant stimuli (e.g., food, sex, psychoactive drugs) and involves increased transmission in the dopaminergic system, a pathway related to reward, reinforcement and motivation. [18] [19] Other studies suggest morphine as one of the molecules involved in the process of how music induces relaxation and pain relief. Music may stimulate its release from the limbic system that then produces its effect centrally and peripherally. [20] In recent years, decreased activity from the parasympathetic system and an abnormal prolonged stress response have been proposed as among the causes for ICU delirium and systemic inflammation. [21] In this context, pain may be associated with incremental feedback causing more stress and inflammation. Stimulation of the parasympathetic system with non-pharmacologic interventions like music has the potential to not only reduce pain and anxiety but also to reduce the incidence of ICU delirium.

1.1.3 Music in Adult Intensive Care Units

A systematic review studied the available evidence for the use of music in 805 mechanically ventilated adult patients. [22] The use of music was associated with lower levels of anxiety, lower sedation requirements, and lower heart rate and respiratory rate suggesting relaxation. [23] A more recent randomized controlled trial (RCT) on patient-directed music demonstrated that music was associated with a reduction in anxiety, and in sedation requirements in critically ill adults. [23] A secondary analysis of this study showed that this intervention was not only clinically useful but also cost-effective with an estimated saving of > $2,000 /day. [24] This saving was based mainly in fewer days in mechanical ventilation. The authors suggest that impact on ICU related cost could be even larger if the music intervention is applied earlier in the ICU admission. In terms of the effects of music on pain in critically ill adults, a systematic review conducted by Richard-Lalonde et al., found that music was efficacious to reduce pain in

critically ill patients but that interventions needed to be at least 20-30 minutes long. [25] A recent study showed that music can also improve sleep in the ICU. [22] In summary, available evidence suggests that music reduces anxiety, sedation requirements, and may help to promote sleep in the adult ICU.

1.1.4 Music in the Pediatric setting

In children, music has been studied mainly in awake children undergoing invasive procedures. [14] A systematic review conducted by Klassen et al. demonstrated that music can reduce procedural pain in a variety of clinical settings. [15] A recent systematic review evaluated the effect of music on pain, stress and anxiety in children going for surgery. [9] This review, with 196 patients, showed lower pain scores and reductions in stress and anxiety with the use of music. Other studies have shown similar results. [16] [26] [27]

1.1.5 Music in Neonatal Intensive Care Units

Several studies have explored the effect of music in neonates, especially in premature infants. These studies have signifiant methodological differences and differ in terms of age range, type of intervention, duration of the intervention, and outcomes. [28] [29] [30] [31] [9]In term and premature infants, music has been shown to be effective in reducing pain and stress behaviours after invasive procedures. Some studies have also shown an association between music exposure and better sleep quality in premature infants admitted to neonatal intensive care units (NICU). [32] [33] [34]Music is also associated with more stable vital signs, increased weight gain, shorter length of stay and increased parental satisfaction. [35] [29] Several systematic reviews have shown similar results. [28] [35] [36] [37] One of the reviews suggested that studies using multiple music sessions may have a greater efficacy when compared with those using single interventions. [28] Whether this is due to multiple interventions or to their cumulative effect is

not clear. A large RCT including more than 200 neonates confirmed that music is associated with better vital signs, improved feeding behaviour and prolonged quiet time. [38] Moreover, the structured auditory stimuli of music may have a beneficial effect in the neurodevelopment of high risk infants exposed to the adverse environment of the NICU. [28] In summary, neonatal studies suggest that music is safe and beneficial even in this fragile population.

1.1.6 Music in Pediatric Intensive Care Units

The use of music in critically ill children has only been formally explored in the last few years. One of the first reports was an observational study in which two siblings with severe traumatic brain injury were exposed to familiar songs played by a music therapist. [39] A few years later, a group of researchers in Madrid conducted a series of studies exploring the use of live music played by a music therapist in the PICU environment. [40] [41] First they conducted a pilot trial involving 14 patients aged 3-6 years old. The interventions lasted 10 minutes and were performed as group or individual sessions at the time of family visits. [40] In this study, the authors excluded patients under sedation and they focused on vital signs changes before, during and after the intervention. Although they reported vital signs variability with the music intervention, these changes reflected an increase or decrease based on the intention of the interventions. In the second study conducted by this group, 87 infants < 6 months of age were subjected to an infant-adult interaction with and without music. [41] Heart rate, respiratory rate and oxygen saturations were assessed before, during and after each intervention. The music intervention consisted of live music performed by a music therapist with an electric keyboard and a Spanish classical guitar. The tempo used was 80 or 90 beats per minute depending on whether the rhythm was binary or ternary. The use of major and minor keys and the dynamics of the intervention were modified based on the infant's reaction and the environmental noise. Each

intervention lasted only 10 minutes. Although not mandatory, singing by the adult caregiver was encouraged. This study found lower heart rate and respiratory rate during and after the adult interaction with music, while oxygen saturations were higher suggesting a benefit of adding music to the infant-adult interaction. However, with the exception of the decrease in heart rate, these differences were very small and unlikely to be clinically relevant. Also, the decrease in heart rate was more pronounced with a binary rhythm compared to a ternary one. This study collected only vital signs information that, although historically used, are well known to not be an adequate surrogate of sedation and comfort in critically ill patients. Hatem et al. conducted the only RCT on music in critically ill children, who received either 30 minutes of music or placebo. They evaluated the effects of music on vital signs and pain scores. Results showed significantly lower vital signs (heart rate, respiratory rate) and pain scores in the music group. [27] However, this trial used music only once in the first 24 hours after surgery and did not investigate effects on sedation requirements. This study showed a possible benefit of music in the PICU, and made a call for further research. Whether these benefits will be observed with frequent use over several days in PICU is not clear. Three more studies have recently used music in the PICU setting. [42] [43] [44] Yurkovich et al. conducted a pilot study exposing five infants with congenital heart disease to a live music intervention conducted by a music therapist. [42] The intention of this intervention was to synchronize the music with the patient's heart rate and then decrease the tempo in order to stabilize the patient's heart rate, a process called "entrainment". Outcomes of this study were heart rate, blood pressure and oxygen saturations measured before, during and after the intervention. Music therapy entrainment was applied for 20 minutes, 3-5 times a week for a maximum of 3 weeks. The authors observed a trend towards more stable heart rates, lower blood pressure and higher oxygen saturations. In Rennick et al.'s study, music was used at the

end of a soothing (touch and reading) intervention. [43] Music was well accepted by parents and thought to calm their children (n=10). However, details on the type music and the effects on sedation requirements were not reported. On the other hand, Liu investigated the effect of music on sedation scores, vital signs and midazolam utilization (n=50). [44] They found a significant difference between groups, with improved vital signs and sedation scores suggestion a relaxing or sedative effect produced by the music intervention. However, these differences were small and may not be clinically relevant. Data on analgesia and other sedatives was not reported. Overall, these two pilot studies add to the evidence that a music intervention in PICU is well accepted by parents and the health care team and needs to be further investigated.

1.2 Potential Concerns in Critically Ill Children

Although music can have a positive effect, the contrary is also possible. [45] There is evidence that pleasant music can alleviate pain perception, but unpleasant music may have no significant effect. [46] [47] Moreover, there is a close correlation between music and physiologic responses. So, although the response to music can be subjective, the physiological reaction to this response is objective and can be monitored. [9] Music can pose a challenge for patient communication. [16] Our proposed patient population is already unable to freely communicate and is highly monitored with one nurse assigned to each patient. As recommended by the American Academy of Pediatrics, we will keep the volume < 45 dB. [48] Although music can reduce pain and anxiety, patients should not receive music as the sole source of sedation. [49] Our study aims to investigate the benefits of music as an adjunct intervention and not to completely replace the need for sedation and analgesia drugs.

1.3 Significant knowledge gaps in the use of music for critically ill children

a) The effects of music in critically ill children.

b) The optimal administration (type, mode, dose and frequency) of music in PICU.

To address these gaps, I aim to conduct a RCT to demonstrate the effects of music in critically ill children.

1.4 Magnitude of the problem and importance of this research

While children constitute only 9% of the Canadian acute care inpatient population, they are amongst the highest users of acute care services. In Edmonton alone, > 1,000 children require admission to PICU every year, with 50% of these children requiring mechanical ventilation and almost all of them needing sedation and analgesia.

I believe we have the obligation not only to help these children survive their acute illness, but also to do it while providing adequate comfort and with fewer complications.

1.5 Conceptual Framework Please refer to Appendix 1.

Chapter 2: Methods

2.1 Rationale for the Thesis

In order to provide comfort while avoiding the common complications of sedatives and narcotics in critically ill patients there has been a call for the use of non-pharmacologic interventions including music. [6] [7] Despite these recommendations, there is limited evidence on which non-pharmacologic interventions can be effectively used for sedation and analgesia in critically ill patients and on which is the best way to deliver them. The lack of evidence on this topic is even more pronounced in pediatric critical care. Almost every child admitted to a critical care unit receives, at one point of his/her admission, some kind of sedative and/or a narcotic. The administration of sedation/analgesia is one of the most common interventions provided to critically ill children, but there is limited evidence about what is the best approach to do this safely. However, it seems intuitive that non-pharmacologic interventions such as the provision of a calm, comfortable and quiet environment would help to reduce pain, anxiety and the need for excessive amounts of sedative/analgesia drugs. Why would interventions that we use to calm a healthy child not be effective in the critical care setting? On the other hand, why should we expect critically ill children to be calm and settled in an environment in which they are constantly exposed to invasive procedures, noise, light, and lack of adequate sleep, together with separation from their parents and disruption of their normal routine? The lack of available evidence in this field led me to develop a research program that would ultimately help to answer the question on whether music, as a non-pharmacologic intervention, could be used as an adjunct to provide sedation and analgesia in critically ill children. The use of music in the critical care setting by no means would pretend to be the sole treatment for anxiety and pain but could potentially provide comfort and reduce the need for sedatives and narcotics and their well-known side effects. Since

there is extremely limited available evidence on the use of music in the pediatric critical care setting, the question of whether or not music could be used to provide sedation/analgesia in critically ill children cannot be answered with a single trial. This question needs the development of a research program that would gather the necessary information to fill the knowledge gaps around the use of non-pharmacologic interventions, specifically music, in pediatric critical care. The development of this program aimed to establish: First, common practice on sedation/analgesia, including non-pharmacologic interventions, in critically ill children. Second, to determine if sound levels are associated with sedation/analgesia requirements in these children. Third, to summarize the available evidence on the use of music for sedation and analgesia in critical care. Last, to establish the feasibility of a music intervention in critically ill children and to obtain necessary information to plan a larger and definitive trial investigation on the efficacy of music for sedation/analgesia in pediatric critical care.

2.2 Research Question

Does music reduce sedation requirements and delirium in critically ill children?

2.3 Purpose statement

To conduct a research program that will lead to the development of a pilot RCT to determine the feasibility of a pediatric music medicine trial, and to study the effects of music on sedation requirements in children admitted to PICU.

2.4 Objectives

2.4.1 Describe the use of sedation, analgesia and comfort measures in Canadian PICUs.

Knowing current practice in Canadian PICUs is a necessary first step to inform the current state of practice around sedation and analgesia in critically ill children as this is the main outcome of our future clinical trial. Also, conducting the survey will give us the opportunity to evaluate if non-pharmacologic measures are being used and if there are existing protocols to guide their use. Furthermore, the survey will be able to assess pediatric intensivist interest in a clinical trial looking at the effect of music on sedation and analgesia requirements in PICU and what are clinically meaningful outcomes.

2.4.2 Determine the sound levels at one of the Stollery PICUs, the determinants of higher sound levels and the association of high levels with the need for extra-sedation.

Noise could potentially be a significant confounder for the music intervention. How much sound levels impact sedation and analgesia requirements is unknown. Therefore, to better inform the future development of a music intervention trial we will investigate noise levels in PICU and their impact on sedative and analgesic drugs administration.

2.4.3 Summarize the evidence for the use of music for sedation/analgesia in critically ill patients.

A systematic review looking at the effects of music on sedation and analgesia requirements in critical care is the next step before the design and conduct of a randomized trial on music for sedation and analgesia in critically ill children. This review will inform regarding current evidence and previous studies that have implemented a similar intervention in a critical care environment.

2.4.4 Determine the effect of music on sedation and analgesia requirements in critically ill children.

The fourth and final step is the conduct of a pilot randomized controlled trial to demonstrate feasibility of a clinical trial investigating the use of music for sedation and analgesia in critically ill children, the MUSiCC trial: Music Use for Sedation in Critically ill Children. This pilot study will also allow the collection of meaningful and accurate information for the planning and conduct of a larger clinical trial.

2.5 Hypotheses

The hypotheses for each of the studies are as follows:

a) There is significant variation in the use of sedation and analgesia in Canadian PICUs. Sedation protocols are uncommon. Comfort measures, especially music, are not commonly used.

b) Sound levels are above the recommendations in our PICU. Sound levels remain high at night. There is an association between isolation rooms and lower sound levels. Sign-over, rounds, admissions and emergency procedures are associated with higher sound levels. High sound levels are associated with the need for extra doses of sedation (PRN).

c) There is little evidence for the use of music for sedation in critically ill patients.

d) A randomized controlled trial on the use of music for sedation and analgesia in critically ill children is feasible.

2.6 Methodology for each of the studies within the research program

a) To describe the use of sedation, analgesia and comfort measures in Canadian PICUs we will conduct a physician survey.

Since there was no information on usual practice around sedation and analgesia in Canadian PICUs we decided to conduct a physician survey as the first step of this research program. The survey will allow us to establish common practices on sedation, analgesia and non-pharmacological interventions used to provide comfort in Canadian PICUs. The survey also will help us to establish if there is interest in the conduct of clinical trials to demonstrate the efficacy of non-pharmacologic interventions, including music, on sedation and analgesia of critically ill children. Moreover, we will be able to determine what Canadian pediatric intensivists consider a meaningful outcome for these trials and what would be the minimum clinically important difference (MCID) in such a trial. In order to develop the survey, a literature review will be conducted to identify the most commonly used drugs, sedation scores, and non-pharmacologic comfort measures. After identifying potential items from the literature search, focus group meetings with the Sedation Withdrawal and Analgesia Team (SWAT) will be conducted to identify other relevant items to be included in the questionnaire. SWAT is a multidisciplinary group that involves major stakeholders involved in the management of sedation and analgesia in our PICU/PCICU at the Stollery Children's Hospital. This team includes: pediatric intensivists, nurses, anesthesiologists and pharmacists. The survey will be pilot tested and validated by 5 pediatric intensivists using a clinical sensibility tool. [50] The survey will be distributed to Canadian pediatric intensivists by email using the Research Electronic Data Capture [REDCap] system. [51] Descriptive methods with mean, standard deviation (SD), and proportions will be used to describe the responses.

b) To determine the sound levels at the Stollery PICU, determinants of higher sound levels and the association of high sound levels with the need for sedation we will conduct a prospective cohort study in which sound levels will be measured continuously (24 hours/day) at the Stollery Children's Hospital PCICU.

This study is needed to determine the association of sound levels and sedation requirements. If the association is significant, this information will determine methods to deliver the music intervention in the last study of this research program and also the need for a third arm in the MUSiCC pilot RCT. In this study sound pressure levels will be recorded with a sound level meter SoundEarPro® (Sound Noise meters Inc., Berkley, MI, USA). The study will be conducted at the Stollery Children's Hospital PCICU, a unit with a large open area and two single rooms. Two noise meters will be used to measure sound in the open area and in a single room simultaneously. The study will include all children admitted to the PCICU during the study period. The following information will be recorded: unit and patient demographics, unit events and sedation use. The main outcome of this study will be sound levels. Sound levels will be recorded in slow A weighted decibels dB(A). Sound levels will be analyzed as average sound level (LAeq) and the hourly maximum sound level (LAmax). To explore the association between sedation drug use and sound levels, we will record drug use as intermittent (PRNs) doses. For the analysis sound levels will be presented as the hourly average (LAeq) and the hourly maximum (LAmax). Comparisons between day/night, week-day/weekends, and open area/single room will be performed with time series analysis using auto regressive integrated moving average (ARIMA) models. The association between unit events and sound levels will be analyzed using mixed effect models with autoregressive moving average (ARMA) covariance structure. The association

between PRN doses of sedatives and noise levels will be explored using the Granger test for causality. [52]

c) To summarize the evidence for the use of music for sedation in critically ill patients, we will conduct a systematic review on the efficacy of music on sedation and analgesia requirements, and delirium in critically ill patients.

In order to not duplicate work previously conducted by other researchers and to explore the available information on how to conduct a music intervention in the ICU setting, we conducted a systematic review (SR) on the efficacy of music on sedation and analgesia requirements, and delirium in critically ill patients. The review process will follow methodological standards for conducting and reporting systematic reviews. [53] [54] The review will include all RCTs evaluating the use of music in critically ill patients receiving sedative and analgesic drugs. The outcomes of this systematic review will be to assess the efficacy of music to provide sedation in critically ill patients, and the efficacy of music to reduce the incidence of delirium. [55] The methods for the literature search will involve a research librarian who will develop a comprehensive search strategy. Also, hand searches will be conducted of the reference lists of each included study. The selection of relevant articles will be conducted at two levels of screening by two independent researchers. For data extraction and management a data collection tool will be developed prior to the literature search and agreed upon by all authors. Data collection will follow the recommendations from the Cochrane Systematic Reviews Handbook. [54] The assessment of risk of bias of included studies will be conducted using the Cochrane Collaboration's tool for assessing risk of bias. [54] For the analysis of the results we will perform a descriptive analysis of the results reported in the included studies. We will report treatment

effects observed in the individual trials and we will attempt to perform a meta-analysis using random-effects models, as we expect heterogeneity; a subgroup analysis based on three age groups is also planned: neonatal, pediatric and adult patients.

d) To demonstrate the feasibility of a music RCT in pediatric critical care and to obtain accurate information needed to design a future larger randomized controlled trial, we will conduct a pilot 3 arm RCT.

A total of 60 patients will be randomly assigned in a 1:1:1 ratio to receive music, noise cancellation or control. The study will be conducted at the Pediatric Intensive Care Units (Pediatric Cardiac Intensive Care Unit and Pediatric General Intensive Care Unit) at the Stollery Children's Hospital. The study population included children admitted to the ICU, on sedation and receiving mechanical ventilation for > 24 hours. The interventions will consist of music and noise cancellation and will be delivered for 30 minutes, 3 times a day. The control group will receive usual care. Music will be delivered through noise cancellation headphones and an iPod touch (Apple, California). Classical music will be selected by a pediatric music therapist based on its observed properties to settle and calm children. In the noise cancellation group, the same headphones will be connected to an iPod with a silent recording. Sedation status will be assessed with the State Behavioral Scale (SBS) and withdrawal will be assessed with the Withdrawal Assessment Tool-1 (WAT-1) score; both are well validated tools. [56] [57] [58] Patients will remain on protocol for a maximum of 7 days, as long as they are on invasive mechanical ventilation and receiving sedatives. Data will be prospectively collected and variables will be recorded in an anonymized database using REDCap, Research Electronic Data Capture. [51] Primary outcome variables of this trial will be feasibility and sedation requirements. In order to

determine feasibility, we will collect information on: number of eligible patients, number of patients enrolled, rate of enrollment, time to complete participation, protocol adherence and reasons for protocol deviation. Protocol adherence will be defined as receiving the allocated intervention (30 minutes 3 times/day) at least 80% of the time that the patient remains in the study. Feasibility will be defined as a consent rate of 70% with enrolment of an average of 6 patients per month and protocol adherence of at least 80%. Secondary outcomes will include: sedation requirements captured as a daily intensity score and intermittent dose (PRN) frequency, and delirium. [23] [55] The sample size for this pilot trial was calculated based on protocol adherence as the primary outcome. Assuming a protocol acceptance/completion of 80%, 60 patients will be needed to estimate the rate within 10% with 95% confidence. [59] For the analysis, descriptive methods and binomial exact method will be used to calculate the proportion of patients who did not adhere to the protocol. Mixed-effects models will be used to analyze the primary effect of the music on sedation requirements.

Chapter 3: Survey of Sedation and Analgesia Practice Among Canadian Pediatric Critical Care Physicians

3.1 Abstract

Background: Despite the fact that almost all critically ill children experience some degree of pain or anxiety, there is a lack of high quality evidence to inform preferred approaches to sedation, analgesia, and comfort measures in this environment. We conducted this survey to better understand current comfort and sedation practices among Canadian pediatric intensivists.

Methods: The survey was conducted after a literature review and initial focus groups. The survey was then pretested and validated. The final survey was distributed by email to 134 intensivists from 17 PICUs across Canada using the Research Electronic Data Capture system.

Results: The response rate was 73% (98/134). The most commonly used sedation scores are Face, Legs, Activity, Cry, and Consolability (42%) and COMFORT (41%). Withdrawal scores are commonly used (65%). In contrast, delirium scores are used by only 16% of the respondents. Only 36% of respondents have routinely used sedation protocols. The majority (66%) do not use noise reduction methods, whereas only 23% of respondents have a protocol to promote day/night cycles. Comfort measures including music, swaddling, soother, television, and sucrose solutions are frequently used. The drugs most commonly used to provide analgesia are morphine and acetaminophen. Midazolam and chloral hydrate were the most frequent sedatives.

Conclusion: Our survey demonstrates great variation in practice in the management of pain and anxiety in Canadian PICUs. Standardized strategies for sedation, delirium and withdrawal, and sleep promotion are lacking. There is a need for research in this field and the development of evidence-based, pediatric sedation and analgesia guidelines.

3.2 INTRODUCTION

Stress secondary to pain and anxiety is common in patients in PICUs and can impede recovery and delivery of care. [60] Children admitted to PICUs experience pain and anxiety for a variety of reasons including underlying illness, invasive procedures, mechanical ventilation, monitoring, separation from parents, and loss of self-control. [2] Children with inadequate sedation and/or analgesia are at risk of loss of vascular access, unplanned extubation, self-injury, post-traumatic stress disorder, and impaired neurodevelopment. [3] Treating patients to avoid these complications is challenging. In children, the distinction between pain, anxiety, and delirium can be challenging, in part, due to developmental communication limitations and critical illness. Also, the most commonly used drugs (narcotics and benzodiazepines) can put patients at risk for hemodynamic and respiratory instability, prolonged mechanical ventilation, withdrawal symptoms, delirium, nosocomial infection, and critical illness neuromyopathy; all of which increase length of stay and healthcare costs . [60] [61] [5]Although less harmful, nonpharmacological interventions may decrease the need for these medications, they have not been adequately evaluated in PICU. [5] Finally, there is a lack of high-quality studies providing evidence for preferred approaches to sedation/analgesia and comfort measures in this environment. Previous surveys in other countries and systematic reviews on the topic have shown large variations in practice between pediatric intensive care physicians and within countries . [62] [63] [64] [65] [66] [67] [68] [69] [70] [71]However, none of these studies have shown superior outcomes with one treatment regimen versus another. The purpose of this survey was to gain a better understanding of the use of drugs and comfort measures for sedation/analgesia in Canadian PICUs in order to inform future interventional trials.

3.3 METHODS

3.3.1 Survey Development

A MEDLINE and EMBASE literature review was conducted to identify the most commonly used drugs, sedation scores, sedation-analgesia algorithms/protocols, pharmacy support, clinical practice guidelines, nonpharmacological comfort measures, and previous surveys in critically ill children. After identifying potential items from the literature search, focus group meetings with the Sedation Withdrawal and Analgesia Team (SWAT) at the Stollery Children's Hospital were conducted to identify other relevant items to be included in the questionnaire. The SWAT is a multidisciplinary team that includes pediatric intensivists, nurses, and pharmacists from the general and cardiovascular PICUs at the Stollery Children's Hospital in Edmonton, Alberta, Canada. After the main domains and items were identified, a draft questionnaire was developed. The draft questionnaire was then reviewed by four intensivists with experience in survey methodology to determine clarity of the instrument, and a final revision was agreed upon. Survey Pretesting and Validation The survey was pilot tested and validated among five pediatric intensivist members of the Canadian Critical Care Trials Group (CCCTG) using a clinical sensibility tool. [50] This was followed by semi-structured feedback on each question in the survey regarding its comprehensiveness and wording, presence of any redundant or inappropriate items, and whether the questionnaire addressed the objectives of the survey. The pilot-test responses were not included in the main reported survey results.

3.3.2 Survey Characteristics

The survey consisted of 23 questions and four clinical scenarios that varied depending upon the work setting (i.e., cardiac and/ or general PICU). The questions were primarily close ended, consisting of binary (yes/no), nominal, and ordinal response formats. Of the 27 questions, 14 also contained open-ended components. The survey had four main sections. The first section included general questions about the respondents and their units including the use of sedation/analgesia protocols, assessment scores, and comfort measures. The second section included questions on their use of drugs to provide sedation and analgesia to mechanically ventilated critically ill children. The third section asked about the minimal clinically important difference (MCID) that intensivists thought would be relevant in sedation/analgesia trials, and the need for future studies on nonpharmacological comfort measures. Finally, the fourth section included clinical scenarios of mechanically ventilated critically ill children with either chest tubes (as a clear source of pain) or poor heart function (Appendix II).

3.3.3 Survey Distribution

An email notification was sent 1 week prior to distribution of the survey to all potential participants. A week later, an invitation email was sent with an introductory letter and the link for the survey. The survey was distributed by email using an electronic, secure, survey distribution and collection system (Research Electronic Data Capture [REDCap]) hosted by the University of Alberta. [51] REDCap is a secure, web-based application that anonymizes data, aggregates results, and ensures that individual responses are not identified. The survey was initially emailed to all 146 pediatric intensive care physicians and subspecialty critical care residents/fellows from all 17 PICUs across Canada. Intensivists in training have an active role in

the prescription of sedation and analgesia, especially during night hours. Hence, they were included in this survey. The participants' email contact list was generated by the investigators and expanded upon by contacting intensivists, administrative assistants, and program directors in each PICU. The first invitation was emailed in March 2015, and up to three reminders were sent weekly to those who did not respond. As an incentive for completion of the survey, a donation to the Canadian Intensive Care Foundation was advertised if the response rate was higher than 70%. The survey was closed on April 2015. Completion and submission of the survey indicated consent to participate. Ethical approval for this study was obtained from the University of Alberta Health Research Ethics Board.

3.3.4 Statistical Analysis

Data were analyzed using the statistical data analysis package, STATA (Stata Statistical Software: Release 10, 2007; StataCorp LP, College Station, TX). Descriptive methods with mean, sds, and proportions were used to describe the responses. Pre-specified categories were created for operational beds and proportion of mechanically ventilated patients in the respondent's units to identify large- and/or high-acuity PICUs. Large-acuity PICUs were defined as having more than 10 beds. High-acuity PICUs were defined as having more than 50% of the patients on mechanical ventilation. Incomplete surveys were included as the information provided for the answered questions contribute to the evidence around a specific topic within the survey. For each particular question, the denominator is based on the number of respondents.

3.4 RESULTS

3.4.1 Demographics of the Respondents

After the initial email notification, we identified 11 physicians no longer working in PICU and one on leave who was not available to answer emails during the study period (Fig. 3.1). The overall survey response rate was 73% (98/134) (Table 3.1). At least one clinician from each of the 17 PICUs across Canada responded. Ten surveys were returned incomplete and were included in final statistical analysis. Demographics and characteristics of the respondents are shown in Table 3.1.

3.4.2 Sedation/Analgesia Assessment and Protocols

Eighty-three (84%) intensivists responded that sedation and analgesia scores are commonly used in their units. Among those who reported the use of scores, COMFORT (n = 38; 41%) and COMFORT B (n = 14; 15%) were the most common sedation scores, whereas Face, Legs, Activity, Cry, and Consolability (FLACC) (n = 42; 45%) and the Visual Analog Scale (n = 20; 22%) were the most common scores to assess pain (Figure 3.1). Withdrawal scores were commonly used with the majority of the respondents using Withdrawal Assessment Tool-1 (n = 61; 65%) followed by the Neonatal Abstinence Scoring System (Finnegan Tool; n = 33; 35%); 11% (n = 10) only use clinical suspicion, whereas 4% (n = 4) do not screen for withdrawal (Fig. 3.2). When asked about the use of a delirium score, 84% (n = 78) responded that they do not use any delirium score, whereas 12% (n = 11) did not know whether they were being used in their unit. The remainder indicated the use of a delirium score reported using either the Pediatric Confusion Assessment Method for the Intensive Care Unit or the Cornell Assessment of Pediatric Delirium (Fig. 3.3) Daily interruption of continuous sedation and analgesia is practiced by only 5% (n = 5) of respondents.

Most respondents (n = 60; 64%) indicated that they do not have routinely used sedation/analgesia protocols. When used, 82% of protocols (n = 28) are physician led, followed

by those led by nurses and pharmacists. Seventy-seven percent of the respondents (n = 75) reported having a pharmacist present during rounds 3–5 days a week, 14% (n = 14) have one present 6–7 days a week, and 7% (n = 7) never have pharmacists present during rounds.

3.4.3 PICU Environment, Noise, and Sleep Promotion

Most intensivists reported working in a PICU with a combination of single and shared rooms (69%), whereas 31% reported having only single rooms. The median (interquartile range [IQR]) proportion of patient's rooms with access to natural light is 80% (50–97%) (Table 3.1). The majority of respondents (n = 66; 70%) have no protocols in place to reduce light exposure or protocols to promote day/night cycles. Those who do use dimming of lights at night/sleep time (n= 22; 100%), mask/eye covers (n = 7; 32%), and other interventions (n = 3; 14%). When intensivists were asked about noise reduction strategies in their PICU, the majority responded that they do not use any (n = 59; 60%), 20% (n = 19) reported using earplugs, 14% (n = 13) use headphones, 12% (n = 11) have noise detectors with visual alarms, and 2% (n = 2) use other methods.

3.4.4 Sedation and Analgesia Agents

Pediatric intensivists were asked to report the frequency of continuous infusions for sedation and analgesia in critically ill intubated children, and the use of adjunct medications in the same patients. Midazolam and morphine are the agents most commonly used to provide continuous sedation in the PICU. Propofol is used as continuous infusion by at least 60% of the respondents. Chloral hydrate, diphenhydramine, and clonidine are the most common adjunct sedatives (Fig. 3.4). Morphine is the most common agent for continuous analgesia in intubated

critically ill children. Acetaminophen and ibuprofen are by farther most common adjunct analgesics (Fig. 3.5).

In order to further determine which sedative/analgesic agents are more frequently administered as a continuous infusion and how they are combined, intensivists were presented with two clinical scenarios according to their scope of practice (i.e., cardiac vs general PICU). They were asked their preference for sedation/analgesia regarding continuous infusion versus intermittent dosing and their first, second, and third medication choices for the initial and subsequent sedative/analgesic agents (in case the first choices were not adequate). Most (89%) general PICU intensivists presented with the case of a 6-monthold infant on mechanical ventilation with a chest tube, chose a continuous infusion. Morphine was the first choice for 65% of the responders, with midazolam (71%) as a second choice and dexmedetomidine (64%) as a third choice. Presented with a 10-year-old hemodynamically unstable mechanically ventilated patient with severe sepsis, almost all of the general PICU intensivists (90%) decided to start a continuous infusion for sedation. In this case, fentanyl was the first choice (40%) followed by midazolam (32%) as a second choice and ketamine (32%) as a third choice.

Cardiac PICU physicians were presented with the case of a hemodynamically stable, intubated neonate post-arterial switch repair with a mediastinal chest tube. Among cardiac intensivists, 96% decided to start a continuous infusion, with most of the respondents (63%) selecting morphine as their first choice. Midazolam (54%) and dexmedetomidine (46%) were the most common second and third choices, respectively. Presented with a case of a 7-year-old intubated patient with cardiomyopathy and very poor heart function, cardiac intensivists (87%) also chose to use a continuous infusion. Fentanyl was the first choice for 43% of the respondents, followed by dexmedetomidine (39%) and midazolam (38%).

3.4.5 Nonpharmacological Comfort Measures

Physicians were asked about nonpharmacological comfort measures for their intubated mechanically ventilated patients. The most common interventions, each used by approximately 75% of respondents, were soother/pacifier, television and videos, music, and swaddling. Sucrose solutions, holding by nurse/caregiver, rocking, noise reduction, and reading were each reported by 30–50% of respondents (Fig. 3.6). For those respondents who use music for their intubated patients, 94% use music played at the head of the bed, 43% use music played by a music therapist, and 41% use music played with headsets. The type of music is usually selected by parents/family members (91%) and nurses (73%), followed by music therapists (31%).

3.4.6 Future Steps

Pediatric intensivists were asked their opinion on whether nonpharmacological interventions or therapies to promote comfort in pediatric critical care (e.g., music therapy) should be studied in a randomized controlled trial. Eighty-five percent of the respondents answered positively. In order to inform the sample size of future studies, physicians were also asked about the MCID for sedation/analgesia in critical care whether a new safe and effective pharmacological or nonpharmacological intervention was made available to them. Intensivist reported a median (IQR) reduction in use of sedating or analgesic medications by 20% (20–25%).

3.5 DISCUSSION

This study shows that pain/sedation and withdrawal symptoms are routinely assessed in Canadian PICUs. On the other hand, sedation guidelines and protocols to safely minimize

sedation, to prevent delirium and withdrawal symptoms, and to promote sleep are lacking. Despite great variation in practice, morphine and midazolam are the most common drugs administered to provide sedation, whereas morphine and fentanyl are the most common choices for analgesia. Nonpharmacological comfort measures are commonly used in Canadian PICUs. Although the majority of children admitted to PICUs require some degree of sedation/analgesia, there are currently no clear guidelines on how this should be provided and which interventions are more effective. The last similar attempt was done almost 10 years ago when the U.K. Pediatric Intensive Care Society proposed clinical guidelines. [7]

Although informative, these guidelines have not been updated to reflect current knowledge and new therapies. During the same time period, adult guidelines have been published highlighting the importance of pain assessment, light levels of sedation, use of nonpharmacological interventions, sleep promotion, and prevention of delirium. [72] The use of guidelines, especially in combination with bundles that include spontaneous breathing trials and early mobilization, has shown to safely reduce sedation requirements, days on mechanical ventilation, ICU length of stay, and delirium. [73] [74] [75] Even more, this approach has also reduced cost related to ICU care.

One of the key points of developing sedation guidelines and protocols is the objective assessment of pain and agitation using validated, pediatric specific tools. The majority of Canadian pediatric intensivists reported the use of sedation/pain scores for the daily assessment of their patients, most commonly using COMFORT and FLACC. This proportion is similar to that reported by Twite et al. [68] in their survey of program directors in the United States. In a more recent survey, Kudchadkar et al. [65] found that although 70% of the respondents have sedation scores in place in their units, only 42% use them routinely to determine patient-care

goals. Other studies have reported the use of sedation/pain scores by only 20–50% of the units surveyed. [62] [66] [67] [69] [70]Whether these scores are actually used in the daily management of patients is not clear. The majority of previous surveys also report the COMFORT scale as most commonly used. [65] [68] [70] Although more accurate and easy to use, COMFORT B is not commonly used. [76] FLACC is frequently used to assess pain in a wide range of ages and circumstances; however, its validity outside the original population has recently been challenged. [77] Surprisingly, tools that have never been validated for children, like the Richmond Agitation-Sedation Scale, are being used. [78]

Despite existing, validated tools for the screening of opioid and benzodiazepine withdrawal symptoms, previous surveys have not explored the use of these instruments in the usual care of critically ill children. [62] [65] [66] [67] [68] [69] [70] [71] [58] [79] According to our results, among Canadian pediatric intensivists, withdrawal scores are frequently used in Canadian PICUs. The routine use of tools to detect and treat withdrawal symptoms might help to understand its risk factors, prevent its occurrence, and adequately treat those who develop symptoms.

Delirium has been increasingly recognized as a frequent complication of critical care and has been clearly associated with negative outcomes including mortality; adult sedation guidelines recommend its routine monitoring. [7] [80] However, there is a lack of high-quality pediatric studies, and current prevalence estimates range from 13% to 28%. [81] Furthermore, the best approach for prevention, detection, and management of pediatric delirium is unclear. Any treatment strategy, however, depends on recognition and routine monitoring as the necessary first step. Our study shows that delirium screening is not routinely done in Canadian PICUs, calling for the need for quality improvement initiatives to address this issue.

Although recommended by adult and pediatric sedation guidelines, sedation protocols have failed to demonstrate a clear benefit in terms of concrete outcomes (14, 30–35). [70] A systematic review conducted by Poh et al [82]highlighted the lack of evidence to support the use of sedation protocols and algorithms in pediatric critical care. Since then, three pre- and post-protocol implementation pediatric studies, and a recent large cluster randomized controlled trial found no clear benefits in the use of sedation protocols. [83] [84] [85] [86] [87]As one of the authors mentioned, a complex relationship between wakefulness, sedation, pain, and agitation may exist. [84] In our survey, sedation protocols are used only by 36% of the respondents. In contrast to most recent studies, the majority of responding physicians in our survey are using physician as opposed to nurse-driven protocols. [65] [83] [84]

It seems intuitive that a quiet environment with exposure to natural light during the day and reduced exposure to artificial light during the night will help to promote normal day/night cycles. There is evidence that suggests that single rooms improve quality of sleep and reduce the prevalence of delirium in ICU settings. [88] [89] Most Canadian PICUs still have a combination of single (mainly for isolation purposes) and shared rooms. Access to natural light is common, but protocols to reduce exposure to noise and light at nighttime are lacking. Simple interventions like eye masks, earplugs, and other noise reduction strategies have been recommended by pediatric and adult guidelines but were infrequently reported in our survey. [7] [72]

In order to provide sedation for intubated children, Canadian intensivists prefer to use drugs as a continuous infusion, with midazolam and morphine as the most common agents. These results are similar to previous surveys that report midazolam as the first choice for sedation. [62] [65] [66] [67] [70] Despite recommendations not to use propofol in critically ill children, especially as a continuous infusion, our survey shows that propofol is still being used

(although we did not determine the dose or duration being used) [7]. We also explored the use of adjunct intermittent drugs used in combination with continuous infusions. Chloral hydrate, diphenhydramine, and clonidine are common choices, something that has not been shown in previous surveys. When the intention is to provide analgesia to intubated children, respondents also prefer to use continuous infusions with morphine as their first choice. Acetaminophen is by far the most common option to provide adjunct pain relief. Interestingly, when general and cardiac pediatric intensivists were presented with a case in which the patient was hemodynamically unstable, fentanyl became their first choice to provide sedation/analgesia. This may be due to the lower prevalence of hypotension with synthetic opioids. [7] As a second choice, general intensivists were more likely to use midazolam whereas cardiac intensivists preferred dexmedetomidine.

Compared to previous surveys, dexmedetomidine has become a frequent choice for second- or third-line therapy. Our survey shows that dexmedetomidine and clonidine use are increasing. [62] [66] [68] [69] [70] [71] Interestingly, dexmedetomidine is being used for pain management when it actually has very limited analgesic effect. [72]

Nonpharmacological comfort measures have been recommended by pediatric and adult sedation guidelines. [7] [72] Comfort measure are commonly used in PICUs despite the lack of evidence of efficacy or guidelines on implementation, possibly based on data in other pediatric populations, ease of use and relatively low cost.

In our survey, soother/pacifier, television/videos, music, and swaddling were the most common interventions. Self-initiated, patient directed music has been shown to reduce the frequency and the intensity of sedation in critically ill adults. [23] Neonatal studies have also demonstrated some physiologic and behavioral benefits of music to provide comfort. [29] A high

proportion (75%) of our respondents are using music in their units. However, the majority provides this intervention with music played at the head of the bed as chosen by parents/family with little intervention from a music therapist. Whether this is an effective way to provide music to critically ill children remains unknown. Previous studies have shown that the use of noise cancellation with headphones by itself may provide some benefit. [29] In order to inform future studies, we asked the respondents whether nonpharmacological interventions to promote comfort in pediatric critical care (e.g., music therapy) should be further studied and what would be a meaningful outcome. Canadian pediatric intensivists expressed interest in formal study of nonpharmacological interventions in the PICU and provided an estimation of what intensivists would consider a meaningful and significant outcome for these studies.

This study has several strengths. This is the first Canadian survey on sedation and analgesia in critically ill children. The survey was developed and validated using strict methodology with the support of a multidisciplinary team (SWAT) and a group with extensive experience in clinical research (CCCTG). Unlike some of the previous surveys that used the PICUs as the unit of analysis, we have conducted our study at a physician level. We have achieved a response rate higher than 70% with answers from every PICU in Canada, making our results representative of common practice among Canadian pediatric intensivists. In keeping with the adult recommendations, we have explored the use of not only sedation/analgesia drugs but also sedation, withdrawal and delirium assessment, ICU environment, sleep promotion, and nonpharmacological interventions. Nonpharmacological comfort measures have not been well studied in previous surveys. We have also been able to obtain information not only on those drugs used as a continuous infusion but also about agents used as adjuncts

by intermittent doses. Using clinical scenarios, we were able to establish the intensivists' preference when faced with hemodynamically stable and unstable patients. Our study also has limitations. It was conducted in one country, representing only Canadian practice. Response bias, although unlikely based on the high response rate, cannot be excluded. Stated responses may not reflect what is actually taking place at the patients' bedside, and we cannot determine whether scores and protocols are actually used to direct goals of care. Although actively involved in the administration of sedation and analgesia, and especially in the use of nonpharmacological comfort measures, PICU nurses were not surveyed. This is because physicians are responsible for prescribing sedation and analgesia in Canadian PICUs, and nurse-driven protocols for this in Canada are rare. It is possible that physicians were not aware of some nursing practices in this area, particularly regarding nonpharmacological measures. It is important that future work considers both physician and nursing perspectives. Due to the length of the survey, we were not able to obtain details on dosing and frequency of the different pharmacological and nonpharmacological interventions.

3.6 CONCLUSION

Almost every critically ill child will receive sedation and analgesia at one point or another during his/her PICU stay. We believe that the administration of sedation and analgesia has a great impact on the outcome of critically ill children, and that the use of nonpharmacological interventions has the potential to improve outcomes. However, our survey demonstrates that there is great variation in practice and that implementation of strategies to safely minimize sedation, to prevent delirium and withdrawal symptoms, and to promote sleep are lacking. The results of this survey highlight the need for research in this field, including

pharmacokinetic/pharmacodynamic dosing, and the development of evidence-based pediatric sedation and analgesia guidelines.

Table 3.1 Demographics of survey respondents.

Demographics	n (%)
Physicians	
Staff	80 (83)
Subspecialty Critical Care Fellows or Residents	12 (12)
Clinical Assistants or Associates	5 (5)
PICU type	
General only	36 (37)
Cardiac only	9 (9)
Mixed general/cardiac	45 (46)
Separate general /cardiac	9 (7)
Years of experience in PICU	
< 1 year	2 (2)
1 to 5 years	25 (26)
6 to 10 years	23 (24)
> 10 years	47 (49)
Size of PICU	
< 10 beds	23 (24)
11 to 20 beds	52 (52)
> 20 beds	23 (24)
Proportion of intubated mechanically ventilated patients in the PICU	
< 25 %	12 (13)
25 to 50 %	38 (40)
51 to 75%	40 (42)
> 75%	6 (6)
Subspecialty Training Program in the PICU	
Yes	71 (73)
No	26 (27)
PICU layout	
Single rooms	30 (31)

Shared rooms	0 (0)
Combination single and shared rooms	67 (69)
Proportion of rooms with access to natural light (%) – Median (IQR)	80 (50-97)
Pharmacist present during rounds	
Never	7 (7)
1-2 days/week	1 (1)
3-5 days/week	75 (77)
6-7 days/week	14 (14)

Clinical Assistants or Associates: Physicians with pediatric critical care training but without a staff attending position in the PICU.PICU: Pediatric Intensive Care Unit.

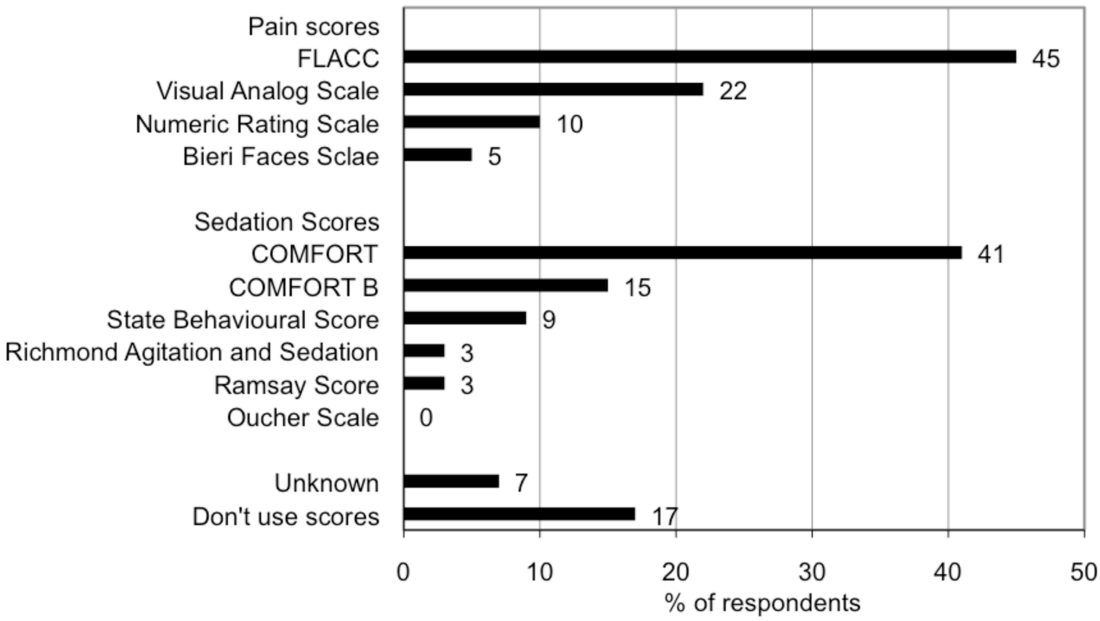


Figure 3.1 Sedation/Analgesia scores commonly used for daily assessment of critically ill children. FLACC, Face, legs, activity, cry, consolability scale; NRS, Numeric rating scale; RAAS, Richmond agitation and sedation scale; VAS, visual analog scale.

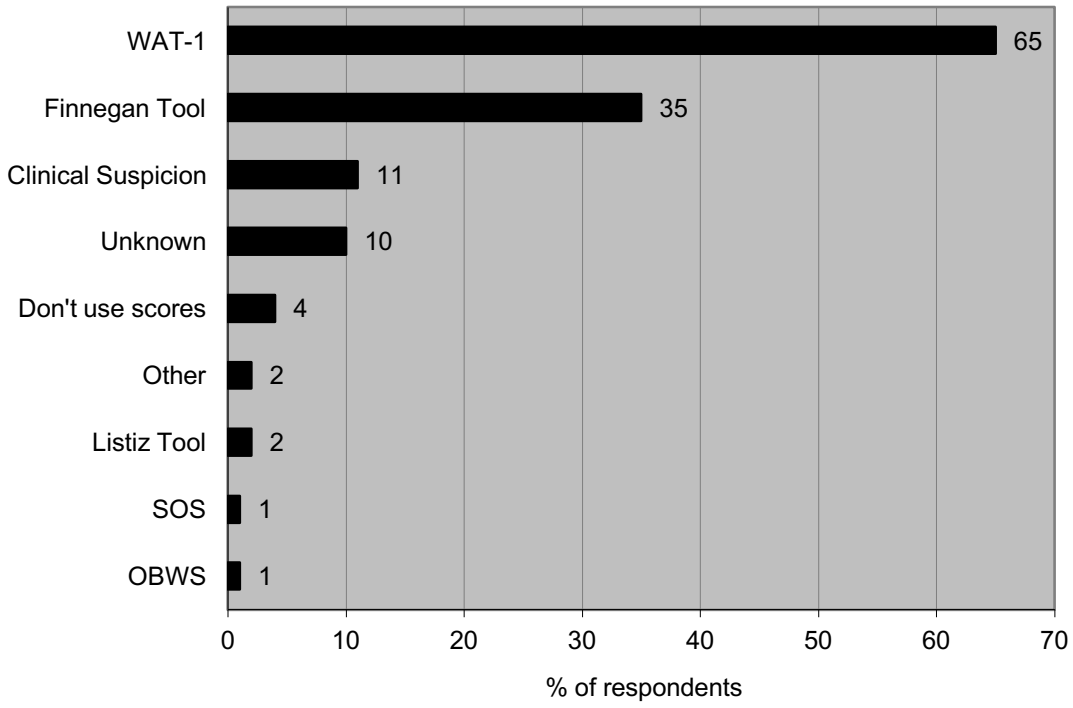


Figure 3.2 Withdrawal scores commonly used for daily assessment of critically ill children. OBWS, Opioid and Benzodiazepine Withdrawal Score; SOS, Sophia Observation Withdrawal Symptoms Scale; WAT-1, Withdrawal Assessment Tool.

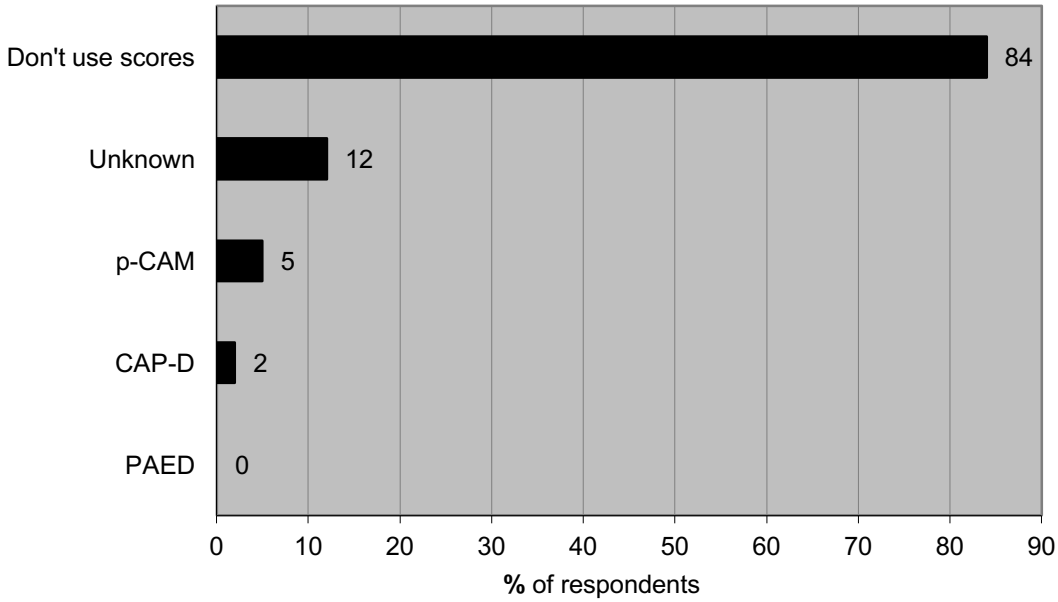


Figure 3.3 Delirium scores commonly used for daily assessment of critically ill children. CAP-D, Cornell Assessment of Pediatric Delirium; PAED, Pediatric Anesthesia Emergence Delirium Scale; p-CAM, Pediatric Confusion Assessment Method for the Intensive care unit.

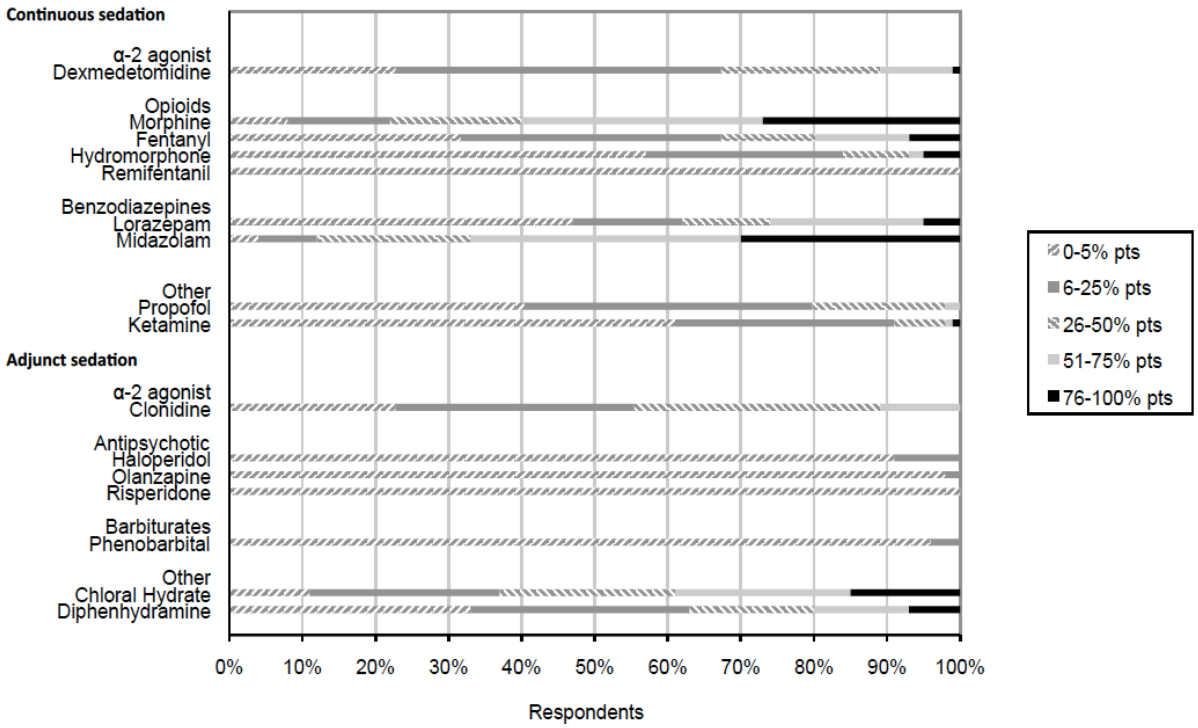


Figure 3.4 Frequency of use by respondents of various sedative agents in mechanically ventilated children in PICU. NSAIDs = nonsteroidal anti-inflammatory drugs.

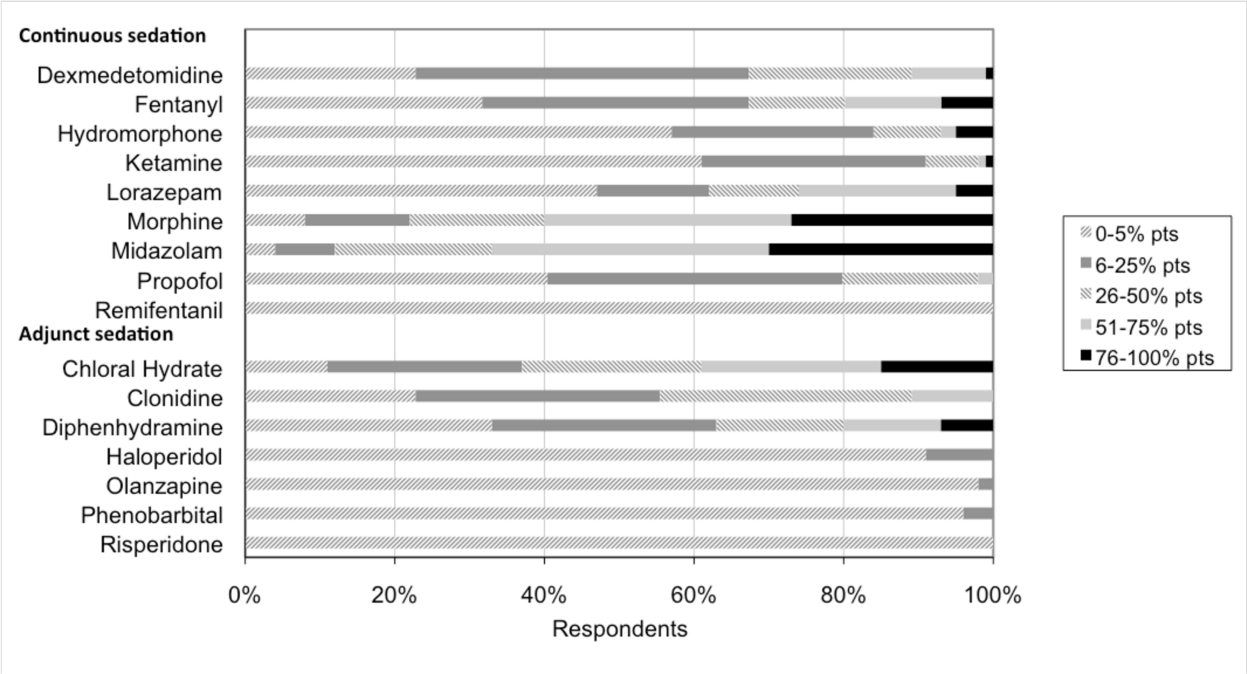


Figure 3.5 Frequency of use by respondents of various analgesic agents in mechanically ventilated children in PICU.

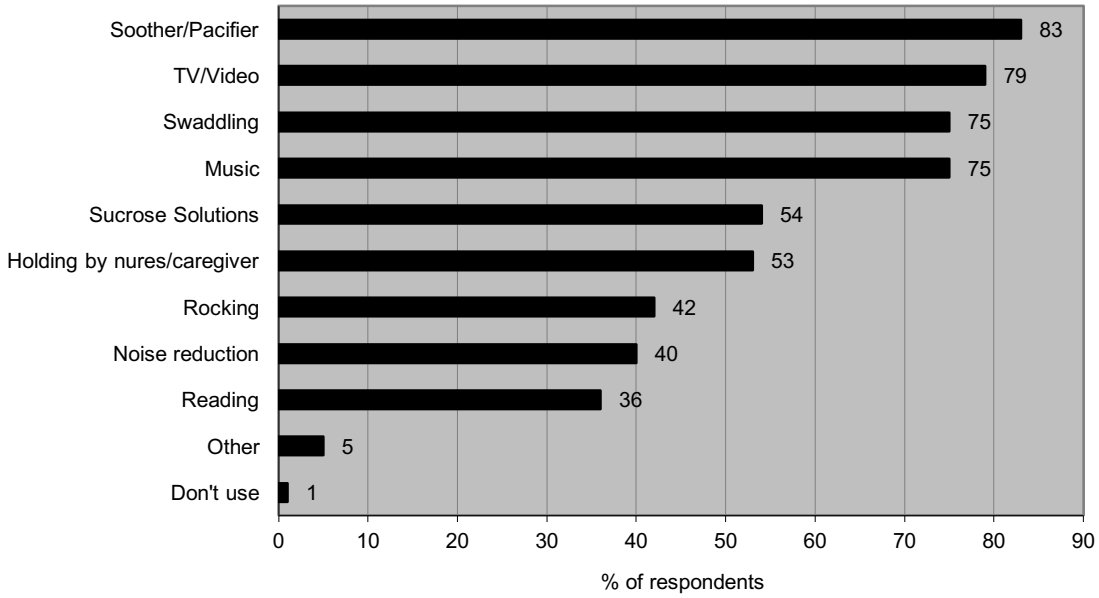


Figure 3.6 Nonpharmacological comfort measures commonly used in intubated patients.

Chapter 4: Prospective cohort study on noise levels in a pediatric cardiac intensive care unit

4.1 Abstract

Purpose

To describe noise levels in a pediatric cardiac intensive care unit, and to determine the relationship between sound levels and patient sedation requirements.

Materials and Methods

Prospective observational study at a pediatric cardiac intensive care unit (PCICU). Sound levels were measured continuously in slow A weighted decibels dB(A) with a sound level meter SoundEarPro® during a 4-week period. Sedation requirement was assessed using the number of intermittent (PRNs) doses given per hour. Analysis was conducted with autoregressive moving average models and the Granger test for causality.

Results

39 children were included in the study. The average (SD) sound level in the open area was 59.4 (2.5) dB(A) with a statistically significant but clinically unimportant difference between day/night hours (60.1 vs. 58.6; p-value < 0.001). There was no significant difference between sound levels in the open area/single room (59.4 vs. 60.8, p-value = 0.108). Peak noise levels were > 90 dB. There was a significant association between average (p-value = 0.030) and peak sound levels (p-value = 0.006), and number of sedation PRNs.

Conclusion

Sound levels were above the recommended values with no differences between day/night or open area/single room. High sound levels were significantly associated with sedation requirements.

4.2 Introduction

Sound is described as a vibration in a medium. [90] On the other hand, noise is an unpleasant sound that is disruptive and stressful. [91] [92] The World Health Organization and Environmental Protection Agency recommend that hospital sound levels not exceed 40–45 dB(A) during the day and 35 dB(A) at night. [93] [94] The American Academy of Pediatrics has recommended keeping sound levels b45 dB (A) in hospitals. [91] Sound levels above 50 dB(A) are sufficient to cause sleep disturbance, and sustained levels above 85 dB(A) can damage hearing. [95] In recent years, there has been increased concern about noise in hospitals, especially in intensive care units (ICUs). [96] [97]

High sound levels in hospitals have been associated with patient discomfort, stress, abnormal sleep, increased length of stay, sensitivity to pain, and delirium. [98] [99] [100] [101] [102] [103] [104] [105]ICUs are busy environments in which equipment, alarms, staff communication, and frequent transit contribute as sources of noise. [106] [107]Studies conducted in pediatric intensive care units (PICUs) have all found that sound levels exceed the recommendations. [95] [106] [108] [109] [110] [111] [112] [113] High sound levels in the PCICU environment can lead to discomfort, sleep disturbance, delirium and hemodynamic instability related to agitation or the use of sedation to control it. [114] These effects may be particularly important in young children in the PCICU who are recovering from complex cardiac surgery, often with single ventricle physiology, being very sensitive to changes in systemic and pulmonary vascular resistances and heart rate, and already at significant risk of hearing impairment. [115]

The primary objective of this study was to describe sound levels in the pediatric cardiac intensive care unit (PCICU), and to test whether these levels were above recommended standards. Our secondary objectives were to a) identify pre-specified major events that may contribute to high sound levels, b) compare sound levels between different areas of the unit, and c) explore the association between sound levels and patient sedation/analgesia requirements. We hypothesized that our PCICU has higher than recommended sound levels, that open areas are louder than single rooms, and that high sound levels are associated with patient discomfort as measured by increased requirements for sedation/analgesia drugs.

4.3 Methods

We conducted a prospective cohort study in which sound levels were measured continuously (24 h/day) at the Stollery Children's Hospital PCICU from mid-September 2015 to mid-October 2015. Recording over a one month provided sound level measurements that were representative of our unit and independent of specific staff or circumstances any particular day. Sound pressure levels were recorded with a sound level meter SoundEarPro® (Sound Noise meters Inc., Berkley, MI, USA). SoundEarPro® provides one-second noise levels in slow A weighted decibels dB(A), within a frequency of 20 Hz to 16 kHz, a range of 40 to 135 dB and a standard deviation of ±3 dB.

The Stollery Children's Hospital PCICU is a 10 bed unit with a large open area (8 beds) and 2 single rooms. Two noise meters were used to measure sound in the open area and in one of the single room simultaneously. In the single room, the device was placed 60 cm from the head of the patient; in the open area, the device was placed at a bedside in the center of the unit. To prevent the Hawthorne effect, the devices were installed in the unit one week prior to study

initiation. Staff outside the research team were unaware of the exact date of study initiation (i.e. onset of recording). Daytime was defined as between 7 am and 7 pm, and nighttime as between 7 pm and 7 am. [95] Weekdays was between Monday 7 am and Friday at 4 pm (based on our call system), and weekends between Friday at 4 pm and Monday at 7 am.

We included all children admitted to the PCICU during the study period, and only excluded those patients admitted to the single room in which there was not a noise meter in place.

During the study period the following information was recorded: unit and patient demographics, major events potentially associated with higher sound levels, and sedation/analgesia use. The following events were identified a priori by the Sedation Withdrawal and Analgesia Team (SWAT) as potentially significant noise events in PCICU: nursing sign over, patient rounds (physician rounds), admissions, discharges, intubations, code blues, and extracorporeal life support (ECLS) cannulations. SWAT is a multi-disciplinary research team within the Stollery Children's Hospital ICUs and includes nurses, pharmacists, anesthetists and critical care physicians.

To explore the association between sedation drug use and sound levels, we recorded drug use as intermittent (PRNs) doses. PRN doses were considered since they represent the response of nurses to acute agitation/discomfort. Continuous infusions of sedatives were not taken into account since they may change based on clinical progression (titration up when patient is admitted and titration down during recovery and weaning) and also may be adjusted based on sedation requirements that occur hours or even days before. These characteristics make it impossible to correlate changes in continuous infusions with the temporary acute event of changes in sound levels. The following PRN drugs were included: opioids, benzodiazepines,

chloral hydrate, and ketamine. Those PRN doses given for pain and/or anxiety related to invasive procedures were not included in the analysis.

There were no other study related interventions, and the clinical care of the patients was according to usual practice and directed by the attending physician and the bedside nurse. The study was funded by the Women and Children's Health Research Institute, and was approved by the University of Alberta Health Research Ethics Board (Pro 00055313).

4.4 Statistical analysis

Categorical variables are described as frequencies and percentage (%), and continuous variables are described as means and standard deviation (SD) or median and interquartile range (IQR) as appropriate. Sound levels are presented as the hourly average sound level (LAeq) and the hourly maximum sound level (LAmax). Comparisons between day/night, week-day/weekends, and open area/single room were performed with time series analysis using auto regressive integrated moving average (ARIMA) models to account for the serial correlation of sound levels over time. The association between unit events and sound levels was analyzed using mixed effect models with autoregressive moving average (ARMA) covariance structure. Results are presented as regression coefficients along with 95%CI and two-sided p values. The association between sedation PRNs and noise levels was explored using the Granger test for causality. [52] The Granger test can be used to evaluate if a time series of X values (sound levels) can provide statistically significant information about future values of Y (sedation PRNs) more than the previous values of Y alone. This is accomplished by taking different lags of one series (sound levels) and using that to model the change in the second series (sedation PRNs).

We considered statistically significant those variables that have a p value of < 0.05. Statistical analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

4.5 Results

During the study 39 children were admitted to the PCICU and met eligibility criteria. Demographics and clinical characteristics of the patients are shown in Table 4.1. In the open area of the PCICU the LAeq (SD) level was 59.4 (2.56) dB. There was a statistically significant difference between the LAeq (SD) levels during day-time 60.1 (2.03) dB and night-time hours 58.6 (2.7) dB (Coef. 1.12; 95%CI 0.76, 1.49; p-value b 0.001). However, there were no significant differences between average (SD) sound levels during the weekends 59.2 (1.62) dB and weekdays 59.4 (2.85) dB (Coef. 0.20; 95%CI −0.69, 1.10; p-value = 0.657). Similarly, in the single room, there was a statistically significant difference between LAeq (SD) day-time 62.1 (2.89) dB and night-time 59.5 (3.59) dB sound levels (Coef. 1.06; 95%CI 0.49, 1.64; p-value b 0.001); while there was no significant difference between weekdays 60.5 (3.68) and weekends 61.5 (2.86) dB (Coef. −0.37; 95%CI 1.83, −1.08; p-value = 0.614). There was no significant difference between LAeq levels in the open area and the isolation room (Coef. 2.05; 95%CI −0.45, 4.56; p-value = 0.108). In both areas, LAeq levels were always above the recommendation of 45 dB during the day and 35 dB during the night (Fig. 4.1). [91] [93]

LAmax levels were at times >90 dB but only for a few seconds at a time and in <10% of the study days. However, in the open area, the hourly LAmax level during the day 75.1 (5.56) dB was statistically significantly higher than during the night 72.9 (6.83) dB (Coef. 1.52; 95%CI 0.65, 2.38; p-value b 0.001); there was no significant difference between weekdays and weekends (data not shown). There was also no significant difference between the LAmax levels

in the open area and the single room (Coef. −1.63; 95%CI −6.48, 3.21; p-value = 0.508). More importantly, the LAmax values were N90% above the recommended 65 dB (Fig. 4.2). [115] [116]

The analysis of events found a positive association between morning patient rounds and LAeq levels (Coef. 0.87; 95%CI 0.46, 1.19; p-value < 0.001), and LAmax (Coef. 2.32; 95%CI 1.46, 3.19; p-value < 0.001) (Table 4.2). However, there was no association between other unit events and sound levels (Table 4.3). This analysis was limited due to the low number of some of the events during the study time period (Table 4.4).

The Granger analysis showed a significant correlation between the two-time series (sedation PRNs and sound levels). The LAeq level at each time (t) point was highly correlated with the number of sedation PRNs given within the following 5 h (p value = 0.030). Meaning that higher sound levels have a statistically significant correlation with the number of PRNs administered in the following 2, 3, 4 and 5 h. Moreover, higher sound levels better predicted the number of subsequent PRNs administered than did the previous requirement for PRN medication. Between 4 and 6% of the variation in PRN administration was explained by the LAeq levels. This correlation was positive and it showed that higher sound levels were correlated with a higher number of sedation PRNs. Similarly, higher LAmax levels were correlated with more sedation PRN doses (p value = 0.006); but in this case the LAmax level at each time (t) point was highly correlated with sedation PRNs given within 2 h. 3–4% of the variation in PRN administration was explained by the LAmax levels.

4.6 Discussion

This prospective cohort study on sound levels in a tertiary PCICU showed that sound levels were consistently higher than recommended values, not only during day time but also during night hours. Although there was a statistically significant difference between day and night levels, this difference was b2 dB, barely perceptible to the human ear, and not clinically relevant. [117] We did not find any differences between the open area and the single room. Morning patient rounds were the only event significantly associated with high LAeq and LAmax levels. More importantly, we found an association between sound levels and sedation requirements suggesting that elevated sound levels likely represent noise (affecting patient comfort).

The full definition of noise is complex because noise involves both volume and subjective components such as social and cultural factors, appropriateness, and the ability to control the sound. [90] Recommended sound levels for hospital and, especially, intensive care settings are < 45 dB. [110] Moreover, lower levels are recommended at night since sleep is affected by levels above 40 dB. [106] [108] [109] Keeping sound levels within the recommended values is important: high levels have been associated with increased patient discomfort, abnormal sleep, increased length of stay, increased sensitivity to pain, and delirium. [98] [99] [100] [101] [102] [103] [104] [105] [109] [114] In newborns, high sound levels can be even more detrimental, as levels continuously above 45 dB can affect their capacity to discriminate meaningful sounds and the human voice, both important for neurodevelopment. [113] These findings suggest that sound levels are clinically relevant and we should create a less noisy environment for critically ill children.

Previous studies on sound levels in PICU have also found that sound levels are higher than recommended, with values of 40–60 dB and no significant day/night variation. [95] [106]

[108] [109] [110] [111] [112] [113] Our study showed similar values, with LAeq levels around 60 dB and LAmax levels of 75 dB but differs from previous investigations in important respects. Our sound levels were measured continuously throughout a 4-week period, accommodating for variations between day and night, and also from different personnel and levels of activity in the unit that can vary from one day to another. Despite these efforts, sound levels were found to be quite consistent, with no significant differences from one day to another. Evidence provided by this and previous studies confirm that sound levels in our PCICU and other PICU settings are above recommended values and, even more concerning, that there is no clinically relevant day/night variation, important issues that can adversely affect sleep, behavior, and circadian rhythms. The lack of a normal circadian rhythm and sleep disturbances are known to have a negative effect in different organs homeostasis, immunity, catabolism and neurocognitive development. [118]

The implications of high sound levels in PICU have not been investigated in detail. Al-Samsam et al. explored the association between sound levels and sleep in PICU and found that LAmax levels ≥ 75 dB were associated with more awake states. [109] Previous studies have suggested the need to investigate the effect of noise on sedation requirements. [112] Our study demonstrates that high LAeq levels were associated with increased sedation requirements within 5 h while LAmax levels were associated with the need for extra doses of sedation within 2 h. These data suggest that elevated sound levels in PICU represent “noise” and have negative impacts on patients' sleep and comfort. The use of sedatives and narcotics has been shown to be a risk factor for pediatric delirium. [119] [65] In an era where it is recognized that over sedation can lead to hemodynamic instability, prolonged mechanical ventilation, delirium, and withdrawal symptoms, interventions to decrease noise may reduce sedation requirements and improve

patients' outcomes [120], including neurodevelopment in small infants. [113] [121] Moreover, the administration of unnecessary doses of sedatives can lead to substantial hemodynamic instability in children with cardiac disease who may already have decrease heart function and receiving vasoactive drugs. [122]

In order to reduce noise in the PICU, it is important to determine its cause. Our study found an association between morning patient rounds and high LAeq and LAmax levels. This aligns with 2 previous studies in which higher activity in the unit was associated with high sound levels. [95] [108] But while morning bedside rounds are a busy time, activity and communication may not be the main issue. Recent studies have identified equipment, including alarms, as the primary source of high and annoying sound levels [111] [112] [113], presenting a significant challenge to the goal of reducing sound levels, especially from essential equipment such as monitors and ventilators. Noise reduction from medical equipment may not be easy to achieve.

Strategies to reduce sound levels in hospitals and especially in critical care areas range from education, designated quiet time, quick assessment of alarms, central monitoring, visual signs, single rooms, changes in the architectural design of units, earplugs, etc. However, not all of these interventions have been demonstrated to be effective. Sound in a single room in the PICU has been studied, demonstrating similar levels compared to open areas in our study and others. [95] [112] [113] [123]Further, closing the doors of single rooms has been associated with higher sound levels [123], possibly because smaller environments do not allow dispersion of sound waves that come from within the room.

Although it could be argued that in a busy ICU LAeq levels will always be above 45 dB, there is no doubt that LAmax levels N65 dB cause distress and affect the sleep of critically ill patients. The publication of these recommended noise levels in the Guidelines for Construction

and Design of Health Care Facilities suggests that these limits are feasible and realistic. [117] It is up to the health care team and the experts on equipment and unit design to take the challenge and work towards a safer and less noisy environment.

This study has several strengths. First, noise levels were measured continuously over a four-week period allowing an observation period that was likely less sensitive to variation in PICU activity and/or staff. Second, measurements in an open area and a single room allowed the comparison of sound levels in 2 different environments. Third, a prolonged observation period and PICU staff who were unaware of the exact time of recording makes bias secondary to Hawthorne effect less likely. Finally, our study not only investigated sound levels in the PICU setting but also the association of these levels with the sedation requirements of critically ill children. The study also has some limitations. The device used to record sound levels has a lower limit of 40 dB; however, during the study this lower limit was never reached. Sound levels in the open area were measured from the center of the unit, but other areas could have been subjected to different sound levels. In critically ill children, sedation PRNs are given for various reasons and the association found between sound levels and sedation requirements is not necessarily a causal relationship. This study did not investigate the association between sound levels and delirium or other clinical outcomes. Finally, our results reflect sound levels of a single center PCICU and may not apply to other units.

4.7 Conclusion

Our prospective study showed that sound levels in PICU are consistently above the recommended standards with no significant variation between day and night. Morning patient rounds, which reflect periods of high activity, were associated with higher sound levels. More

importantly, we found a positive association between sound levels and sedation requirements, suggesting a negative impact of high sound levels, or “noise”, on patient comfort. Noise reduction strategies may help reduce sedation requirements and its negative consequences. There is a need for more research to determine which interventions can help create a less noisy and safer environment for critically ill children.

Table 4.1 Demographic and patients' characteristics

Variable	**Median (IQR)**
Age (months)	5.5 (3.0-55.0)
Sex Male n (%)	25 (64)
Diagnosis n (%)	
Aortic Stenosis	6 (15)
Atrial Septal Defect/Ventricular Septal Defect	4 (10)
Atrioventricular Septal Defect	6 (15)
Cardiomyopathy	1 (3)
Coarctation of the Aorta	1 (3)
Endocarditis	1 (3)
Hypoplastic Left Heart Syndrome and variants	12 (30)
Mitral Valve Insufficiency	1 (3)
Pulmonary Stenosis	2 (5)
Supraventricular Tachycardia	1 (3)
Total Anomalous Pulmonary Venous Return	1 (3)
Transposition of the Great Arteries	2 (5)
Ventricular Septal Defect	1 (3)
PRISM score	8.5 (6.0-12.5)
PRNs (number/day)	2.8 (1.0-7.5)
Mechanical Ventilation (days)	2.0 (0-4.0)
PCICU Length of Stay (days)	3.5 (2.0-9.0)

Table 4.2 Association between unit events and LAeq and LAmax sound levels.

	Reg. coef. (95%CI)	P value
LAeq		
Admission	0.34 (-0.04, 0.74)	0.082
Discharges	-0.18 (-0.59, 0.22)	0.370
Nursing sign-over, *morning*	-0.04 (-0.50, 0.42	0.860
Nursing sign-over *evening*	-0.14 (-0.66, 0.36)	0.569
Patient rounds, *morning*	0.95 (0.45, 1.29)	< 0.0001
Patient rounds, *evening*	-0.37 (-0.55, 0.27)	0.499
LAmax.		
Admission (n=45)	0.21 (-0.80, 1.23)	0.675
Discharges (n=39)	-0.09 (-1.14, 0.95)	0.858
Nursing sign-over, *morning*	0.002 (-1.27, 1.28)	0.996
Nursing sign-over *evening*	-0.22 (-1.36, 0.92)	0.703
Patient rounds, *morning*	2.32 (1.46, 3.19)	< 0.0001
Patient rounds, *evening*	0.05 (-0.78, 0.88)	0.898

LAeq, hourly average sound level; LAmax, hourly maximum sound level

Table 4.3 Association between unit events and LAeq and LAmax. sound levels.

	Reg. coef. (95%CI)	P value
LAeq		
Admission (n=45)	0.34 (-0.04, 0.74)	0.082
Discharges (n=39)	-0.18 (-0.59, 0.22)	0.370
Nursing sign-over, *morning* (n=26)	-0.04 (-0.50, 0.42	0.860
Nursing sign-over *evening* (n=26)	-0.14 (-0.66, 0.36)	0.569
Patient rounds, *morning* (n=26)	0.95 (0.45, 1.29)	< 0.0001
Patient rounds, *evening* (n=26)	-0.37 (-0.55, 0.27)	0.499
LAmax.		
Admission (n=45)	0.21 (-0.80, 1.23)	0.675
Discharges (n=39)	-0.09 (-1.14, 0.95)	0.858
Nursing sign-over, *morning* (n=26)	0.002 (-1.27, 1.28)	0.996
Nursing sign-over *evening* (n=26)	-0.22 (-1.36, 0.92)	0.703
Patient rounds, *morning* (n=26)	2.32 (1.46, 3.19)	< 0.0001
Patient rounds, *evening* (n=26)	0.05 (-0.78, 0.88)	0.898

Table 4.4 Unit events during the study period

Unit events	n
Admissions	45
Discharges	39
Intubations	3
CPR	1
Chest closure	3
Chest tube	1
Bronchoscopy	1
Line insertion	3

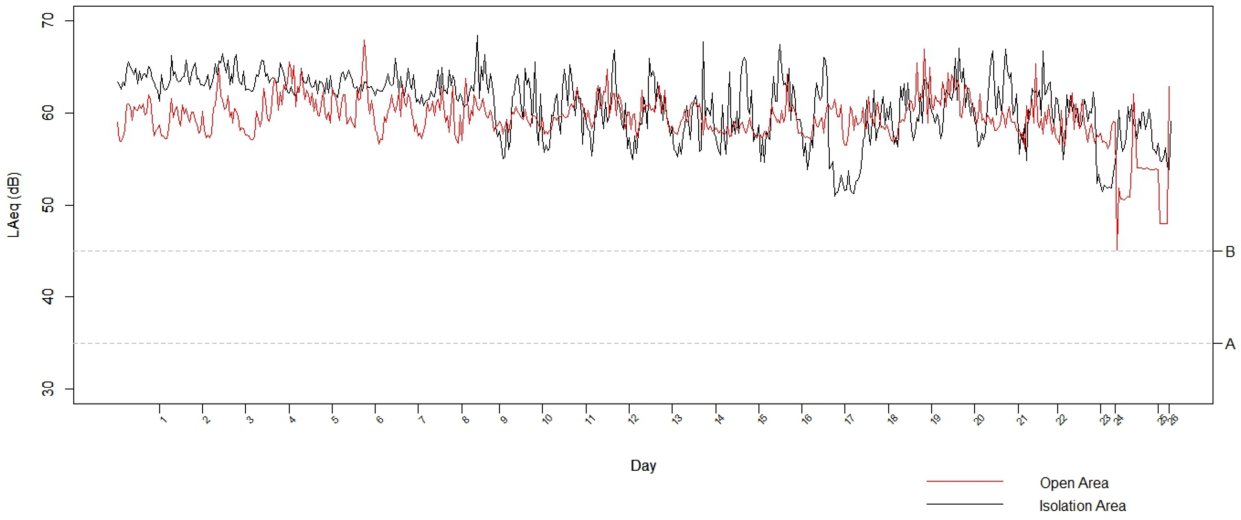


Figure 4.1 LAeq. hourly average sound level in dB. A: recommended sound level during night-time hours. B: recommended sound levels during day-time hours.

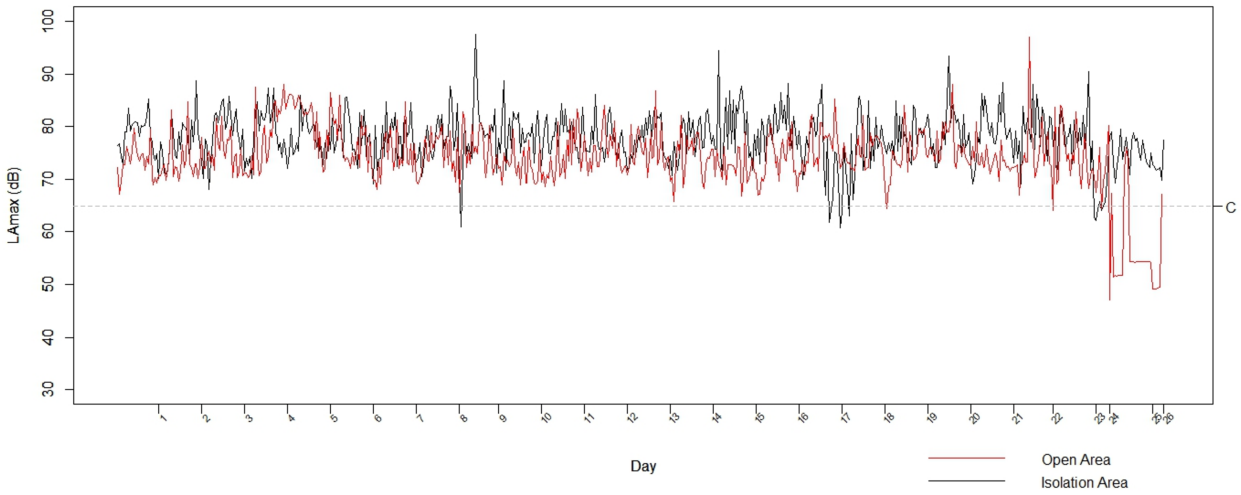


Figure 4.2 LAmax. hourly maximum sound level in dB. C: recommended limit for LAmax sound levels.

CHAPTER 5: Efficacy of music on sedation, analgesia and delirium in critically ill patients. A systematic review of randomized controlled trials.

5.1 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.

5.2 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] [2] [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] [7] [124]Music is believed to provided sedation/analgesia by distraction, sympathetic nervous system suppression, limbic system stimulation and the release of endogenous endorphins. [14] [22] 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. [23] [26]Studies in neonatal ICUs have shown that music helps stabilize vital signs and improves feeding tolerance, suggesting a relaxing effect. [125] 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. [22]

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.

5.3 Methods

We conducted a SR to obtain a comprehensive and objective summary of the best available evidence on the effects of music for sedation 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). [53] [126] [127] [128] 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.

5.4 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. [129] [130] 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.

5.5 Literature search

The full search strategy is outlined in Appendix III. 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.

5.6 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* (Appendix IV). The final list of included publications was agreed upon by all authors. A data collection tool (Appendix V) was developed prior to the literature search and agreed by all authors. Data collection followed the recommendations from the Cochrane Systematic Reviews Handbook. [126]

5.7 Analysis

We used the Cochrane Collaboration's tool for assessing risk of bias. [126] 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). [131]

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.

5.8 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 (Figure 1). Only 6 adult studies included sedation and/or analgesia requirements as an outcome [11, 21-25] [23] [132] [133] [134] [135]

[136], of which one also assessed ICU delirium. [135] Studies characteristics can be seen in Tables 1 and 2. Four studies included patients in a stable weaning phase of mechanical ventilation [23] [132] [134] [135], and one study did not specify this condition [133]. The music intervention differed across studies. Only Chlan et al used patient-selected music [23]; 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 [23] [136], the other studies used classical music [132] [133] [134] [135]. No music intervention included vocals. Timing, duration, and frequency 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. [23] [136] Outcomes were also different across studies. Hence, we provide a narrative description of the results of the different studies.

5.8.1 Risk of bias in included studies

The summary risk of bias is presented in Figure 2 while the risk of bias for each individual trial is shown in Figure 3. Half the studies clearly described their randomization technique and used allocation concealment. [23] [132] [136] 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. [132] [133] 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. [23] 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 more than 14 days. [134] Chlan et al excluded 98/373 (26%) patients who remained in the study for < 48 hours. [23] In Iblher et al's study, 34/160 (21%) patients dropped out, 10 because of post-operative complications and 24 due to organizational problems. [135] 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. [132] 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. [135] Similarly, Ames et al did not report the use of benzodiazepines, and 95% CI and p-values were not reported for any outcomes. [136] To et al reported the success rate of sedation vacations but did not provide any statistical analysis. [133] The risk of bias for each individual study is shown in Figure 3. We were unsuccessful in contacting four authors and there was no further data available from the study by To. [132] [133] [134] [135] [136] Overall the quality of the evidence is low according to the GRADE method. (Table 3)

5.8.2 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. [134] Iblher et al reported analgesia requirements by use of pethidine and piritramide separately but did not report sedation data. [135] 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. [133] Despite a higher rate of success in the music group, the difference was not

statistically significant. In 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. [23] Beaulieu-Boire et al evaluated daily requirements for narcotics and sedatives in a two day crossover design [132] 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. [136] (Supplemental Content IV)

5.8.3 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. [135] 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.

5.8.4 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. [134] On the other hand, Iblher 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; $P < 0.05$). [135] 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.

5.9 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. [23] 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. [132] [133] [134] [136]

While we were not able to perform a meta-analysis, this SR provides important information to inform future trials. The included studies had several characteristics in common. First, half used classical music [132] [133] [135] while the rest used “relaxing” music. [23] [134]

[136] 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. [15] According to the gate control theory of pain, music can block certain neural pathways and diminish the amount of perceived pain. [14] [23] [15] [137] [17]Stress-reducing music usually has a slow tempo (60-80 beats per minute) without significant variations in intensity. [138] [139] [140] 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. [45] The use of headphones may allow blinding of the intervention and prevent confounding by noise, which is common in the ICU setting. [141] 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. [23] [15] [142]Since the "optimal dose" of music is unknown, it is possible that patients were "undertreated" and hence no effect was noted. [124] [23] [132] [133] [134] [135] [136] 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. [22]

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.

5.10 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.

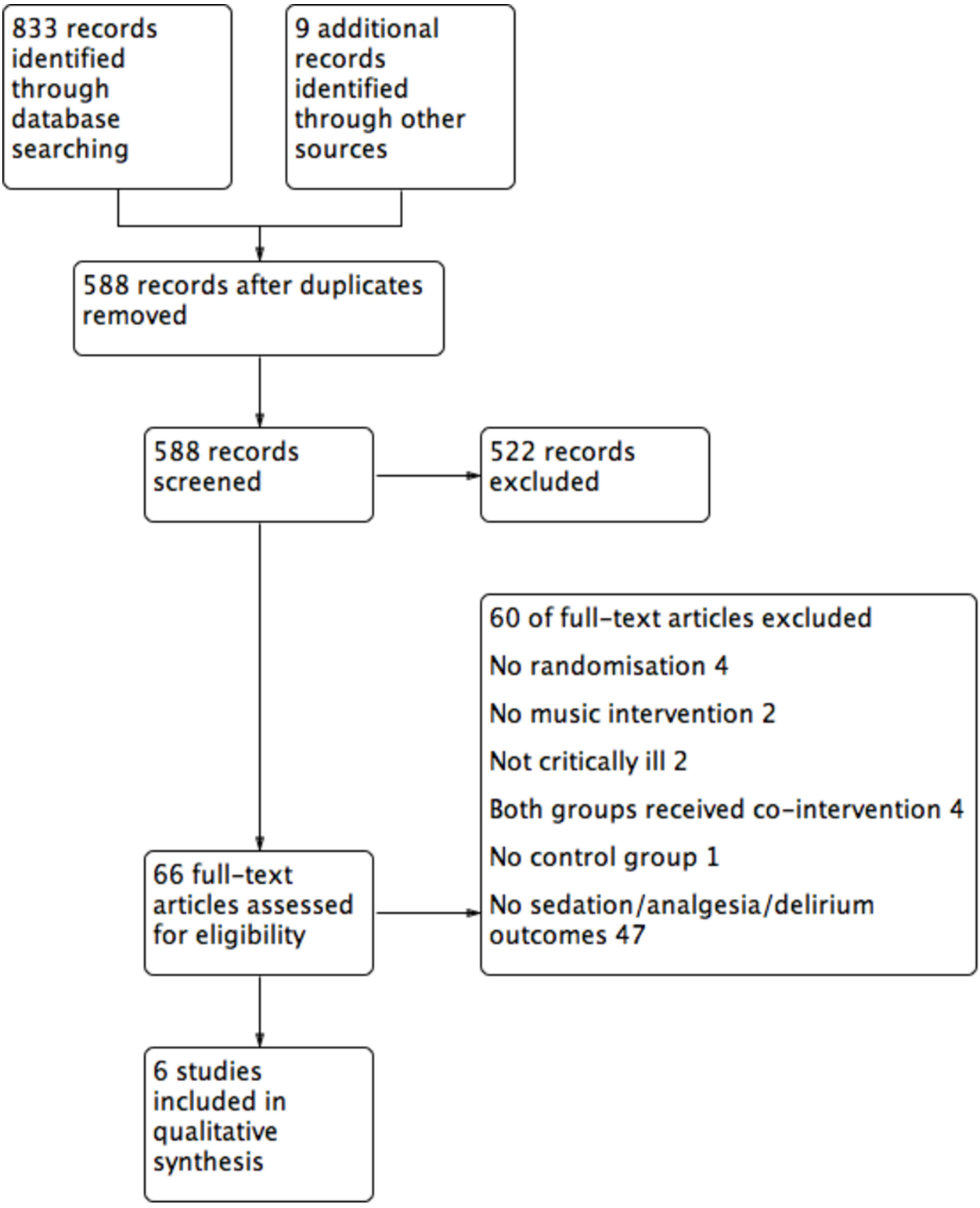


Figure 5.1 Study flow diagram.

Table 5.1 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, 2013 [9]	Parallel	Standard of care	Noise cancellation headphones	373	No	Yes	Yes	VAS-A, Sedation Intensity Sco Sedation frequency, Urine cortisol levels
Beaulieu-Boire et al, 2013 [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, 2013 [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, 1995 [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, 2011 [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, 2017 [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.

Table 5.2 Music intervention characteristics.

Publication	Population	Mechanical ventilation	Music Intervention					
			Type of music	Selection	Time	Duration	Frequency	Days
Chlan et al, 2013[9]	Adult mixed ICU, awake and stable	Yes	Relaxing	Patient	Day and night	As per patient	As per patient	Max.30 da
Beaulieu-Boire et al, 2013 [20]	Adults mixed ICU, stable	Yes	Classical	Music therapist	Day	60 minutes	2/day	2 days
To et al, 2013 [21]	Adult mixed ICU	Yes	Classical	Researcher	Day	240 minutes	1/day	1 day
Blankfield et al, 1995 [22]	Adult cardiac ICU post CABG/valvular surgery	Not specified	New Age Relaxing	Researcher	Day	30 minutes	2/day	During wh admission
Iblher et al, 2011 [23]	Adult cardiac ICU	Yes	Classical Baroque	Researcher	Day	60 minutes	1/day	1 day
Ames et al, 2017 [24]	Adult mixed ICU Post-surgery	No	Relaxing	Researcher	Day and night	50 minutes	3-6/day	2 days

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

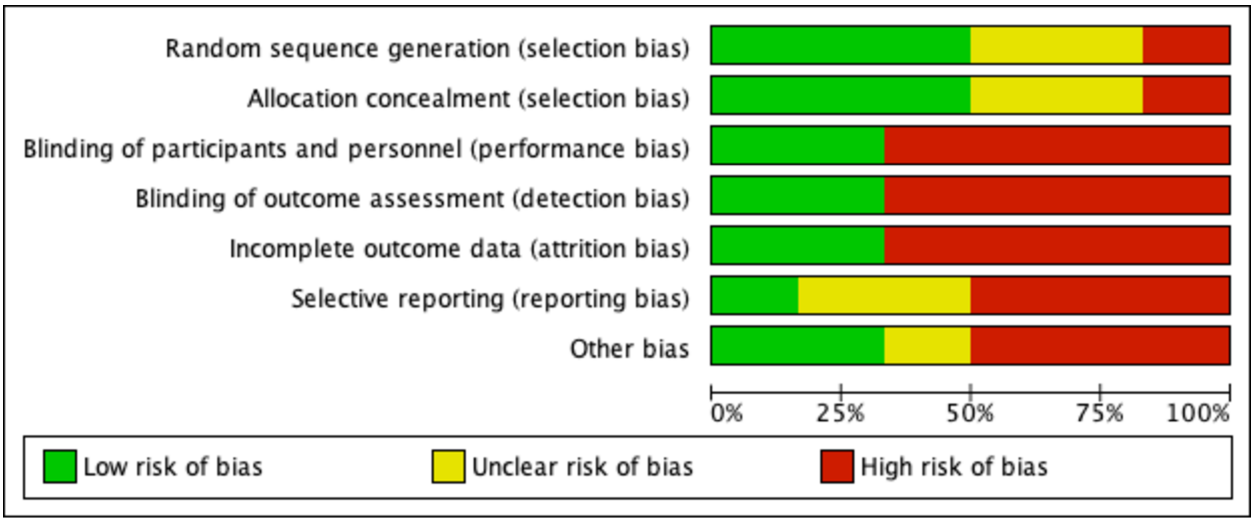


Figure 5.2 Risk of bias graph (n = 6 studies).

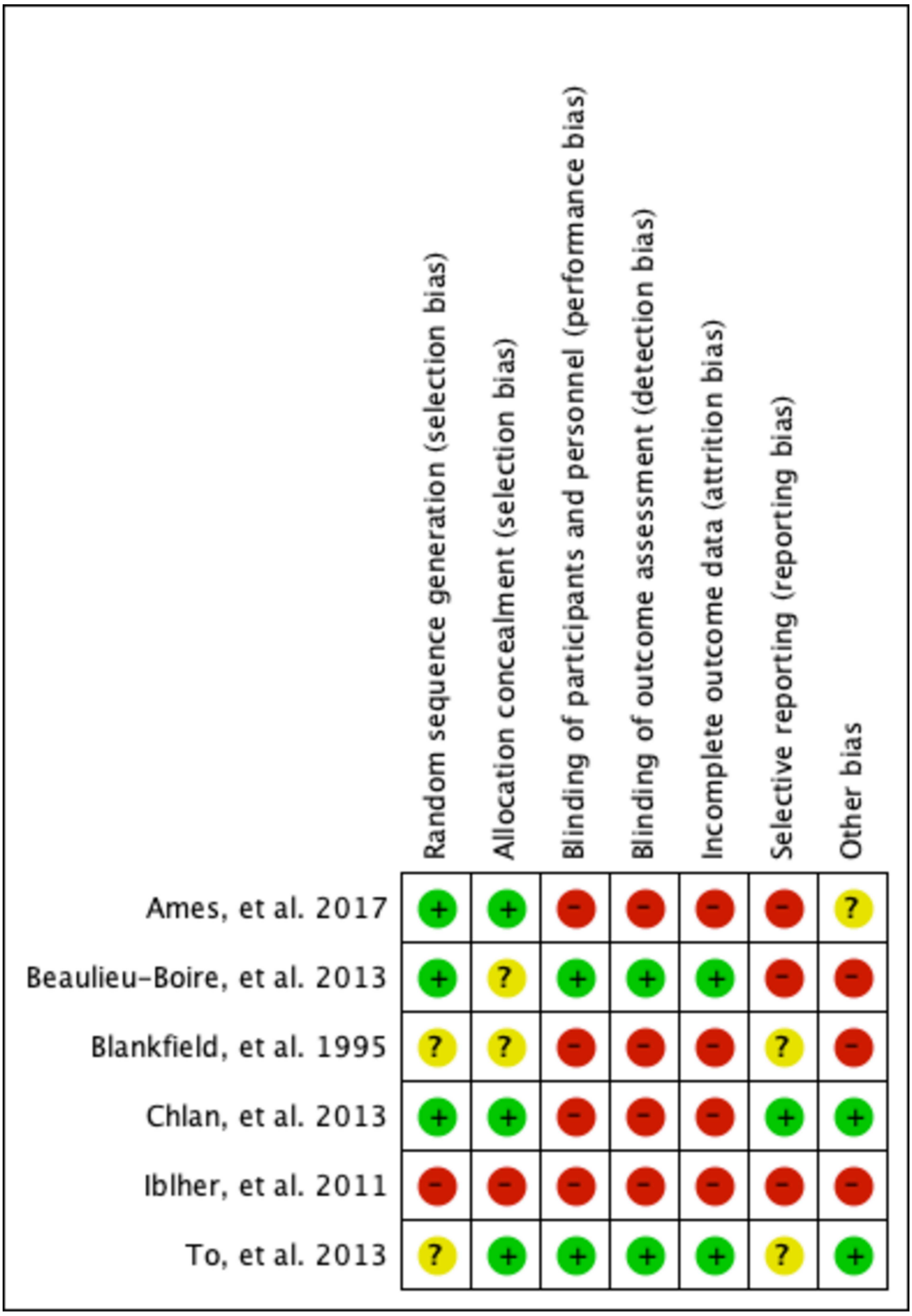


Figure 5.3 Risk of bias summary.

Table 5.3

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

Explanations

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.

Table 5.4 Description of study results

Publication	Sedation intensity	Sedation frequency	Delirium	Others
Chlan et al, 2013 [9]	Music vs. Standard of care: - Sedation Intensity β(95%CI) -0.18 (-0.36 to -0.004), P = 0.05)	Music vs. Standard of care: - Sedation Frequency β(95%CI) -0.21 (-0.37 to -0.05, P = 0.01) Music vs Noise cancellation - Sedation Frequency β(95%CI) -0.18 (-0.36 to -0.004) P = 0.04	-	Music vs Standard of care - VAS-A: -19.5 points (95%CI) -32.2 to -6.8) (P = 0.003) No difference in urine cortisol levels
Beaulieu-Boire et al, 2013 [20]	Pre-Music vs. Music mean (SD): - Fentanyl daily dose (mcg): 1597 (1418) vs 1343 (1342), P = 0.06 - Benzodiazepine daily dose (mg): 42 (88) vs. 36 (94), P = 0.06 - Hypnotics-propofol daily dose (mg): 291 (732) vs. 284 (730) mg, P = Not significant (P value not provided)	-	-	Pre-Music vs. Music mean (SD) - HR and RR: no difference (Data not provided) - SBP (mmHg): 123(27) vs. 120.5(24), P = Not significant (P value not provided) - ACTH/cortisol ratio 0.04 (0.016) - Blood Cortisol (nmol/L): 815 (126) vs. 727 (98), P = 0.02 - Leptin (ng/ml): 19(4) vs. 19.6(4), P = Not significant (P value not provided) - Met-enkephalin (pg/ml): 251(63) vs. 252(68), P = Not significant (P value not provided) - Prolactin μg/L: 29.3 (3.5) vs. 27.4 (3.4), P = 0.038
To et al, 2013 [21]	-	Music vs. control - Sedation vacation success rate: 64% vs. 52%, P = 0.39	-	Overall change in mean(SD) - HR -5.46(16.8), P= 0.27 - RR 0.05(6.14), P= 0.98 - SBP 5.50(23.8), P= 0.42 - Ramsay scores 0(0), P=0.86.

Blankfield et al, 1995 [22]	Music vs. control mean (SD): - Morphine (mg): 15.6 (11.2) vs. 20.2 (15.7) - Meperidine (mg): 46.6 (96.7) vs. 61.9 (234) - Opioids equivalent (mg): 2 0.3 (16.6) vs. 26.4 (34.5) Differences were not significant (P value not provided)	-	-	Music vs. control mean (SD) - ICU LOS (days): 1.5(0.7) vs. 1.4 (0.9), P = Not significant (P value not provided) - Depression scale: 3.0 (2.6) vs. 2.8 (3.0), P = Not significant (P value not provided) - Daily leaving activity scale: 3.7 (4.8) vs. 4.0(4.5) - Cardiac Symptoms scale: 2.1(1.4) vs. 2.3 (1.8)
Iblher et al, 2011 [23]	Early music vs. late music vs. control mean (SD): - Pethidine (mg): 45,5 (22,8) vs. 54.7(38.5) vs. 47.0 (28.3), P = 0.670 - Piritramid (mg): 17.6 (9.2) vs. 15.4 (7.8) vs. 13.9 (9.1), P = 0.287	-	No difference in Confusion Assessment Method (CAM) score 3 days after ICU discharge. (Data not provided)	Early music vs. late music vs. control mean (SD): - HR: 94 (9) vs. 93 (7) vs. 93 (7), P = 0.860 - SBP (mmHg): 124 (16) vs. 123 (16) vs. 123 (15), P = 0.583 - DBP (mmHg): 59 (11) vs. 58 (6) vs. 59 (8), P = 0.943 - O2Sat (%): 98 (2) vs. 98 (3) vs. 99 (1), P = 0.442 - Dobutamine (mg): 0.7 (3) vs. 1.5 (4) vs. 0.4 (2), P = 0.458 Music vs. control Effect size: - ANP: Remembrance post-op period: 0.48, P < 0.05 Pain operated area: -0.42, P < 0.05 Xerostomia: -0.43, P < 0.05 Nausea/vomiting: -0.43, P < 0.05 Early vs late music Effect size: - ANP:

				Contentment with daily routine day of surgery: 0.51, P < 0.05 Malaise: 0.40, P <0.05 Pain operated area: 0.55, P < 0.01 - BSKE Malaise: 0.68, P <0.01 - No difference between groups in other items from the ANP or BSKE (Data not provided) - AMT: No difference between groups (Data not provided)
Ames et al, 2017 [24]	<u>Music vs. control mean (SD):</u> Total IV Morphine equivalent (mg): 73.6 (29.5) vs. 61.0 (51.0), P = 0.471 Day 1 IV Morphine equivalent (mg): 54.6 (26.8) vs. 45.6 (29.7), P = 0.451 Day 2 IV Morphine equivalent (mg): 37.9 (37.2) vs. 28.2 (31.7), P = 0.639 Total Epidural Fentanyl equivalent (mcg): 1532.3 (1036.2) vs. 1259.9 (1031.8), P = 0.577 Day 1 Epidural Fentanyl equivalent (mcg): 1257.9 (766.3) vs. 803.5 (511.1), P = 0.119 Day 2 Epidural Fentanyl equivalent (mcg): 352.8 (618.3) vs. 547.7 (691.7), P = 0.560	-	-	Pre/Post-intervention difference music vs. control in mean (SE) at each intervention - NRS: 1st Intervention -1.50(0.36) vs. -0.40(0.33) 2nd Intervention 0.15(0.35) vs. -0.31(0.33) 3rd Intervention -0.03(0.39) vs. 0.35(0.35) 4th Intervention -0.18(0.43) vs. -0.80(0.37) - Pain VAS 1st Intervention -13.0(3.8) vs. -7.82(3.60) 2nd Intervention 0.29(3.60) vs. -2.95(3.51) 3rd Intervention 0.92(4.05) vs. 3.93(3.70) 4th Intervention -1.89(4.53) vs. -8.83(4.05) - ET-A 1st Intervention -0.85(0.53) vs. 0.07(0.50) 2nd Intervention -0.46(0.41) vs. -0.18(0.39) 3rd Intervention -0.08(0.25) vs. -0.07(0.23) 4th Intervention -0.69(0.53) vs. 0.46(0.47) - ER-D 1st Intervention -1.35(0.54) vs. -0.12(0.51) 2nd Intervention -0.71(0.25) vs. 0.004(0.23) 3rd Intervention -0.30(0.28) vs. -0.28(0.25)

	4th Intervention -0.37(0.34) vs. -0.19(0.29) (P values not provided)

AMT, Abbreviated Mental Test; ANP, Anesthesiological Questionnaire for patients after anesthesia; BSKE, Condition-scaling using classes and adjectives; DBP, Diastolic blood pressure; 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.

Chapter 6: Music Use for Sedation in Critically ill Children (MUSiCC trial): a pilot randomized controlled trial

6.1 Abstract

Objective: To demonstrate feasibility of a music trial in pediatric intensive care and to obtain the necessary information to plan a larger trial.

Design: Pilot, double blind, three arm parallel randomized controlled trial (RCT).

Setting: Stollery Children's Hospital tertiary care pediatric general intensive care and cardiac intensive care units (PICU/PCICU).

Patients: All children 1 month to 16 years of age admitted to the PICU/PCICU on invasive mechanical ventilation and receiving sedation and/or analgesia drugs.

Interventions: Enrolled patients were randomized in a 1:1:1 ratio to music, noise cancellation or control. The music group received classical music three times a day for 30 minutes using noise cancellation headphones. The noise cancellation group received the same intervention but with no music. The control group received usual care. Children remained in the study until extubation or a maximum of 7 days.

Measurements and Main results: The primary outcomes of the study were feasibility and sedation/analgesia requirements. Secondary outcomes included change in vital signs before and during the intervention, ICU delirium, and adverse effects related to the intervention. A total of 60 patients (20 per group) were included in the study between March 2018 and April 2019. The average enrollment rate was 4.8 patients/month, with 69% of the approached patients giving consent to participate. Protocol adherence was achieved with patients receiving $\geq$ 80% of the protocolized interventions. The main reasons for missing an intervention were: use of paralytic agents, parental request, and unknown cause.

Conclusions

This pilot RCT has demonstrated the feasibility of a music trial in critically ill children. The study has also provided the necessary information to plan a larger trial to evaluate the efficacy of music to reduce sedation/analgesia requirements in PICU.

6.2 Introduction

Stress induced by pain and anxiety is common in pediatric intensive care unit (PICU) patients and can impede the care to children as well as their recovery. [1] Children in PICUs experience pain and anxiety for a wide variety of reasons. [2] In PICU sedation/analgesia are important not only for comfort, but also for safety. Children with inadequate sedation/analgesia are at risk for loss of vascular access, extubation, self-injury, and post-traumatic stress. [3] Sedation/analgesia in PICU is usually achieved through various analgesics and sedatives. However, excessive use of these drugs can put patients at risk for hemodynamic/respiratory instability, prolonged ventilation, withdrawal, delirium, and critical illness polyneuromyopathy. [3] [4] These negative consequences can lead to prolonged PICU stay and increase health care costs. [2] [4] [5]

Non-pharmacologic measures for analgesia/anxiolysis are interventions that do not involve drugs, and thus may reduce the total medication requirement and associated side effects. [5] The use of non-pharmacologic interventions has been recommended by published international sedation guidelines. [72] [7] However, none of these guidelines state how these interventions should be provided. Non-pharmacologic measures in PICU, including music, have been inadequately studied and the need for research around this topic been recently identified. [143] [125] In our survey, 85% of the respondents stated that non-pharmacologic interventions in PICU should be formally studied. A systematic review (SR) also conducted by our group has shown limited evidence to support or refute the use of music to reduce sedation/analgesia requirements in critically ill adults, and no evidence in pediatric and neonatal critically ill patients. [8] The aim of the MUSiCC pilot trial was to determine the feasibility of a pediatric music trial, to study the effects of music on sedation/analgesia requirements and the incidence of

delirium in children admitted to PICU. We hypothesized that an RCT of music in critically ill children will be feasible. Further, we aimed to collect pediatric data on sedation/analgesia requirements, which will be necessary to calculate the sample size for a future, larger, trial.

6.3 Materials and Methods

The MUSiCC trial was an investigator-initiated, three arm parallel RCT examining the use of music for sedation in PICU. A parallel three-group design including a music, a noise cancellation and a control group was based on adult data showing that noise cancellation alone can reduce sedation requirements as well as pediatric evidence that noise levels are associated with sedation requirements. [23] [141] The study included all children admitted to the Stollery Children's Hospital PICU or PCICU, aged 1 month to 16 years, receiving invasive mechanical ventilation for > 24 hours. Exclusion criteria included: known hearing deficit, infants < 1 month old and/or < 3 kilograms, major cranial-facial abnormalities, traumatic brain injury, not receiving sedation and/or analgesia drugs, receiving continuous infusion of paralytic agents, extracorporeal Membrane Oxygenation (ECMO) with neck cannulation, expected to die in the next 48 hours, and/or enrolled in another sedation intervention study. The study protocol and procedures are shown in detail in Appendix VI.

At baseline the following variables were recorded: demographic variables (sex, weight, age, diagnosis), unit of admission, operative status, pediatric risk of mortality score (PRISM) and whether the patient was on sedation and/or analgesia drugs prior to ICU admission. [144] [145] At the time of enrollment we also collected information on the following variables: Pediatric Logistic Organ Dysfunction score (PELOD2), inotrope score, need for invasive procedures, and

presence of invasive lines and tubes. [146] Variables were recorded in an anonymized database using REDCap, Research Electronic Data Capture. [51]

6.4 Randomization procedure and treatment allocation

Randomization was done by a computer-based program to ensure allocation concealment and was performed by the Epidemiology Coordinating and Research Centre (EPICORE), a clinical trials unit at the University of Alberta. A total of 60 patients were consecutively randomly assigned in a 1:1:1 ratio to receive music, noise cancellation or control (Figure 1).

In order to blind the intervention, the research nurse provided a portable music player (Apple iPod^{TM} touch, California, US) with music or silent recording based on group allocation and did not disclose this information to the healthcare team or the family. The iPods assigned to the noise cancellation group had a sham playlist with a silent recording that displayed in the iPod screen as if music was being played. Each 30 minutes playlist (music and sham) started with 1 minute of silent recording in an attempt to maintain blinding of the intervention. The volume in the iPods was set at approximately 45 to 55 dB. Based on the nature of the intervention, it was impossible to blind the use of headphones vs. control. However, collection of outcome data was blinded to group allocation.

After randomization, patients were started on the assigned intervention (music/noise cancellation/control) 24-48 hours after admission to the PICU. In the music and noise cancellation groups, the intervention was delivered three times a day for 30 minutes at a time. The bedside nurse determined the exact time of each intervention so that it didn't interfere with care, within the following time windows: 7am-12 pm (morning intervention), 12-4pm (afternoon intervention), and 4pm-8pm (evening intervention). The control group received usual care.

Music was delivered with the use of noise cancellation headphones (PURO® Sound Labs Kids BT2200 and BT5200, California, US) and an iPod touch. Puro Sound Labs headphones have an intrinsic volume restrictor of 85dB and 82% ambient noise cancellation. Music selection was performed by our music therapist (KH) and consisted of short pieces of classical music with a tempo of around 60 beats/minute with preference for major keys and avoiding dramatic moments, unsettling chords, and minor keys, as they can be associated with sadness. We created four different music playlists of 30 minutes each to add variation to the intervention. In the noise cancellation group, the intervention was provided with the same headphones connected to an iPod with a sham playlist with silent recording as described above. Children were assessed with the Sedation Behavior Scale (SBS) before and during the intervention. [56] Signs of agitation and/or an increase in the SBS by two points indicate failure of the intervention. Patients were to remain on protocol as long as they were receiving invasive mechanical ventilation or for a maximum of 7 days, whichever came first.

Other than the music/noise cancellation interventions, clinical care was not protocolized and was according to usual management. Sedation/analgesia management was not directed by the study protocol; it was up to the attending PICU physician. Assessment of the patients' sedation status and withdrawal symptoms was conducted every 6 hours as part of the routine care using the SBS and WAT-1 scores. [56] [57] [58]

6.5 Outcome measures

The primary outcomes of this trial were feasibility and sedation/analgesia requirements. In order to determine feasibility, we collected information on: number of eligible patients, number of patients enrolled, rate of enrollment, time to complete participation, protocol

adherence and reasons for protocol deviation. Feasibility was defined as a protocol adherence of 80%, and consent rate of 70%, with an average enrolment rate of 5 patients per month. Protocol adherence was defined as receiving the allocated intervention for 30 minutes 3 times/day during the time patient remained in the study.

Information on sedation/analgesia requirements will allow the appropriate sample size calculations for a larger trial. A survey conducted by our group found that reduction in sedation requirements is a meaningful and clinically relevant outcome for a trial on non-pharmacologic interventions in PICU. [143] Sedation/analgesia requirements was captured as a daily intensity score and intermittent dose (PRN) frequency. [23] [147] The Sedation Intensity Score aggregates the amount of sedation/analgesia from different drug classes using a weight-adjusted dose of each sedative administered during 4 hour-time blocks. [23] [147] Every sedation amount, for each drug is then placed in quartiles created by using the patients' data during the time the patients are involved in the study. The values are then summed over the six 4-hours blocks to obtain the daily score. Sedation Frequency was captured by the daily administration of a PRN dose of any of the sedative/analgesia drugs. [23] [147]

This study also explored the effects of music on ICU delirium. Delirium was assessed twice a day (per usual care) with the Cornell Assessment of Pediatric Delirium (CAPD) instrument. [55] Those patients with a score > 9 in two consecutive measurements were considered to have PICU delirium. Vital signs including heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate and oxygen saturation were collected prior to the intervention, at 15 minutes during the intervention, at the end of the intervention and 30 minutes after the intervention. Other adverse events such as intolerance to the intervention and skin and/or ear problems (e.g., pressure injuries) thought to be associated with the use of headphones

were monitored. Duration of invasive mechanical ventilation, PICU stay and PICU mortality were also recorded.

As part of our family centered care approach, we included parents' perspective on the use of music for sedation in critically ill children. Parents' opinions on the intervention (music or nose cancellation) were explored with a survey conducted prior to the patient's discharge from the ICU.

The study was approved by the University of Alberta Health Research Ethics Board (Pro00073775). Informed consent was given in writing by the parents/legal guardians. The study was registered at ClinicalTrials.gov (NCT03497559).

6.6 Statistical analysis

Assuming a protocol acceptance/completion of 80% we calculated a sample size of 60 patients was needed to estimate the rate within 10% of the true rate with 95% confidence. Also, this number of participants per group followed the recommended rules for pilot trials' sample size when the standardized effect size is unknown but expected to be small. [59] Baseline characteristics are presented by descriptive statistics, comparison of these characteristics among groups was done using Kruskal-Wallis test for continuous variables and Fisher exact test for categorical variables. Analysis was conducted by intention to treat. Linear regression and mixed-effects models was used to analyze the primary effect of the music on sedation requirements and treatment effect differences between groups. Mixed-effects models was implemented to accommodate the correlation and inconstant variance between sedation requirements measurements among various time points. Data was analyzed with R software version 3.6.1

(Foundation for Statistical Computing, Vienna, Austria). We considered significant at a p-value of less or equal to 0.05.

6.7 Results

A total of 60 patients (20 per group) were included in the study between March 2018 and April 2019. The average enrollment rate was 4.8 patients/month, with 69% of the approached parents/guardians giving consent to participate. Demographic and baseline characteristics of study participants are displayed in Table 1. The mean (SD) age of participant was 2.0 (3.4) years, with a mean (SD) weight of 10.6 (11.1) kilograms. Recruitment was slightly higher in the PCICU 37 (62%). Hence, 35 (58%) of the participants had a cardiac diagnosis and 36 (60%) were admitted after a surgical intervention. Only 16 (26%) of the children were receiving sedation/analgesia drugs prior to their PICU admission. The presence of central venous lines 54 (90%), arterial lines 52 (87%), mediastinal 24 (40%) and chest tubes 32 (53%) were common. Mean (SD) PRISM III score on admission was 8.1 (6.0), while the PELOD 2 and inotrope scores upon enrollment were 6.7 (2.5) and 7.0 (8.7) respectively. There were no statistically significant differences among baseline characteristics between groups (Table 1). However, children in the music group were a slightly younger and had higher PRISM scores on admission.

6.7.1 Feasibility

Protocol adherence was achieved with patients receiving a total of 358 interventions, which represented 83% (95%CI: 79 – 86%) of the protocolized interventions. The main reasons for missing an intervention were: use of paralytic agents n=28 (38%), parental request n=9 (12%) and unknown cause n=12 (16%). Only 19 (4%) interventions lasted < 30 minutes, with the

reasons for a shorter intervention being an increase of > 2 points in the SBS n=7 (33%), hemodynamic instability n=5 (24%), need for an intervention unrelated to the study n=4 (20%), receiving a paralytic agent n=1 (5%), nurse thought time was over n=1 (5%), and unknown n=1 (5%).

6.7.2 Sedation and analgesia requirements

The overall mean (SD) daily Sedation Intensity Score for the study population was 52.4 (30.3) with a mean (SD) Sedation frequency of 9.75 (7.21) PRN doses per day. There was no significant difference in mean Sedation Intensity Score (SD) and Sedation frequency (SD) between groups (Table 2). The control group had a mean Sedation Intensity Score (SD) 47.6 (26.0) vs. music group 53.7 (36.9) and noise cancellation group 55.6 (26.1), p-value = 0.561. The Sedation frequency was also similar across groups with the control group receiving a mean (SD) PRNs/day of 8.58 (6.11), vs. music group 9.75 (7.1) and noise cancellation group 10.9(8.14), p-value = 0.511. A graphic display of the Sedation Intensity Score and Sedation frequency by group can be found in Figure 2 and 3. Mean (SD) sedation, analgesia, withdrawal and delirium score were also not different across groups for the length of the trial (Table 3).

6.7.3 Vital signs before, during and after the music and noise cancellation interventions

There was a statistically significant decrease in heart rate at the beginning of the music intervention as well as at the beginning of the noise cancellation (Table 4). After noise cancellation, the respiratory rate also decreased. However, these changes were very small and probably clinically irrelevant. There were no significant differences in systolic, diastolic blood pressure and arterial oxygen saturations before, during and after the interventions (Table 4). The

changes in vital signs across different time points related to the interventions are graphically display in Figure 4.

6.7.4 Parent survey

Parents of those patients allocated to an intervention (music/noise cancellation) were given the option to receive the survey, either by email or in paper. Twenty-six (65%) of the parents answered the survey, being the hard copy the most effective way to obtain their opinion with 88% of the respondents choosing this modality. Eighteen (70%) of the respondent parents thought the intervention was useful during their child's ICU admission. Sixteen (62%) thought the intervention reduced their child's anxiety, while 9 (35%) thought it helped to reduce pain. However, only 11 (42%) perceived that the intervention helped to reduce the need for sedatives and analgesics. The majority of the parents, 23 (88%), thought the headphones were comfortable while only 2 (8%) believed they were uncomfortable for their child. The majority, 19 (73%) described their child's reaction during the intervention as "more settled and asleep"; however, 3 (11%) of the parents thought their child became more agitated during the intervention. A full description of the questions and their answers can be found in Appendix VII)

Discussion

While music appears to be a promising intervention, there is presently no evidence that it decreases use of pharmacologic therapies for sedation/analgesia in critically ill children. [8] A pilot RCT was a necessary first step toward the conduct of a future definitive music trial in critically ill children. Our MUSiCC trial has demonstrated the feasibility of a music and a noise cancellation intervention in the pediatric intensive care environment. The study was conducted

with a consent rate of about 70%, and with an enrollment rate, as predicted, of almost 5 patients/month. Patients received > 80% of the protocolized interventions. Missed interventions were mainly due to the intermittent use of paralytic agents around the times of interventions. Only 9 (2%) of the interventions were not conducted based on parental request. These requests were based on the concern of their children being too sick rather than the belief that the intervention was harmful or causing distress. Of the received interventions, only 7 out of 358 (2%) were stopped due to patient agitation. The most common impression from those parents who answered the survey after the study was that their children were more settled and asleep during the interventions.

A pilot study was also needed to allow formal sample size calculation for a future larger trial. This is the first study to use Chlan's Sedation Intensity Score in the PICU environment. [23] [147] The Sedation Intensity Score allows to aggregate all the different sedation/analgesia drugs given to critically ill patients despite the inability to calculate equivalent doses for drugs of different classes. In recent years, it has been recognized that over-sedation not only puts patients at risk for hemodynamic/respiratory instability, but also for prolonged ventilation, withdrawal, delirium, and the inalbility to mobilize critically ill patients leading to weakness and longer times for recovery. [3] [148] In this context, a goal directed pain and sedation strategy establishing and reassessing daily goals of sedation/analgesia has been implemented across ICUs and is known as the "ICU liberation" strategy. [148] Hence, sedation and analgesia scores are utilized not only to assess the patients' level of pain and sedation, but also to establish goals as part of the daily care plan. Because of this, pain and sedation scores cannot be the primary outcome of trials looking at the effect of non-pharmacologic interventions as sedation/analgesia drugs are titrated to target a specific score appropriate to the patient's condition. A reduction on sedation/analgesia drugs

requirements was identified in our previous survey as a meaningful clinical outcome that should be used in clinical trials investigating new sedation/analgesia strategies including non-pharmacologic interventions. [143] In this survey, a reduction of sedation/analgesia drugs requirements of 20% was established as the minimal clinically important difference. [143]

Although music has been used for years in healthcare, the exact mechanisms by which it can reduce pain/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. [14] According to the gate control theory of pain, distractions such as music can block certain neural pathways and diminish the amount of perceived pain. [14] [140]

A SR on the use of music in mechanically ventilated adults found that music was associated with lower levels of anxiety, lower sedation requirements, and better vital signs suggesting relaxation. [22] A large RCT on patient-directed music demonstrated reductions in anxiety and in sedation requirements in critically ill adults. [23]

In pediatrics, music has been shown to reduce procedural pain in a variety of clinical settings. [15] Several studies have demonstrated that music is associated with lower pain scores and anxiety in children going for surgery. [125] [17] [35] Although these studies proved that music can be used in pediatrics, they had the objective of causing distraction in the context of a painful procedure or surgical intervention and did not include critically ill children. The evidence for the use of music in the pediatric critical care setting is very limited and doesn't include studies assessing the impact of music on sedation and analgesia requirements. [8] In newborns, music has been shown to be effective in reducing pain and stress behaviours during procedures; and has also been associated with more stable vital signs, better weight gain, shorter length of stay and increased parental satisfaction in this population. [35] [29] [36] [37] [38] [45]

To our knowledge, there has been only one RCT evaluating the effects of music on vital signs and pain scores in critically ill children. [27] While results were positive, this trial only used music once in the first 24 hours after cardiovascular surgery and did not assess sedation requirements. Two recently published pilot trials used music interventions in PICU. [43] [44] Rennick et al. used music at the end of a soothing (touch and reading) intervention. [43] Music was well accepted by parents and thought to calm their children. However, details on the type music and effects on sedation requirements were not reported. On the other hand, Liu et al investigated the effect of music on sedation scores, vital signs and midazolam utilization. [44] Although they found significant difference between groups, these were small and may not be clinically relevant. Data on analgesia and other sedatives was not reported. However, these two pilot studies add to the evidence that a music intervention in PICU is well accepted by parents and the health care team.

Our trial differs from previous studies looking at the use of music in ICU in several important aspects. Studies in critically ill children have most often been limited to premature newborns who were not on mechanical ventilation nor on sedatives. [35] [29] [36] [37] [38] [45] [27] Patients included in critically ill adult trials were relatively stable and the majority were in a weaning phase from their mechanical ventilation. [23] [132] [133] [134] [135] [136] None of the studies evaluated heavily sedated patients in the acute phase of their illness; 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. Ideally, if non-pharmacologic interventions aim to reduce the use sedation/analgesia drugs and their side effects, they should be implemented early in the patient's admission. This approach has significant challenges since in PICU most patients will not be able to select their own music or decide when they would like the intervention to take place.

This pilot RCT has the following strengths. First, this is the first RCT exploring the use of music for sedation in mechanically ventilated critically ill children in the acute phase of their illness. Second, this pilot trial was built upon a previous survey, cohort study and SR that provided the information necessary to determine the appropriate design and outcomes. [143] [141] [8] Third, a sample size was pre-determined to be able to prove feasibility and to obtain adequate data for sample size calculations in future larger trials. [59] Fourth, this is the first study to use the Sedation Intensity Score in the PICU environment. [23] [147] Last, the protocol for this pilot RCT was registered and published prior to study completion and data analysis.

This pilot RCT also has limitations. First, the goal of this pilot RCT was not to determine a difference in sedation/analgesia requirements between groups nor a difference in other secondary outcomes like vital signs and ICU delirium. Second, the frequency and length of the music intervention was chosen based on limited available evidence on the use of music in critically ill patients. [8] Third, the type of music was also selected with limited evidence that classical music with a tempo of around 60 beats per minute and a preference for major keys can provide sedation and is appropriate for all ages. [140] Whether other types of music or different dosing of the music intervention could be more effective for critically ill children is unknown. Fourth, music therapy is defined as the clinical and evidence-based use of music by a qualified music therapist to obtain individualized goals for a certain patient or group of patients. [15] Ideally, each intervention should be conducted by a music therapist who can adjust the intervention based on the patient's response. However, the conduct of a clinical trial with the implementation of such an intervention in mechanically ventilated and critically ill children would not be feasible.

Conclusion

This pilot RCT has demonstrated the feasibility of a music clinical trial in critically ill children. The study has also provided the necessary information to plan a larger trial to determine the efficacy of music to reduce sedation/analgesia requirements in PICU. Whether music can be used to decrease use of pharmacologic therapies for sedation and analgesia in critically ill children remains to be determined.

Table 6.1 Baseline characteristics

Characteristic	Control	Music	Noise Cancellation
Age – Years[a]	2.02 (3.5)	1.16 (3.5)	2.02 (3.5)
Weight - Kilograms[a]	12.05(14.54)	7.22(14.54)	12.05(14.54)
Sex – Male[b]	9(45%)	13(65%)	9(45%)
PRISM Score[a]	6.65(4.94)	8.45(4.94)	6.65(4.94)
Inotrope Score on admission[a]	4.08(3.83)	10.2(3.83)	4.08(3.83)
PELOD Score on enrollment[a]	6.45(1.79)	7(1.79)	6.45(1.79)
Type of ICU			
PCICU[b]	10(50%)	15(75%)	12(60%)
PICU[b]	10(50%)	5(25%)	8(40%)
Sedation prior to ICU - Yes[b]	7(35%)	4(20%)	5(25%)
Post-operative - Yes[b]	13(65%)	12(60%)	11(55%)
Cardiac Diagnosis - Yes[b]	10(50%)	13(65%)	12(60%)
Diagnosis[b]			
Cardiac arrest	1(5%)	0(0%)	0(0%)
Gastrointestinal	2(10%)	0(0%)	1(5%)
Post-operative	10(50%)	12(60%)	10(50%)
Respiratory	3(15%)	7(35%)	4(20%)
Shock	2(10%)	1(5%)	1(5%)
Trauma	1(5%)	0(0%)	1(5%)
Other	1(5%)	0(0%)	3(15%)
Arterial Line - Yes[b]	17(85%)	18(90%)	17(85%)
Central line - Yes[b]	18(90%)	18(90%)	18(90%)
Chest tube - Yes[b]	11(55%)	11(55%)	10(50%)
Mediastinal tube - Yes[b]	9(45%)	9(45%)	6(30%)

[a] Mean (SD)

[b] n (%)

Table 6.2 Descriptive results for sedation variables

Variables	**Control**	**Music**	**Noise cancellation**	**P-value**
Sedation Intensity Score/day*	47.6(26.0)	53.7(36.9)	55.6(26.1)	0.561
Sedation Frequency/day*	8.58(6.11)	9.75(7.10)	10.9(8.14)	0.511

*Mean (SD)

Table 6.3 Mean (SD) sedation, pain, withdrawal and delirium scores by group.

Variables	Control	Music	Noise cancellation	P-value
SBS	-0.76(0.87)	-0.74(0.95)	-0.53(0.96)	0.866
FLACC	1.30(1.36)	1.17(1.26)	1.62(1.72)	0.847
WAT	1.12(1.17)	1.85(1.54)	1.65(1.14)	0.064
CAPD	12.47(4.56)	13.09(5.54)	13.86(4.66)	0.420

SBS, State Behavioral Scale; FLACC, Face Legs Activity Cry Consolability scale; WAT, Withdrawal Assessment Tool; CAPD, Cornell Assessment of Pediatric Delirium

Table 6.4 Mean (SD) vital signs before, during and after the intervention by group.

Variables	**Prior to the intervention**	**15 minutes of the intervention**	**The end of the intervention**	**30 minutes after the intervention**	**P-value**
Music					
HR/minute	122 (23.3)	119 (25.2)∗	120 (24.7)	121 (25.6)	0.004
RR/minute	27.2 (7.7)	27.0 (7.65)	27.2 (9.29)	27.9 (8.74)	0.631
SBP - mmHg	88.3 (13.1)	88.6 (12.91)	87.4 (13.4)	87.8 (13.8)	0.438
DBP - mmHg	49.9 (9.62)	49.6 (9.41)	48.9 (9.75)	49.4 (9.69)	0.306
Oxygen saturation - %	92.9 (7.92)	92.7 (8.24)	91.7 (11.1)	92.8 (8.39)	0.378
Noise cancellation					
HR/minute	126 (23.3)	124 (21.6)+	124 (21.5)	125 (22.1)	0.021
RR/minute	27.2 (6.58)	25.5 (6.03)±	26.6 (6.76)	27 (8.22)	0.001
SBP - mmHg	85.6 (13.7)	82.9 (11.6)	83.9 (13.1)	84.6 (11.6)	0.112
DBP - mmHg	48.3 (9.72)	47.2 (8.12)	47.5 (9.04)	47.8 (9.64)	0.265
Oxygen saturation - %	93.6 (7.84)	93.7 (7.39)	93.8 (7.16)	93.7 (7.47)	0.481

HR, Heart Rate; RR, Respiratory Rate; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure.

∗ P-value = 0.008 compare to the "Prior to the intervention value"

+P-value = 0.008 compare to the "Prior to the intervention value"

±P-value = 0.008 compare to the "Prior to the intervention value"

Table 6.5 Outcome variables by group

Variables	Control	Music	Noise cancellation	P-value
Mechanical ventilation – Days*	7.3 (5.49)	8.2 (5.49)	7.3 (5.49)	0.723
ICU LOS – Days*	11.1 (8.33)	16.0 (8.33)	11.1 (8.33)	0.145
Hospital LOS – Days*	39.6 (47.0)	59.2 (47.0)	39.6 (47.0)	0.585
Survival to hospital discharge n (%) - Yes	18 (90%)	17 (94.5%)	19.0 (95%)	0.999

*Mean (SD)

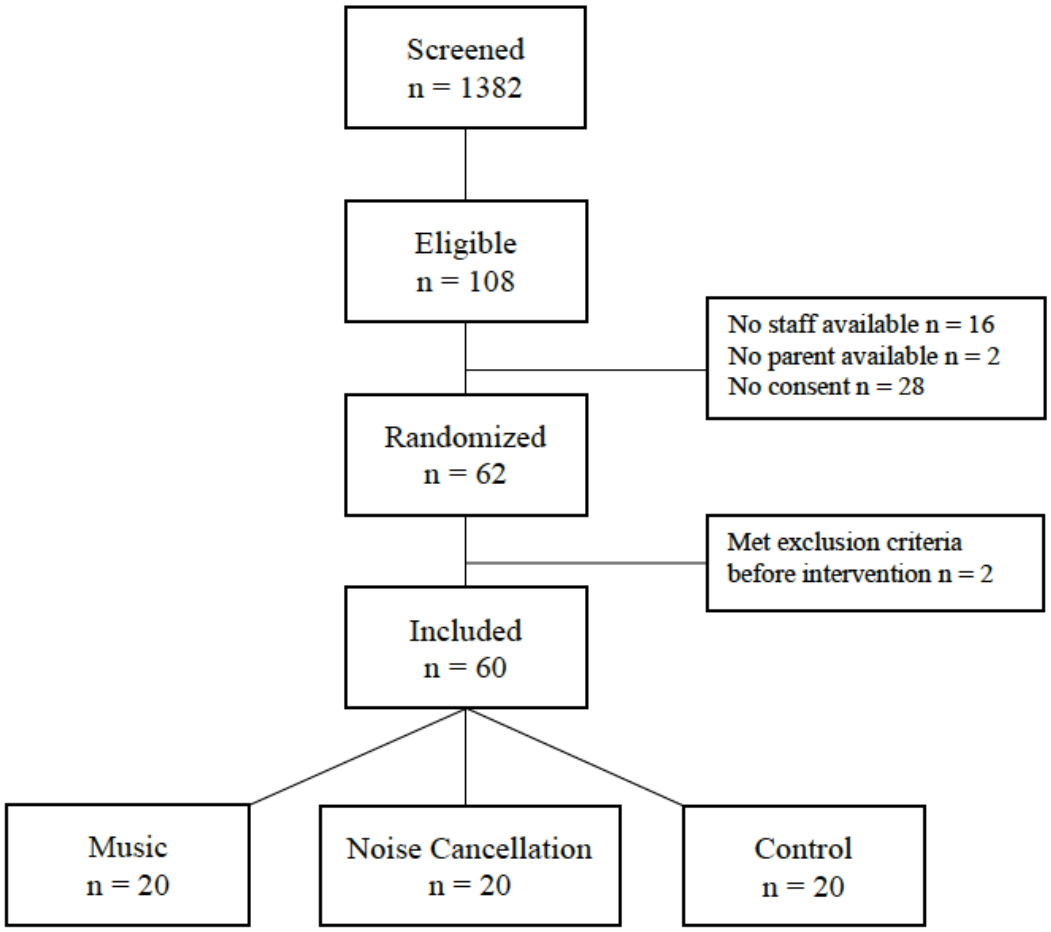


Figure 6.1 Flow chart

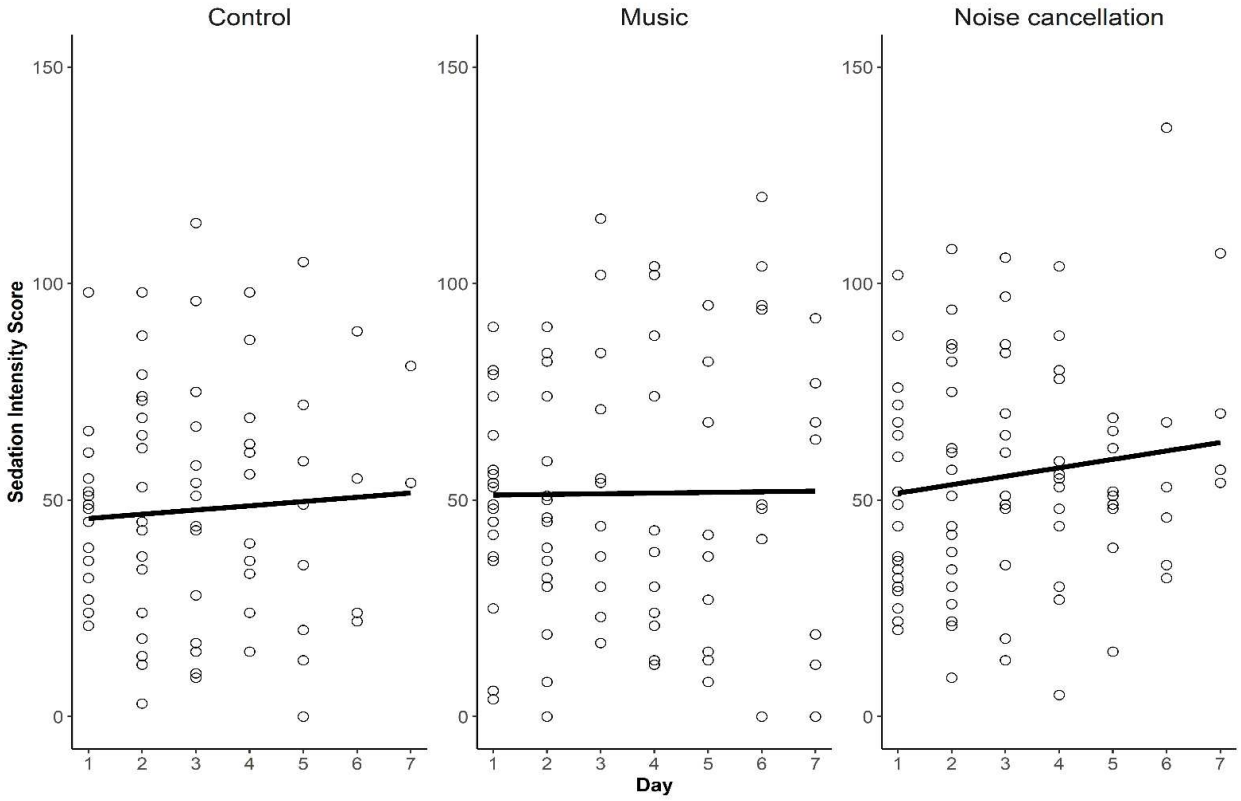


Figure 6.2 Sedation Intensity Score scatterplots by group

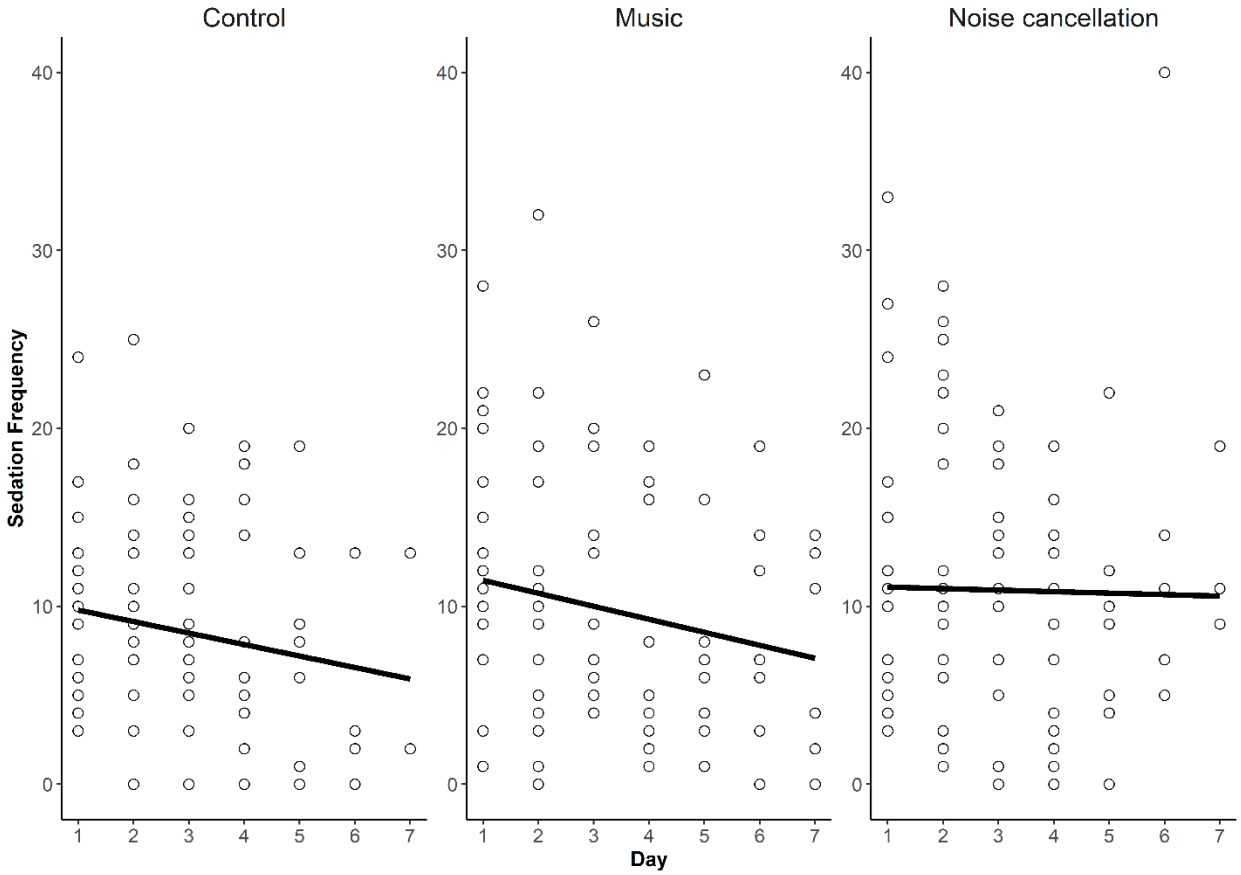


Figure 6.3 Sedation Frequency scatterplots by group

Chapter 7: Conclusion

This PhD thesis investigates the topic of sedation/analgesia in critically ill children. Specifically, it explores the use non-pharmacologic interventions, in particular music, to provide sedation/analgesia in the PICU environment. Hence, this thesis provides valuable information on a sedation/analgesia strategy that has been recommended but poorly studied. [72] [7] [8] The use of music and other non-pharmacologic interventions have the potential to reduce the use of narcotics and sedatives in PICU and their well described adverse effects. [2] [3] [4] [5]

7.1 Summary of findings

The four studies presented in this thesis follow a research program aimed at gathering the necessary information to conduct a large randomized controlled trial to investigate the effectiveness of music for sedation/analgesia in critically ill children.

The first study shows that pain/sedation and withdrawal symptoms are routinely assessed in Canadian PICUs. On the other hand, sedation guidelines and protocols to safely minimize sedation, to prevent delirium and withdrawal symptoms, and to promote sleep are lacking. Access to natural light is common, but protocols to reduce exposure to noise and light at nighttime are lacking. Simple interventions like eye masks, earplugs, and other noise reduction strategies are infrequently used. Non-pharmacologic comfort measures are commonly used in PICUs despite the lack of evidence of efficacy or guidelines for their implementation. In this context, a high proportion (75%) of our respondents are using music in their units. However, the majority use music played at the head of the bed as chosen by parents/family with little intervention or guidance from a music therapist. Whether this is an effective way to provide music to critically ill children remains unknown. Through this survey, we found that Canadian intensivists believe that non-pharmacologic interventions to promote comfort in pediatric critical

care (e.g., music) should be further studied. They expressed interest in the formal study of non-pharmacologic interventions in the PICU and that sedation/analgesia requirements would be a meaningful and significant outcome for these studies.

The second study of this thesis explored sound levels in the pediatric critical care environment and their association with sedation/analgesia requirements. The study showed that sound levels were consistently higher than recommended values, not only during daytime but also during night hours. Morning patient rounds were significantly associated with high LAeq and LAmax levels and can be the target for an intervention to decrease sound levels in PICU. More importantly, we found an association between sound levels and sedation requirements suggesting that elevated sound levels likely represent noise (affecting patient comfort). These findings suggest that sound levels are clinically relevant and we should create a less noisy environment for critically ill children. Also, this information together with the available adult data suggests that noise can be a significant confounder in a music trial involving the use of headphones to deliver the intervention. [23]

The third study had the aim 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. This review found only six studies, all involving adult ICU patients, reporting 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 investigating the use of music for sedation/analgesia in PICU. 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 was low due to inconsistency and imprecision. Only one study demonstrated that music was statistically

associated with less sedation requirements. [23] Also, it is important to note that patients in the included studies were relatively stable and the majority was in a weaning phase from their mechanical ventilation. This has two important implications: none of the studies evaluated heavily sedated patients in the acute phase of their illness; and the included patients would already have been on narcotics and sedatives for some time, with variability in the ICU length of stay at the time of study entry. Overall, our 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. This information confirmed that further research is needed to determine the role of music in the ICU setting, especially in pediatrics, which lead to our fourth project.

The fourth study of this thesis consisted of a parallel three-group double blind randomized controlled trial consisting of a music, a noise cancellation and a control group: the MUSiCC trial. A pilot RCT is a necessary first step toward the conduct of a future definitive music trial in critically ill children. Our MUSiCC trial has demonstrated the feasibility of a music and a noise cancellation intervention in the pediatric intensive care environment. The study showed adequate consent rate, rate of enrollment, and protocol adherence. Missed interventions were mainly due to the intermittent use of paralytic agents around the times of interventions. The most common impression from the parents was that their children were often more settled and asleep during the interventions. We did not find any adverse events related to the music intervention. The MUSiCC pilot trial was the first study to use Chlan's Sedation Intensity Score in the PICU environment, and provided the needed data to allow formal sample size calculation for a future larger trial. [23] [147]

7.2 Implications for clinical practice

Stress secondary to pain and anxiety is common in critically ill children. Inadequate treatment of pain and anxiety can lead to loss of vascular access, unplanned extubation, self-injury, post-traumatic stress and impaired neurodevelopment. [3] Treating pain and agitation in critically ill children is challenging as the most commonly used drugs (narcotics and benzodiazepines) can have significant side effects. [2] [61] [5] Based on current recommendations suggesting the use of non-pharmacologic interventions to reduce the use of sedative/analgesia drugs, I developed my thesis in order to provide useful information on sedation and analgesia in PICU, and to establish whether music can be used to mitigate the use of excessive sedation in this fragile population. In my thesis, I have gained important knowledge that I believe is important for clinical practice.

a) There is significant variability in sedation/analgesia practices in PICU

Strategies to sedate and provide pain relief for critically ill children have significant variability among Canadian pediatric intensivists. This highlights the lack of high quality evidence available to guide the best approach for sedation and analgesia management in PICU. Due to this gap, and despite the theoretical benefit in reducing drug requirements, sedation/analgesia protocols are not commonly used. The use of Dexmedetomidine in PICU is increasing. This drug has the benefit of maintaining the respiratory drive and may be associated with shorter times on mechanical ventilation and lower incidence of ICU delirium. [149] [150]

Despite the suggested association between benzodiazepine use and ICU delirium and the potential negative effects benzodiazepines may have in the neurodevelopmental outcomes of critically ill children exposed at a young age, these sedatives are still commonly used in PICU. [7] [72] [121]The use of other sedatives and other strategies, including, non-pharmacologic

interventions, may help to reduce the use of benzodiazepines and their side effects in this population.

b) Non-pharmacologic interventions are being used but are not yet standardized

Non-pharmacologic interventions are being used in Canadian PICUs but their implementation is not protocolized and vary considerably from unit to unit. A systematic approach to using non-pharmacologic interventions that includes measures that normally provide comfort to children together with a quiet and calm environment may help to reduce over-sedation in critically ill children.

c) Sound levels in PICU are too high and are associated with increased sedation requirements

The prospective study of sound levels in PCICU presented in this thesis demonstrates that PICUs are busy environments with noise levels above recommendations and with little day/night variation. High sound levels are associated with poor sleep in PICU. [109] The study presented in chapter 4 of this thesis shows that high noise levels are also associated with increased sedation/analgesia requirements, and could be the target of interventions to reduce the use of these drugs in critically ill children.

d) There is not enough evidence to support or refute the use of music to reduce sedation and analgesia requirements, or to reduce delirium

Although music appears to be a promising intervention, our systematic review demonstrates there is presently not enough evidence that it decreases use of pharmacologic therapies for sedation/analgesia in critically ill children.

e) Music interventions are well tolerated by critically ill children

Our pilot RCT and a few other, similar, studies demonstrate that music is safe and well tolerated by children. Also, parents indicate that music is useful and their children are more settled and comfortable while music is being played. Although music is not yet ready to be formally implemented as a recommended strategy to reduce sedation/analgesia requirements in critically ill children, this intervention looks promising.

7.3 Implications for research

a) Research on non-pharmacologic interventions is welcomed by pediatric intensivists

The survey presented in this thesis shows that Canadian intensivists are interested in the formal investigation of non-pharmacologic interventions in PICU. Despite being used in many Canadian PICUs, intensivists recognize that this is a field that has not been formally studied and in which further research is needed to demonstrate which interventions are useful to provide comfort in critically ill children, and what is the best way to apply these interventions.

b) Sedation/analgesia requirements are a meaningful clinical outcome when studying non-pharmacologic interventions in PICU

Our survey has shown that pediatric intensivists believe that, in an era in which sedation and analgesia scores have become target goals as part of the daily health care plan for critically ill patients, sedation/analgesia requirements are a meaningful outcome for future research in this field. Non-pharmacologic interventions may provide comfort and analgesia while reducing the overall need for sedatives and narcotics and their side effects.

c) The MCID in reduction of sedation/analgesia requirements is 20%

The survey presented in this thesis established the MCID for sedation/analgesia in critical care in the event that a new safe and effective pharmacologic or non-pharmacologic intervention

was available. Canadian intensivists believe that a 20% reduction in sedation/analgesia requirements would be a meaningful reduction that would prompt them to implement the new intervention.

d) Noise is a significant confounder

The study on sound levels presented in this thesis suggests that noise is a potential confounder in studies using headphones (with some degree of noise cancellation) to explore the effect of music on sedation/analgesia in critically ill patients. Noise is not only associated with sedation/analgesia requirements but its reduction can also help to minimize the use of narcotics and sedatives. [23] Future studies using headphones to provide music in ICU should seriously consider a three-arm design that includes music-noise cancellation-control in order to distinguish the effects of music from those purely related to a quieter environment.

e) A music intervention in PICU is feasible

The final project of this thesis demonstrated that a study on music for sedation/analgesia in pediatric critical care is feasible. The novel approach of our pilot RCT included sedated and mechanically ventilated children in the acute phase of their illness. The study was well tolerated by children and was well accepted by parents. In this study, we did not identify any significant side effects or concerns regarding the use of a music intervention.

f) There is need for further research on music

The content of this thesis brings new information about the use of music in pediatric critical care but there are still many questions that need to be answered before it can be implemented as usual practice. First, the efficacy of music to provide comfort and reduce sedation/analgesia requirements in critically ill children still needs to be demonstrated. Second,

while our pilot study has proved the feasibility of the intervention, it was not powered to show a significant difference in sedation/analgesia requirements between groups. Importantly, the MUSiCC pilot trial is the first pediatric study to use the SIS and has collected valuable information that will allow a sample size calculation for future larger trials on music or other interventions aimed at reducing the use of sedation/analgesia drugs in PICU. Third, the optimal type of music and its dosing needs to be determined. The frequency and length of our music intervention was chosen based on limited available evidence on the use of music in critically ill patients. [8] Also, the type of music was selected with limited evidence that classical music can provide sedation and is appropriate for all ages. [140] Whether other types of music or different dosing of the music intervention could be more effective for critically ill children is unknown. Our MUSiCC trial intervention was administered in a fixed duration and frequency of 30 minutes, three times/day, which may fall short of demonstrating an effect in reducing daily sedation/analgesia requirements in critically ill patients who are receiving sedation 24 hours/day. A more flexible and pragmatic approach that allows the bedside nurse to titrate the intervention to effect may be more appropriate. Lastly, the effect of a music intervention for agitation (similar to a sedative PRN) is currently unknown and could be beneficial.

The MUSiCC trial forms the basis for future investigations on music interventions for comfort in the pediatric critical care environment and has provided information for an adequate sample size calculation. A future trial with the aim to demonstrate a significant difference of at least a 20% reduction in sedation/analgesia requirements with an alpha of 0.05 and a power of 80% will require 170 subjects per group. However, a more conservative estimate of sample size is based on an alpha of 0.005. Assuming the pre-study odds of music being effective 9:1, an alpha of 0.005 will reduce the false positive rate to 5%. [151] This approach yields a sample size

of 292 subjects per group. To obtain such a sample size will require a multicenter RCT design. The conduct of a multicenter pilot RCT is a reasonable next step to establish its feasibility across different institutions.

7.4 Next steps

In summary, based on the information provided in this thesis I believe the necessary next steps to advance the knowledge on music as an intervention to provide comfort and reduce sedation/analgesia requirements in critically ill children are:

- To investigate the optimal "dose", including duration and frequency, of music in critical care. A pragmatic approach could involve a fixed number of interventions plus extra music interventions as PRNs,
- To establish which type of music is more effective in the critical care setting. This may require RCTs comparing different types of music,
- To explore the underlying mechanisms by which music may produce sedation and analgesia in this population,
- To demonstrate the feasibility of a music intervention in critically ill children across institutions,
- To determine the efficacy of music to reduce sedation/analgesia requirements in critically ill children, and
- To investigate the effect of music on PICU delirium.

References

[1] Anand KJ, Clark AE, Willson DF, Berger J, Meert KL, Zimmerman JJ, Harrison R, Carcillo JA, Newth CJ, Bisping S, Holubkov R, Dean JM, Nicholson CE; Eunice Kennedy Shriver National Institute of Child Health; Himan Development (NICHD) Collaborative Pediatric Critical Care Research Network (CPCCRN). Opioid analgesia in mechanically ventilated children: results from the multicenter Measuring Opioid Tolerance Induced by Fentanyl study. Pediatr Crit Care Med. 2013 Jan;14(1):27-36.

[2] Tobias J. Sedation and Analgesia. In: Pediatric Critical Care Medicine, Basic Science and clinical evidence. , vol. Chapter 136 , London, Springer-Verlag, pp. 1642-1660.

[3] Johnson PN, Miller JL, Hagemann TM. Sedation and analgesia in critically ill children. AACN Adv Crit Care. 2012 Oct-Dec;23(4):415-434.

[4] Gupta K, Gupta VK, Jayashree M, Singhi S. Randomized controlled trial of interrupted versus continous sedative infusions in ventilated children. Pediatr Crit Care Med. 2012 Mar;13(2):131-135.

[5] Lambert RL, Brink LW, Maffei FA. Sedation and Analgesia. In Pediatric Critical Care Study Guide, Text and Review., vol. Chapter 18, London, Springer-Verlag, 2012, pp. 382-405.

[6] Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, Watson PL, Weinhouse GL, Nunnally ME, Rochwerg B, Balas MC, van den Boogaard M[1], Bosma KJ, Brummel NE, Chanques G, Denehy L, Drouot X, Fraser GL, Harris JE, Joffe AM, Kho ME, Kress JP, Lanphere JA[33], McKinley S, Neufeld KJ, Pisani MA, Payen JF, Pun BT, Puntillo KA, Riker RR, Robinson BRH, Shehabi Y, Szumita PM, Winkelman C, Centofanti JE, Price C, Nikayin S, Misak CJ, Flood PD, Kiedrowski K, Alhazzani W. 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 Sep;46(9):e825-e873.

[7] Playfor S, Jenkins I, Boyles C, Choonara I, Davies G, Haywood T, Hinson G, Mayer A, Morton N, Ralph T, Wolf A; United Kingdom Paediatric Intensive Care Society Sedation; Analgesia and Neuromuscular Blockade Working Group. Consensus guidelines on sedation and analgesia in critically ill children. Intensive Care Med. 2006 Aug;32(8):1125-1136.

[8] Garcia Guerra G, Almeida L, Zorzela L, King-Jones S, Joffe AR, Hartling L, Jou H, Vohra S; Canadian Critical Care Trials Group. Efficacy of music on sedation, analgesia and delirium in critically ill patients. A systematic review of randomized controlled trials. J Crit Care. 2019 Oct;53:75-80.

[9] van der Heijden MJ, Oliai Araghi S, vanDijk M, Jeekel J, Hunink MG. The Effects of Perioperative Music Interventions in Pediatric Surgery: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. PLoS One. 2015 Aug 6;10(8):e0133608.

[10] Tauth MH. Music as therapy in early history. Prog Brain Res. Prog Brain Res. 2015;217:143-158.

[11] Lee JH. The Effects of Music on Pain: A Meta-Analysis. J Music Ther. 2016 Winter;53(4):430-477.

[12] Chorna O, Filippa M, De Almeida JS, Lordier L, Monaci MG, Hüppi P, Grandjean D, Guzzetta A. Neuroprocessing Mechanisms of Music during Fetal and Neonatal Development: A Role in Neuroplasticity and Neurodevelopment. *Neural Plast.* Neural Plast. 2019 Mar 20;2019:3972918.

[13] Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965 Nov 19;150(3699):971-979.

[14] Bernatzky G, Presch M, Anderson M, Panksepp J. Emotional foundations of music as a non-pharmacological pain management tool in modern medicine. Neurosci Biobehav Rev. 2011 Oct;35(9):1989-1999.

[15] Klassen JA, Liang Y, Tjosvold L, Klassen TP, Hartling L. Music for pain and anxiety in children undergoing medical procedures: a systematic review of randomized controlled trials. *Ambul Pediat.* Ambul Pediatr. 2008 Mar-Apr;8(2):117-128.

[16] Nilsson U. The anxiety- and pain-reducing effects of music interventions: a systematic review. *ARON J.* 2008 Apr;87(4):780-807.

[17] Nilsson S, Kokinsky E, Nilsson U, Sidenvall B, Enskär K. School-aged children's experiences of postoperative music medicine on pain, distress, and anxiety. *Paediatr Anaesth.* 2009 Dec;19(12):1184-90.

[18] Chai PR, Carreiro S, Ranney ML, Karanam K, Ahtisaari M, Edwards R, Schreiber KL, Ben-Ghaly L, Erickson TB, Boyer EW. Music as an Adjunct to Opioid-Based Analgesia. J Med Toxicol. 2017 Sep;13(3):249-254.

[19] Lunde SJ, Vuust P, Garza-Villarreal EA, Vase L. Music-induced analgesia: how does music relieve pain?. Pain. 2019 May;160(5):989-993.

[20] Stefano GB, Zhu W, Cadet P, Salamon E, Mantione KJ. Music alters constitutively expressed opiate and cytokine processes in listeners. Med Sci Monit. 2004 Jun;10(6):MS18-27.

[21] Papathanassoglou EDE, Skrobik Y, Hegadoren K, Thompson P, Stelfox HT, Norris C, Rose L, Bagshaw SM, Meier M, LoCicero C, Ashmore R, Sparrow Brulotte T, Hassan I, Park T, Kutsogiannis DJ. Relaxation for Critically ill Patient Outcomes and Stress-coping Enhancement (REPOSE): a protocol for a pilot randomised trial of an integrative intervention to improve critically ill patients' delirium and related outcomes. BMJ Open. 2019 Jan 15;9(1):e023961.

[22] Bradt J, Dileo C. Music interventions for mechanically ventilated patients. Cochrane Database Syst Rev. 2014;(12):CD006902.

[23] Chlan LL, Weinert CR, Heiderscheit A, Tracy MF, Skaar DJ, Guttormson JL, Savik K. 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 Jun 12;309(22):2335-2344.

[24] Chlan LL, Heiderscheit A, Skaar DJ, Neidecker MV. Economic Evaluation of a Patient-Directed Music Intervention for ICU Patients Receiving Mechanical Ventilatory Support. Crit Care Med. 2018 Sep;46(9):1430-1435.

[25] Richard-Lalonde M, Gélinas C, Boitor M, Gosselin E, Feeley N, Cossette S, Chlan LL. The effect of music on pain in the adult intensive care unit: A systematic review of randomized controlled trials. J Pain Symptom Manage. 2019 Dec 24. pii: S0885-3924(19)31064-4.

[26] Hu RF, Jiang XY, Hegadoren KM, Zhang YH. Effects of earplugs and eye masks combined with relaxing music on sleep, melatonin and cortisol levels in ICU patients: a randomized controlled trial. Crit Care. 2015 Mar 27;19:115.

[27] Hatem TP, Lira PI, Mattos SS. The therapeutic effects of music in children following cardiac surgery. J Pediatr (Rio J). 2006 May-Jun;82(3):186-192.

[28] Anderson DE, Patel AD. Infants born preterm, stress, and neurodevelopment in the neonatal intensive care unit: might music have an impact?. Dev Med Child Neurol. 2018 Mar;60(3):256-266.

[29] Hartling L, Shaik MS, Tjosvold L, Leicht R, Liang Y, Kumar M. Music for medical indications in the neonatal period: a systematic review of randomised controlled trials. Arch Dis Child Fetal Neonatal Ed. 2009 Sep;94(5):F349-354.

[30] Haslbeck FB. Music therapy for premature infants and their parents: an integrative review. Nordic Journal of Music Therapy. 2012;21(3):203-226.

[31] Hodges AL, WilsonLL. Effects of music therapy on preterm infants in the neonatal intensive care unit. Alternative Therapies in Health and Medicine. 2010 Sep-Oct;16(5):72-73

[32] Davis AS, Gantz MG, Do B, Shankaran S, Hamrick SE, Kennedy KA, Tyson JE, Chalak LF, Laptook AR, Goldstein RF, Hintz SR, Das A, Higgins RD, Ball MB, Hale EC, Van Meurs KP; Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network. Serial aEEG recordings in a cohort of extremely preterm infants: feasibility and safety. J Perinatol. 2015 May;35(5):373-378.

[33] Olischar M, Shoemark H, Holton T, Weninger M, Hunt RW. The influence of music on aEEG activity in neurologically healthy newborns≥ 32 weeks' gestational age. Acta Paediatr. 2011 May;100(5):670-675.

[34] Stokes A, Agthe AG, El Metwally D. Music exposure and maturation of late preterm sleep-wake cycles: a randomised crossover trial. Acta Paediatr. 2018 Apr;107(4):582-586. Acta Paediatr. 2018 Apr;107(4):582-586.

[35] Bradt J. The effects of music entrainment on postoperative pain perception in pediatric patients. Music and Medicine. 2010;2(3):150-157.

[36] Amini E, Rafiei P, Zarei K, Gohari M, Hamidi M. Effect of lullaby and classical music on physiologic stability of hospitalized preterm infants: A randomized trial. J Neonatal Perinatal Med. 2013 Jan 1;6(4):295-301

[37] Cignacco E, Hamers JP, Stoffel L, van Lingen RA, Gessler P, McDougall J, Nelle M. The efficacy of non-pharmacological interventions in the management of procedural pain in

preterm and term neonates. A systematic literature review. Eur J Pain. 2007 Feb;11(2):139-152.

[38] Standley J. Music therapy research in the NICU: an updated meta-analysis. Neonatal Netw. 2012 Sep-Oct;31(5):311-316.

[39] Kennelly J, Edwards J. Providing music therapy to the unconcious child in the paediatric intensive care unit. The Australian Journal of Music Therapy. 1997;8:18-29

[40] Drake L, Ben-Yelun F, del Olmo MJ. Musicoterapia en una UCI pediátrica: El uso de la música como emergente emocional en el proceso de intervención con niños en situación de riesgo. Revista de Investigación en Musicoterapi. 2017;1:14-31.

[41] del Olmo, Rodriguez Garrido C, Ruza Tarrio F. Music therapy in the PICU: 0- to 6-month-old babies. Music and Medicine.2010;2(3):158-166.

[42] Yurkovich J, Burns DS, Harrison T. The Effect of Music Therapy Entrainment on Physiologic Measures of Infants in the Cardiac Intensive Care Unit: Single Case Withdrawal Pilot Study. J Music Ther. 2018 Mar 9;55(1):62-82.

[43] Rennick JE, Stremler R, Horwood L, Aita M, Lavoie T, Majnemer A, Antonacci M, Knox A, Constantin E. A Pilot Randomized Controlled Trial of an Intervention to Promote Well-Being in Critically Ill Children: Soothing Through Touch, Reading, and Music. Pediatr Crit Care Med. 2018 Jul;19(7):e358-e366.

[44] Liu MH, Zhu LH, Peng JX, Zhang XP, Xiao ZH, Liu QJ, Qiu J, Latour JM. Effect of Personalized Music Intervention in Mechanically Ventilated Children in PICU: A Pilot Study. Pediatr Crit Care Med. 2020 Jan;21(1):e8-e14.

[45] Loewy J, Stewart K, Dassler AM, Telsey A, Homel P. The effects of music therapy on vital signs, feeding, and sleep in premature infants. Pediatrics. 2013 May;131(5):902-918.

[46] Heiderscheit A, Chlan L, Donley K. Instituting a music listening intervention for critically ill patients receiving mechanical ventilation: Examplars from two patient cases. Music Med. 2011 Oct 1;3(4):239-246.

[47] Roy M, Peretz I, Rainville P. Emotional valence contributes to music-induced analgesia. Pain. 2008 Jan;134(1-2):140-147.

[48] Zhao H, Chen AC. Both Happy and Sad Melodies Modulate Tonic Human Heat Pain. J Pain. 2009 Sep;10(9):953-960.

[49] Pediatrics AAo, Health CoE. American Academy of Pediatrics. Committee on Environmental Health. Noise: a hazard for the fetus and newborn, Pediatrics. 1997 Oct;100(4):724-727.

[50] Burns KE, Duffett M, Kho ME, Meade MO, Adhikari NK, Sinuff T, Cook DJ; ACCADEMY Group. A guide for the design and conduct of self-administered surveys of clinicians. CMAJ. 2008 Jul 29;179(3):245-252.

[51] Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009 Apr;42(2):377-381.

[52] Granger CWJ. Investigating Causal Relations by Econometric Models and Cross-spectral Methods. Econometrica1969;37(3):424-438.

[53] Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta- Analyses: The PRISMA Statement. PLoS Med. 2009 Jul 21;6(7):e1000097.

[54] Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors). Cochrane Handbook for Systematic Reviews of Interventions version 6.0 (updated July 2019). Cochrane, 2019. Available from www.training.cochrane.org/handbook.

[55] Traube C, Silver G, Kearney J, Patel A, Atkinson TM, Yoon MJ, Halpert S, Augenstein J, Sickles LE, Li C, Greenwald B. Cornell Assessment of Pediatric Delirium: Avalid, rapid, observational tool for screening delirium in the PICU. Crit Care Med. 2014 Mar;42(3):656-663.

[56] Curley MA, Harris SK, Fraser KA, Johnson RA, Arnold JH. State Behavioral Scale (SBS) A Sedation Assessment Instrument for Infants and Young Children Supported on Mechanical Ventilation Pediatr Crit Care Med. 2006 Mar;7(2):107-114.

[57] Franck LS, Harris SK, Soetenga DJ, Amling JK, Curley MA. The Withdrawal Assessment Tool-1 (WAT-1): an assessment instrument for monitoring opioid and benzodiazepine withdrawal symptoms in pediatric patients. Pediatr Crit Care Med. 2008 Nov;9(6):573-580.

[58] Franck LS, Scoppettuolo LA, Wypij D, Curley MA. Validity and generalizability of the Withdrawal Assessment Tool-1 (WAT-1) for monitoring iatrogenic withdrawal syndrome in pediatric patients. Pain. 2012 Jan;153(1):142-148.

[59] Whitehead AL, Julious SA, Cooper CL, Campbell MJ. Estimating the sample size for a pilot randomised trial to minimise the overall trial sample size for the external pilot and main trial for a continuous outcome variable. Stat Methods Med Res. 2016 Jun;25(3):1057-1073.

[60] Tobias JD. Sedation and analgesia in the pediatric intensive care unit. Pediatr Ann. 2005 Aug;34(8):636-645.

[61] Ostermann ME, Keenan SP, Seiferling RA, Sibbald WJ. Sedation in the intensive care unit: A systematic review. JAMA. 2000 Mar 15;283(11):1451-1459.

[62] Benini F, Farina M, Capretta A, Messeri A, Cogo P. Sedoanalgesia in paediatric intensive care: A survey of 19 Italian units. Acta Paediatr. 2010 May;99(5):758-762.

[63] Hartman ME, McCrory DC, Schulman SR. Efficacy of sedation regimens to facilitate mechanical ventilation in the pediatric intensive care unit: A systematic review. Pediatr Crit Care Med. 2009 Mar;10(2):246-255.

[64] Jenkins IA, Playfor SD, Bevan C, Davies G, Wolf AR. Current United Kingdom sedation practice in pediatric intensive care. Paediatr Anaesth. 2007 Jul;17(7):675-683.

[65] Kudchadkar SR, Yaster M, Punjabi NM. Sedation, sleep promotion, and delirium screening practices in the care of mechanically ventilated children: A wake-up call for the pediatric critical care community. Crit Care Med. 2014 Jul;42(7):1592-600.

[66] Mencía S, Botrán M, López-Herce J, del Castillo J; Grupo de Estudio de Sedoanalgesia de la SECIP. Sedative, analgesic and muscle relaxant management in Spanish paediatric intensive care units, An Pediatr (Barc). 2011 Jun;74(6):396-404.

[67] Playfor SD, Thomas DA, Choonara I. Sedation and neuromuscular blockade in paediatric intensive care: A review of current practice in the UK. Paediatr Anaesth. 2003 Feb;13(2):147-151.

[68] Twite MD, Rashid A, Zuk J, Friesen RH. Sedation, analgesia, and neuromuscular blockade in the pediatric intensive care unit: Survey of fellowship training programs. Pediatr Crit Care Med. 2004 Nov;5(6):521-532.

[69] Long D, Horn D, Keogh S. A survey of sedation assessment and management in Australian and New Zealand paediatric intensive care patients requiring prolonged mechanical ventilation," Aust Crit Care. 2005 Nov;18(4):152-157.

[70] Rhoney DH, Murry KR. National survey on the use of sedatives and neuromuscular blocking agents in the pediatric intensive care unit. Pediatr Crit Care Med. 2002 Apr;3(2):129-133.

[71] Marx CM, Rosenberg DI, Ambuel B, Hamlett KW, Blumer JL Pediatric intensive care sedation: Survey of fellowship training programs. Pediatrics. 1993 Feb;91(2):369-378.

[72] Barr J, Fraser GL, Puntillo K, Ely EW, Gélinas C, Dasta JF, Davidson JE, Devlin JW, Kress JP, Joffe AM, Coursin DB, Herr DL, Tung A, Robinson BR, Fontaine DK, Ramsay MA, Riker RR, Sessler CN, Pun B, Skrobik Y, Jaeschke R; American College of Critical Care Medicine. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med. 2013 Jan;41(1):263-306.

[73] Skrobik Y, Ahern S, Leblanc M, Marquis F, Awissi DK, Kavanagh BP. Protocolized intensive care unit management of analgesia, sedation, and delirium improves analgesia and subsyndromal delirium rates. Anesth Analg. 2010 Aug;111(2):451-463.

[74] Balas M, Olsen KM, Gannon DP, Sisson JH, Sullivan JN, Stothert JC, Jawa RS, , Joseph H. Sisson, James N. Sullivan, Joseph Clarke Stothert, Randeep S. Jawa, Vasilevskis EE, Burke WJ, Ely W. Safety and efficacy of the ABCDE bundle in critically-ill patients receiving mechanical ventilation. Crit Care Med. 2012;40:U18.

[75] Awissi DK, Bégin C, Moisan J, Lachaine J, Skrobik Y. I-SAVE study: Impact of sedation, analgesia, and delirium protocols evaluated in the intensive care unit: An economic evaluation, Ann Pharmacother. 2012 Jan;46(1):21-28.

[76] van Dijk M, de Boer JB, Koot HM, Tibboel D, Passchier J, Duivenvoorden HJ. The reliability and validity of the COMFORT scale as a postoperative pain instrument in 0 to 3-year-old infants. Pain. 2000 Feb;84(2-3):367-377.

[77] Crellin DJ, Harrison D, Santamaria N, Babl FE. Systematic review of the Face, Legs, Activity, Cry and Consolability scale for assessing pain in infants and children: Is it reliable, valid, and feasible for use? Pain. 2015 Nov;156(11):2132-51.

[78] Sessler CN, Gosnell MS, Grap MJ, Brophy GM, O'Neal PV, Keane KA, Tesoro EP, Elswick RK. The Richmond Agitation- Sedation Scale: Validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med. 2002 Nov 15;166(10):1338-1344.

[79] Ista E, de Hoog M, Tibboel D, Duivenvoorden HJ, van Dijk M. Psychometric evaluation of the Sophia Observation withdrawal symptoms scale in critically ill children. Pediatr Crit Care Med. 2013 Oct;14(8):761-769.

[80] Ely EW, Shintani A, Truman B, Speroff T, Gordon SM, Harrell FE Jr, Inouye SK, Bernard GR, Dittus RS. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA. 2004 Apr 14;291(14):1753-62.

[81] Daoud A, Diuff JP, Ari R Joffe, and the Alberta Sepsis Network. Diagnostic accuracy of delirium diagnosis in pediatric intensive care: A systematic review. Crit Care. 2014 Sep 26;18(5):489.

[82] Poh YN, Poh PF, Buang SN, Lee JH. Sedation guidelines, protocols, and algorithms in PICUs: A systematic review. Pediatr Crit Care Med. 2014 Nov;15(9):885-892

[83] Keogh SJ, Long DA, Horn DV. Practice guidelines for sedation and analgesia management of critically ill children: A pilot study evaluating guideline impact and feasibility in the PICU. BMJ Open. 2015 Mar 30;5(3):e006428.

[84] Neunhoeffer F, Kumpf M, Renk H, Hanelt M, Berneck N, Bosk A, Gerbig I, Heimberg E, Hofbeck M. Nurse-driven pediatric analgesia and sedation protocol reduces withdrawal symptoms in critically ill medical pediatric patients. Paediatr Anaesth. 2015 Aug;25(8):786-794

[85] Curley MA. RESTORE Study Investigators and the Pediatric Acute Lung Injury and Sepsis Investigators Network: Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: A randomized clinical trial. JAMA. 2015 Jan 27;313(4):379-389

[86] Larson GE, Arnup SJ, Clifford M, Evans J. How does the introduction of a pain and sedation management guideline in the paediatric intensive care impact on clinical practice? A comparison of audits pre and post guideline introduction. Aust Crit Care. 2013 Aug;26(3):118-123.

[87] Thomas M, Dhanani S, Irwin D, Writer H, Doherty D. Development, dissemination and implementation of a sedation and analgesic guideline in a pediatric intensive care unit…it takes creativity and collaboration. Dynamics. 2010 Winter;21(4):16-25.

[88] Van Eijk M. Quality and quantity of sleep in multiple versus single patient room intensive care units. Crit Care Med. 210;38:A206.

[89] Caruso P, Guardian L, Tiengo T, Dos Santos LS, Junior PM. ICU architectural design affects the delirium prevalence: A comparison between single-bed and multibed rooms. Crit Care Med. 2014 Oct;42(10):2204-2210.

[90] Kam P, Kam AC, Thompson JF. Noise pollution in the anesthetic, and intensive care environment. Anaesthesia. 1994 Nov;49(11):982-986.

[91] American Academy of Pediatrics. Committee on Environmental Health. Noise: a hazard for the fetus and newborn. Pediatrics. 1997 Oct;100(4):724-727.

[92] Darcy AE, Hancock LE, Ware EJ. A descriptive study of noise in the neonatal intensive care unit: ambient levels and perceptions of contributing factors. Adv Neonatal Care. 2008 Jun;8(3):165-175.

[93] Berlung B, Lindvall T Dietrich HS. Guidelines for cummunity noise. World Health Organization. 1993;April:43.

[94] Agency EP.Information on levels of environmental noise requisite to protect public health and welfare with an adequate margin of safety (report no 550- 9-74-004). Washington, DC: Environmental Protection Agency; 1974.

[95] Morrison W, Haas EC, Shaffner DH, Garrett ES, Fackler JC. Noise, stress, and annoyance in a pediatric intensive care unit. Crit Care Med. 2003 Jan;31(1):113-9.

[96] Grumet GW. Pandemonium in the modern hospital. N Engl J Med. 1993 Feb 11;328(6):433-437.

[97] Darbyshire JL, Young JD. An investigation of sound levels on intensive care unitswith reference to the WHO guidelines. Crit Care. 2013Sep 3;17(5):R187

[98] Topf M, Bookman M, Arand D. Critical care unit noise and rapid eye movement (REM) sleep. Heart Lung. 1993;22:252-258.

[99] Hansell HN. The behavioral effects of noise on man: the patient with "intensive care unit psychosis. Heart Lung. 1984 Jan;13(1):59-65.

[100] McCarthy DO, Ouimet ME, Daun JM. Shades of Florence Nightingale: potential impact of noise stress on wound healing. Holist Nurs Pract. 1991 Jul;5(4):39-48.

[101] Topf M, Bookman M, Arand D. Effects of critical care unit noise on the subjective quality of sleep. J Adv Nurs. 1996 Sep;24(3):545-551.

[102] Fife D, Rappaport E. Noise and hospital stay. Am J Public Health. 1976 Jul;66(7):680-1.

[103] B. Minckley. A study of noise and its relationship to patient discomfort in the recovery room. Nurs Res. 1968 May-Jun;17(3):247-250.

[104] Novaes MA, Aronovich A, Ferraz MB, Knobel E. Stressors in ICU: patients' evaluation. Intensive Care Med. 1997 Dec;23(12):1282-1285.

[105] Milette I. Decreasing noise level in our NICU: the impact of a noise awareness educational program. Adv Neonatal Care. 2010 Dec;10(6):343-351.

[106] Bailey E, Timmons S. Noise levels in PICU: an evaluative study. Paediatr Nurs. 2005 Dec;17(10):22-26.

[107] Christensen M. Noise levels in a general intensive care unit: a descriptive study. Nurs Crit Care. 2007 Jul-Aug;12(4):188-197.

[108] Carvalho W, Pedreira ML, de Aguiar MA. Noise level in a pediatric intensive care unit. J Pediatr (Rio J). 2005 Nov-Dec;81(6):495-498.

[109] Al-Samsam RH, Cullen P. Sleep and adverse environmental factors in sedated mechanically ventilated pediatric intensive care patients. Pediatr Crit Care Med. 2005 Sep;6(5):562-567.

[110] Jousselme C, Vialet R, Jouve E, Lagier P, Martin C, Michel F. Efficacy and mode of action of a noise-sensor light alarm to decrease noise in the pediatric intensive care unit: a prospective, randomized study. Pediatr Crit Care Med. 2011 Mar;12(2):e69-72.

[111] Kaur H, Rohlik GM, Nemergut ME, Tripathi S.Comparison of staff and family perceptions of causes of noise pollution in the Pediatric Intensive Care Unit and suggested intervention strategies. Noise Health. 2016 Mar-Apr;18(81):78-84.

[112] Kramer B, Joshi P. Heard C. Noise pollution levels in the pediatric intensive care unit. J Crit Care. 2016 Dec;36:111-115.

[113] Shoemark H, Harcourt E, Arnup SJ, Hunt RW. Characterising the ambient sound environment for infants in intensive care wards. J Paediatr Child Health. 2016 Apr;52(4):436-440.

[114] Kawai Y, Weatherhead JR, Traube C, Owens TA, Shaw BE, Fraser EJ, Scott AM, Wojczynski MR, Slaman KL, Cassidy PM, Baker LA, Shellhaas RA, Dahmer MK, Shever LL, Malas NM, Niedner MF. Quality improvement initiative to reduce pediatric intensive care unit noise pollution with the use of a pediatric delirium bundle. J Intensive Care Med. 2019 May;34(5):383-390.

[115] Robertson CM, Alton GY, Bork KT, Joffe AR, Tawfik GC, Sauve RS, Moddemann DM, Ross DB, Rebeyka IM. Bilateral sensory permanent hearing loss after palliative hypoplastic left heart syndrome operation. Ann Thorac Surg. 2012 Apr;93(4):1248-1253.

[116] White R, Smith J, Shepley MM. Recommended standards for newborn NICU design, eighth edition.J Perinatol. 2013 Apr;33 Suppl 1:S2-16.

[117] Liu W. Comparing sound measurements in the single-family room with open-unit design neonatal intensive care unit: the impact of equipment noise. J Perinatol. 2012 May;32(5):368-373.

[118] Kudchadkar SR, Yaster M, Punjabi AN, Quan SF, Goodwin JL, Easley RB, Punjabi NM. Temporal characteristics of the sleep EEG power spectrum in critically ill children. J Clin Sleep Med. 2015 Dec 15;11(12):1449-1454.

[119] Traube C, Silver G, Reeder RW, Doyle H, Hegel E, Wolfe HA, Schneller C, Chung MG, Dervan LA, DiGennaro JL, Buttram SD, Kudchadkar SR, Madden K, Hartman ME, deAlmeida ML, Walson K, Ista E, Baarslag MA, Salonia R, Beca J, Long D, Kawai Y, Cheifetz IM, Gelvez J, Truemper EJ, Smith RL, Peters ME, O'Meara AM, Murphy S, Bokhary A, Greenwald BM, Bell MJ. Delirium in critically ill children: an international point prevalence study. Crit Care Med. 2017 Apr;45(4):584-590.

[120] Harris J, Ramelet AS, van Dijk M, Pokorna P, Wielenga J, Tume L, Tibboel D, Ista E. Clinical recommendations for pain, sedation, withdrawal and delirium assessment in critically ill infants and children: an ESPNIC position statement for healthcare professionals. Intensive Care Med. 2016 Jun;42(6):972-986.

[121] Garcia Guerra G, Robertson CM, Alton GY, Joffe AR, Cave DA, Yasmin F, Dinu IA, Creighton DE, Ross DB, Rebeyka IM; Western Canadian Complex Pediatric Therapies Follow-up Group. Neurotoxicity of sedative and analgesia drugs in young infants with congenital heart disease: 4-year follow-up. Paediatr Anaesth. 2014 Mar;24(3):257-265

[122] Nasr VG, DiNardo JA. Sedation and analgesia in pediatric cardiac critical care. Pediatr Crit Care Med. 2016 Aug;17(8 Suppl 1):S225-31.

[123] Moore M, Nguyen D, Nolan SP, Robinson SP, Ryals B, Imbrie JZ, Spotnitz W. Interventions to reduce decibel levels on patient care units. Am Surg. 1998 Sep;64(9):894-899.

[124] Tick H, Nielsen A, Pelletier KR, Bonakdar R, Simmons S, Glick R, Ratner E, Lemmon RL, Wayne P, Zador V; Pain Task Force of the Academic Consortium for Integrative Medicine and Health. Evidence based nonpharmacologic strategies for comprehensive pain care: The Consortium Pain Task Force White Paper. Explore (NY) 2018 May-Jun;14(3):177-211.

[125] van der Heijden MJ, Oliai Araghi S, Jeekel J, Reiss IK, Hunink MG, van Dijk M Do Hospitalized Premature Infants Benefit from Music Interventions? A Systematic Review of Randomized Controlled Trials. PLoS One. 2016 Sep 8;11(9):e0161848.

[126] Higgins JPT, Sterne JAC, Savović J, Page MJ, Hróbjartsson A, Boutron I, Reeves B. A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). Cochrane Methods. Cochrane Database of Systematic Reviews 2016, Issue 10 (Suppl 1). dx.doi.org/10.1002/14651858.CD201601

[127] Garcia Guerra G, Almeida L, Zorzela L, King-Jones S, Joffe AR, Hartling L, Jou H, Vohra S. Efficacy of music on sedation/analgesia and delirium in critically ill patients: a systematic review of randomized controlled trials," PROSPERO, vol. CRD42017082749, p. Available from: http://www.crd.york.ac.uk/PROSPERO/display _record.php?ID=CRD42017082749, 2017.

[128] Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA; PRISMA-P Group. Preferred Reporting Items for Systematic Review and Meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4:1.

[129] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th edition. Washington, DC: American Psychiatric Association; 2000.

[130] Cavallazzi R, Saad M, Marik PE. Delirium in the ICU: an overview. Ann Intensive Care. 2012 Dec 27;2(1):49.

[131] Schünemann H, Brożek J, Guyatt G, Oxman A, editors. GRADE handbook for grading quality of evidence and strength of recommendations. gdt.gradepro.org/app/handbook/handbook.html (accessed prior to 25 October 2018).

[132] 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 Aug;28(4):442-450.

[133] To WTH, Bertolo T, Dinh V, Jichici D, Cindy M. Hamielec CM. Mozart Piano Sonatas as a Nonpharmacological Adjunct to Facilitate Sedation Vacation in Critically Ill Patients," Music and Medicine. 2013;5(2):119-127.

[134] Blankfield RP, Zyzanski SJ, Flocke SA, Alemagno S, Scheurman K. Taped therapeutic suggestions and taped Music as Adjuncts in the care of coronary-artery-bypass patients. Am J Clin Hypn. 1995 Jan;37(3):32-42.

[135] Iblher P, Mahler H, Heinze H, Huppe M, Klotz KF, Eichler W. Does music harm patients after cardiac surgery? A randomized, controlled study," Applied Cardiopulmonary Pathophysiology 2011;15:14-23.

[136] Ames N, Shuford R, Yang L. Music listening among postoperative patients in intensive care unit: a randomized controlled trial with mixed methods analysis. Integr Med Insights. 2017 Jul 20;12:1178633717716455.

[137] Nilsson U. The anxiety- and pain-reducing effects of music interventions: a systematic review. AORN J. 2008 Apr;87(4):780-807.

[138] Nelson A, Hartl W, Jauch KW, Fricchione GL, Benson H, Warshaw AL, Conrad C. The impact of music on hypermetabolism in critical illness. Curr Opin Clin Nutr Metab Care. 2008 Nov;11(6):790-4.

[139] Tracy MF, Chlan L. Nonpharmacological interventions to manage common symptoms in patients receiving mechanical ventilation. Crit Care Nurse. 2011;3119-3128.

[140] Conrad C, Niess H, Jauch KW, Bruns CJ, Hartl W, Welker L. Overture for growth hormone: requiem for interleukine-6. Crit Care Med. 2007 Dec;35(12):2709-2713.

[141] Garcia Guerra G, Joffe AR, Sheppard C, Pugh J, Moez EK, Dinu IA, Jou H, Hartling L, Vohra S; SedationWithdrawal and Analgesia Team (SWAT); Canadian Critical Care Trials Group (CCCTG). Prospective cohort study on noise levels in a pediatric cardiac intensive care unit. J Crit Care. 2018 Apr;44:318-322.

[142] Bergomi P, Chieppi M, Maini A, Mugnos T, Spotti D, Tzialla C, Scudeller L. Nonpharmacological Techniques to Reduce Pain in Preterm Infants Who Receive Heel-Lance Procedure: A Randomized Controlled Trial. Res Theory Nurs Pract. 2014;28(4):335-348.

[143] Garcia Guerra G, Joffe AR, Cave D, Duff J, Duncan S, Sheppard C, Tawfik G, Hartling L, Jou H, Vohra S; Sedation Withdrawal and Analgesia Team, and the Canadian Critical Care Trials Group. Survey of Sedation and Analgesia Practice Among Canadian Pediatric Critical Care Physicians. Pediatr Crit Care Med. 2016 Sep;17(9):823-830.

[144] Gaies MG, Gurney JG, Yen AH, Napoli ML, Gajarski RJ, Ohye RG, Charpie JR, Hirsch JC.Vasoactive-inotropic score as a predictor of morbidity and mortality in infants after cardiopulmonary bypass. Pediatr Crit Care Med. 2010 Mar;11(2):234-8.

[145] Bilan N, Galehgolab BA, Emadaddin A, Shiva Sh. Risk of mortality in pediatric intensive care unit, assessed by PRISM-III. Pak J Biol Sci. 2009 Mar 15;12(6):480-485.

[146] Duhamel A, Salleron J, Grandbastien B, Lacroix J, Leclerc F; Groupe Francophone de Réanimation et d'Urgences Pédiatriques (GFRUP). PELOD-2: an update of the Pediatric logistic organ dysfunction score. Crit Care Med. 2013 Jul;41(7):1761-1773.

[147] Tracy MF, Chlan L, Savik K, Skaar DJ, Weinert C. A Novel Research Method for Determining Sedative Exposure in Critically Ill Patients. Nurs Res. 2019 Jan/Feb;68(1):73-79.

[148] Ely EW. The ABCDEF Bundle: Science and Philosophy of How ICU Liberation Serves Patients and Families. Crit Care Med. 2017 Feb;45(2):321-330.

[149] Pereira JV, Sanjanwala RM, Mohammed MK, Le ML, Arora RC. Dexmedetomidine versus propofol sedation in reducing delirium among older adults in the ICU: A systematic review and meta-analysis. Eur J Anaesthesiol. 2020 Feb;37(2):121-131.

[150] Pan W, Wang Y, Lin L, Zhou G, Hua X, Mo L. Outcomes of dexmedetomidine treatment in pediatric patients undergoing congenital heart disease surgery: a meta-analysis. Paediatr Anaesth. 2016 Mar;26(3):239-248.

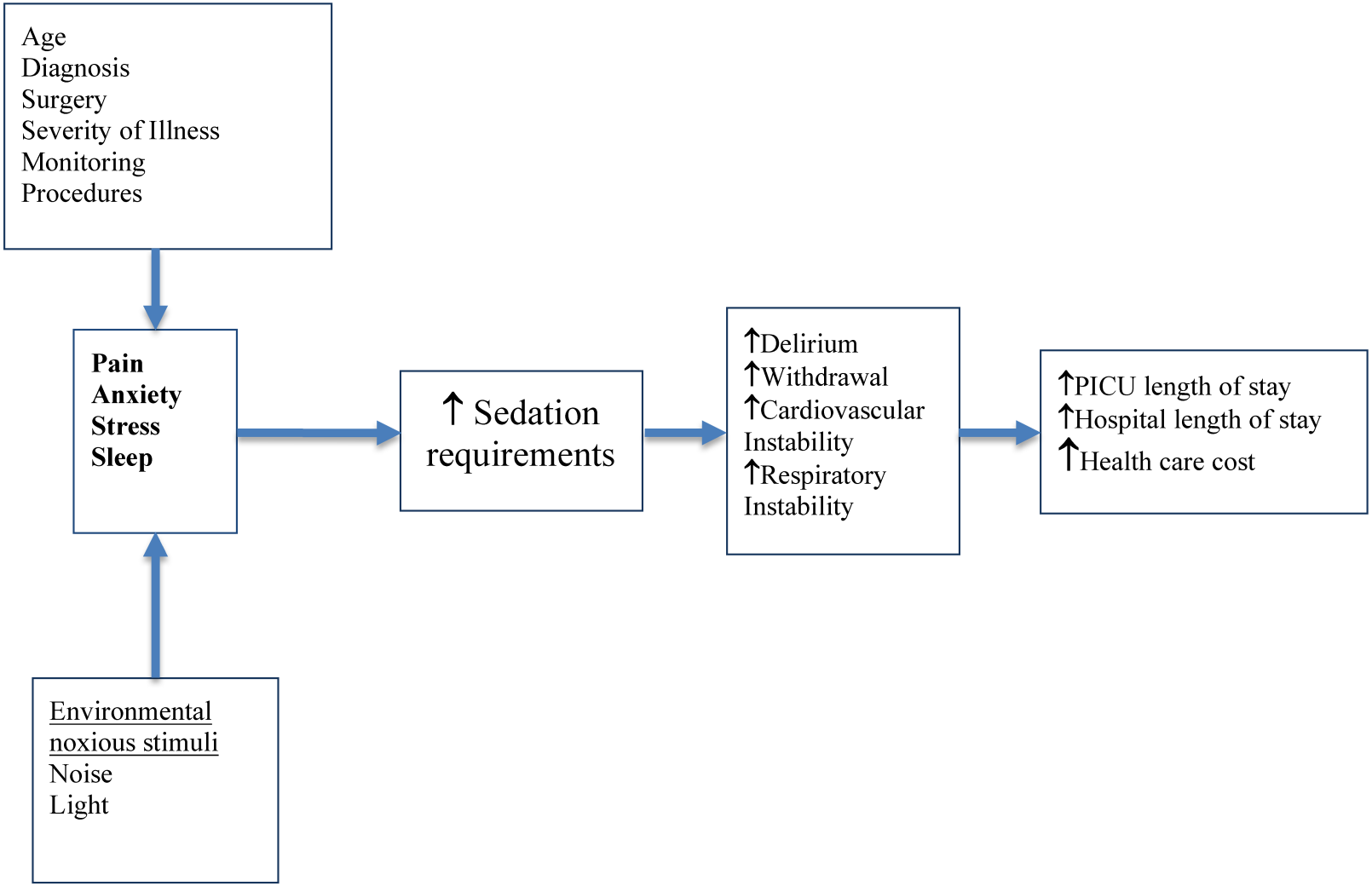
[151] Benjamin DJ, Berger JO, Johannesson M, et al. Redefine statistical significance. Nat Hum Behav. 2018 Jan;2(1):6-10.

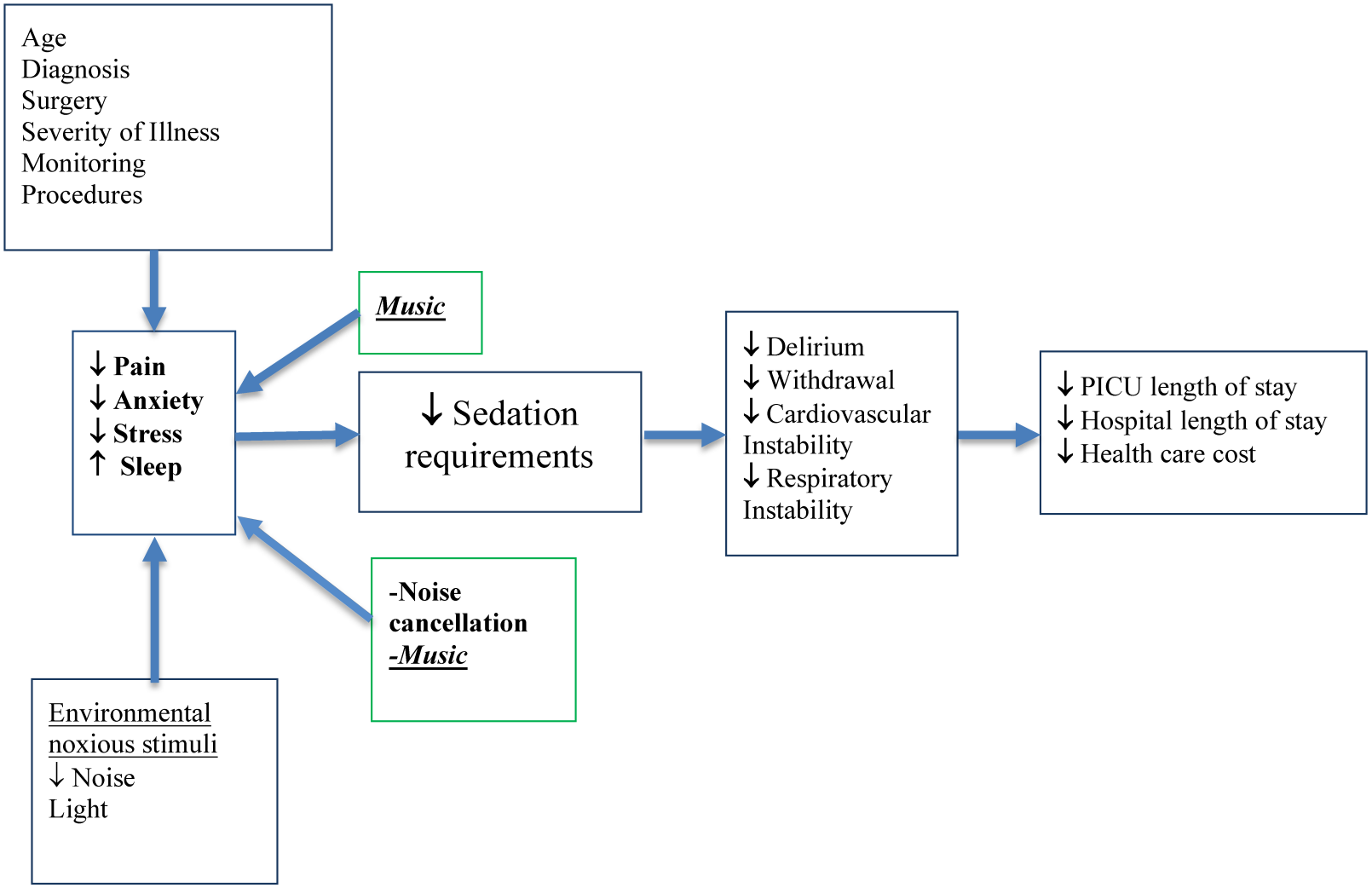
[152] Cepeda SM, Carr DB, Lau J, Alvarez H. Music for pain relief. Cochrane Database Syst Rev. 2006, Issue 2. Art. No.: CD004843. DOI: 10.1002/14651858.CD004843.pub2.

[153] Eldridge SM, Chan CL, Campbell MJ, Bond CM, Hopewell S, Thabane L, Lancaster GA; PAFS consensus group. CONSORT 2010 statement: extension to randomised pilot and feasibility trials. Pilot Feasibility Stud. 2016 Oct 21;2:64.

[154] Kudchadkar SR, Yaster M, Punjabi NM. Sedation, sleep promotion, and delirium screening practices in the care of mechanically ventilated children: a wake-up call for the pediatric critical care community. Crit Care Med. 2014 Jul;42(7):1592-1600.

Appendix I: Conceptual framework




Age
Diagnosis
Surgery
Severity of Illness
Monitoring
Procedures
Music
↓ Pain
↓ Anxiety
↓ Stress
↑ Sleep
↓ Sedation requirements
↓ Delirium
↓ Withdrawal
↓ Cardiovascular Instability
↓ Respiratory Instability
↓ PICU length of stay
↓ Hospital length of stay
↓ Health care cost
-Noise cancellation
-Music
Environmental noxious stimuli
↓ Noise
Light

Appendix II

Survey of Sedation and Analgesia Practice among Canadian Pediatric Critical Care Physicians

Demographics and PICU characteristics:

1. What type of pediatric intensive care unit (PICU) do you work in?

   ☐ General PICU only

   ☐ Cardiac PICU only

   ☐ Mixed unit (both cardiac and general patients)

   ☐ I work in both a separate general and cardiac ICU.

2. Which job title best fits your current position?

   ☐ Staff Intensivist

   ☐ Subspecialty pediatric critical care resident or fellow

   ☐ Clinical Assistant

3. How many years of experience do you have working in a PICU (including your years of PICU training)?

   ☐ < 1 year

   ☐ 1-5 years

   ☐ 6-10 years

   ☐ > 10 years

4. What is the number of operational (staffed) beds in your PICU?

   ☐ < 10 beds

   ☐ 11-20 beds

   ☐ > 20 beds

5. On a typical day what is the proportion of intubated mechanically ventilated patients in your PICU?

   ☐ <25%

   ☐ 25-50%

   ☐ 51-75%

   ☐ > 75%

6. Do you have a Pediatric Critical Care Subspecialty **Training Program** in your PICU?

   ☐ Yes

   ☐ No

7. Which kind of rooms do patients have in your PICU?

   ☐ Single rooms

   ☐ Shared rooms

   ☐ A combination of shared and single rooms

8. What is the proportion of beds in your PICU with a window that has access to natural light?

   _____%

☐ No windows

9. In an average week in your PICU, how often do you have a **pharmacist** present during patient rounds?

☐ Never

☐ 1-2 days/week

☐ 3-5 days/week

☐ 6-7 days/week

☐ Unknown

10. In your PICU, which of the following **SEDATION and/or PAIN scores** are commonly used for daily assessment of your patients? (Indicate ALL that are applicable):

☐ Don't use scores

☐ Bieri Faces Scale

☐ COMFORT Sedation agitation score

☐ COMFORT B

☐ Face, legs, activity, cry, consolability scale (FLACC)

☐ Numeric Rating Scale (NRS)

☐ Oucher Scale

☐ Ramsay score

☐ Richmond Agitation and Sedation Scale (RAAS)

☐ Visual Analog Scale (VAS)

☐ Other (please specify):……

☐ Unknown

11. In your PICU, which of the following **DELIRIUM scores** are commonly used for daily assessment of your patients? (Indicate ALL that are applicable):

- ☐ Don't use scores
- ☐ Cornell Assessment of Pediatric Delirium (CAP-D)
- ☐ Pediatric Anesthesia Emergence Delirium scale (PAED)
- ☐ Pediatric Confusion Assessment Method for the Intensive care unit (p-CAM)
- ☐ Other (please specify):……
- ☐ Unknown

12. In your PICU, which of the following withdrawal scores is commonly used for daily assessment of your patients (Indicate ALL that are applicable):

- ☐ Don't use scores
- ☐ Clinical suspicion
- ☐ Neonatal Abstinence Scoring System (Finnegan Tool)
- ☐ Neonatal Drug Withdrawal Scoring System (Lisitz Tool)
- ☐ Opioid and Benzodiazepine Withdrawal Score (OBWS)
- ☐ Sophia Observation Withdrawal Symptoms-scale (SOS)
- ☐ Withdrawal Assessment Tool-1 (WAT-1)
- ☐ Other (please specify):……
- ☐ Unknown

13. In your PICU, do you have **formal sedation/analgesia protocols** that are routinely use?

☐ Yes ☐ No ☐ Unknown

If yes, are these protocols led by

☐ Physicians ☐ Nurses ☐ Pharmacist

☐ Other

14. In your PICU, do you routinely practice **daily interruption** of continuous sedation/analgesia?

☐ Yes ☐ No ☐ Unknown

15. In your PICU, do you have a protocol to reduce light exposure and promote day/night cycles?

☐ Yes ☐ No ☐ Unknown

If yes, which of the following measures are used (Indicate ALL that are applicable)?

☐ Dimming lights at nighttime and during sleep

☐ Mask/eye covers

☐ Other:……..

☐ Unknown

16. In your PICU, which of the following methods is used to reduce noise exposure (Indicate ALL that are applicable)?

☐ Don't use any methods for noise reduction

☐ Headphones

☐ Earplugs

☐ Noise detectors with visual alarm

☐ Other:……..

☐ Unknown

17. In your PICU, which of the following comfort measures are commonly used in **intubated** patients (Indicate ALL that are applicable):

☐ Don't use comfort measures
☐ Holding by nurse/caregiver
☐ Music
☐ Noise reduction
☐ Reading
☐ Rocking
☐ Soother/Pacifier
☐ Sucrose solutions (For example: Tootsweet)
☐ Swaddling
☐ TV/Video
☐ Other (please specify):……
☐ Unknown

If **music is commonly used in your PICU**, how is the music usually **provided to your intubated** patients (Indicate ALL that are applicable):

☐ Live music played by a music therapist
☐ Recorded music played near the bed
☐ Recorded music played using headsets
☐ Other (please specify):……

The type of music is usually selected by [Indicate ALL that are applicable]:

☐ Music therapist
☐ Nurses
☐ Parents/family members
☐ Physicians

☐ Other (please specify):……

Analgesia

18. For intubated and mechanically ventilated patients **requiring continuous infusion of analgesic** agents, in what proportion of patients do you use the following drugs as continuous infusion?

	0-5%	**6 to 25%**	**26 to 50%**	**51 to 75%**	**76 to 100%**
Dexmedetomidine	☐	☐	☐	☐	☐
Fentanyl	☐	☐	☐	☐	☐
Hydromorphone	☐	☐	☐	☐	☐
Ketamine	☐	☐	☐	☐	☐
Morphine	☐	☐	☐	☐	☐
Remifentanil	☐	☐	☐	☐	☐
Other:……..	☐	☐	☐	☐	☐
Other:……..	☐	☐	☐	☐	☐
Other:…….	☐	☐	☐	☐	☐

☐ Unknown

19. For intubated and mechanically ventilated patients **requiring** continuous infusions of analgesia drug(s), in what proportion of patients do you intermittently (PRNs) use the following **adjunct drugs**?

	0-5%	6 to 25%	26 to 50%	51 to 75%	76 to 100%
Acetaminophen					
Codeine	☐	☐	☐	☐	☐
Ibuprofen	☐	☐	☐	☐	☐
Ketamine	☐	☐	☐	☐	☐
Ketorolac	☐	☐	☐	☐	☐
Other:……..	☐	☐	☐	☐	☐
Other:…….	☐	☐	☐	☐	☐
Other:…….	☐	☐	☐	☐	☐

☐ Unknown

Sedation

20. For intubated mechanically ventilated patients **requiring continuous infusion of sedative agents**, in what proportion of patients do you use the following drugs as continuous infusion?

	0-5%	6 to 25%	26 to 50%	51 to 75%	76 to 100%
Dexmedetomidine					
Fentanyl	☐	☐	☐	☐	☐

Hydromorphone	☐	☐	☐	☐	☐
Ketamine	☐	☐	☐	☐	☐
Lorazepam	☐	☐	☐	☐	☐
Morphine	☐	☐	☐	☐	☐
Midazolam	☐	☐	☐	☐	☐
Propofol	☐	☐	☐	☐	☐
Remifentanil	☐	☐	☐	☐	☐
Other:……..	☐	☐	☐	☐	☐
Other:…….	☐	☐	☐	☐	☐
Other:…….	☐	☐	☐	☐	☐
Other:…….	☐	☐	☐	☐	☐

☐ Unknown

21. For intubated mechanically ventilated patients **requiring** continuous infusion of sedation drug(s), in what proportion of patients do you use the following **adjunct drugs**?

	0-5%	**6 to 25%**	**26 to 50%**	**51 to 75%**	**76 to 100%**
Chloral Hydrate					

Clonidine	☐	☐	☐	☐	☐
Diphenhydramine	☐	☐	☐	☐	☐
Haloperidol	☐	☐	☐	☐	☐
Olanzapine	☐	☐	☐	☐	☐
Phenobarbital	☐	☐	☐	☐	☐
Risperidone	☐	☐	☐	☐	☐
Other:……..	☐	☐	☐	☐	☐
Other:…….	☐	☐	☐	☐	☐

☐ Unknown

22. Imagine that a randomized controlled trial (RCT) shows that a *new* sedation/analgesia intervention (pharmacological or non-pharmacological) can effectively and safely reduce the cumulative dose of continuous sedation/analgesia drugs required in mechanically ventilated patients in PICU without the adverse side effects of other drugs (e.g., withdrawal, prolonged ventilation). What is the minimal percentage in drug use reduction (minimal clinically important difference, MCID) that would lead you to change your practice?

_____%

23. Do you think that non-pharmacological adjunct therapies to promote comfort in pediatric critical care (e.g., music therapy) should be studied in a randomized controlled trial (RCT)?

☐ Yes ☐ No ☐ Unknown

We now present you with scenarios of a patient you are treating in the PICU.

24. You have admitted to your PICU a 6 month old boy with the diagnosis of bronchiolitis. He is intubated, mechanically ventilated, has a central venous line and an arterial line, and a right side chest tube to drain a pneumothorax. He is hemodynamically stable, and ventilator settings are PIP 27 cmH_2O, PEEP 7 cmH_2O, RR 25 per minute and FiO_2 50%. Would you start a continuous infusion of drug/s to provide sedation and/or analgesia during his first day of admission?

☐ Yes ☐ No, I would only use intermittent doses.

Assume you decide to start a continuous infusion. Which drug would you choose as your 1st choice to provide sedation/analgesia as a continuous infusion?

a. (Drop down menu with options)

If the patient requires more sedation/analgesia, which drug would you **add** as a continuous infusion?

b. (Drop down menu with options including other)

If the patient still requires more sedation/analgesia, which drug would you **add** as a continuous infusion?

c. (Drop down menu with options including other)

- Which of the following adjunct therapies would you add to provide comfort to this patient in your usual practice (check all that apply)?

☐	Holding by nurse/caregiver	☐	Sucrose solution
☐	Music		(For example: Tootsweet)
☐	Noise reduction	☐	Swaddling
☐	Reading	☐	TV/Video
☐	Rocking	☐	Other:……
☐	Soother/Pacifier	☐	None of the above

25. You have admitted to your PICU a 10 year old girl with a diagnosis of septic shock. She is intubated and mechanically ventilated, and has a central venous line and arterial line. She is on epinephrine 0.1 mcg/kg/min and norepinephrine 0.1 mcg/kg/min infusions, and her blood pressure is labile. Would you start a continuous infusion of drug(s) to provide sedation and/or analgesia during her first day of admission?

☐ Yes ☐ No, I would only use intermittent doses.

Assume you decide to start a continuous infusion. Which drug would you choose as your 1st choice to provide sedation/analgesia as a continuous infusion?

a. (Drop down menu with options)

If the patient requires more sedation/analgesia, which drug would you **add** as a continuous infusion?

b. (Drop down menu with options including other)

If the patient still requires more sedation/analgesia, which drug would you **add** as a continuous infusion?

c. (Drop down menu with options including other)

- Which of the following adjunct therapies would you add to provide comfort to this patient in your usual practice (check all that apply)?

☐	Holding by nurse/caregiver	☐	Sucrose solution
☐	Music		(For example: Tootsweet)
☐	Noise reduction	☐	Swaddling
☐	Reading	☐	TV/Video
☐	Rocking	☐	Other:……
☐	Soother/Pacifier	☐	None of the above

26. You have admitted to your Cardiovascular PICU a 4 day old girl after an arterial switch repair for transposition of the great arteries. She is intubated and mechanically ventilated, has a central venous and arterial line, and a mediastinal chest tube. She is on milrinone 0.5mcg/kg/minute and epinephrine 0.05 mcg/kg/minute as infusions, and with this is hemodynamically stable. Would you start a continuous infusion of drug/s to provide sedation and/or analgesia during her first day of admission?

☐ Yes ☐ No, I would only use intermittent doses.

Assuming you decide to start a continuous infusion. Which drug would you choose as your 1st choice to provide sedation/analgesia as a continuous?

a. (Drop down menu with options)

If the patient requires more sedation/analgesia, which drug would you **add** as a continuous infusion?

b. (Drop down menu with options including other)

If the patient still requires more sedation/analgesia, which drug would you **add** as a continuous infusion?

c. (Drop down menu with options including other)

- Which of the following adjunct therapies would you add to provide comfort to this patient in your usual practice (check all that apply)?

☐	Holding by nurse/caregiver	☐	Sucrose solution
☐	Music		(For example: Tootsweet)
☐	Noise reduction	☐	Swaddling
☐	Reading	☐	TV/Video
☐	Rocking	☐	Other:……
☐	Soother/Pacifier	☐	None of the above

27. You have admitted to your Cardiovascular PICU a 7 year old boy with the diagnosis of cardiomyopathy. He is intubated and mechanically ventilated, and has a central venous line and arterial line. He is on milrinone 0.5mcg/kg/min and epinephrine at 0.1 mcg/kg/min as infusions. His ejection fraction (EF) is less than 10%. Would you start a continuous infusion of drug(s) to provide sedation and/or analgesia during his first day of admission?

☐ Yes ☐ No, I would only use intermittent doses.

Assume you decide to start a continuous infusion. Which drug would you choose as your 1st choice to provide sedation/analgesia as a continuous infusion?

a. (Drop down menu with options)

If the patient requires more sedation/analgesia, which drug would you **add** as a continuous infusion?

b. (Drop down menu with options including other)

If the patient still requires more sedation/analgesia, which drug would you **add** as a continuous infusion?

c. (Drop down menu with options including other)

- Which of the following adjunct therapies would you add to provide comfort to this patient in your usual practice (check all that apply)?

☐	Holding by nurse/caregiver	☐	Sucrose solution
☐	Music		(For example: Tootsweet)
☐	Noise reduction	☐	Swaddling
☐	Reading	☐	TV/Video
☐	Rocking	☐	Other:……
☐	Soother/Pacifier	☐	None of the above

Thank you for taking the time to complete this survey.

Appendix III: Search Strategy

Medline search strategy (search date: 2018 April 26)

1. exp Music/

2. exp Music Therapy/

3. exp Audioanalgesia/

4. Lullab$.mp.

5. song$.ti,ab.

6. (melodic$ or melody or melodies).ti,ab,kw.

7. music$.ti,ab,kw.

8. Medical resonance therapy music$.mp.

9. Headphones.ti,ab,kw.

10. Singing/

11. pink noise.ti,ab,kw.

12. white noise.ti,ab,kw.

13. Critical Illness/

14. exp Critical Care/

15. exp Intensive Care Units/

16. critically ill.ti,ab,kw.

17. critical care.ti,ab,kw.

18. intensive care.ti,ab,kw.

19. Intensive Care, Neonatal/

20. Intensive Care Units, Pediatric/

21. neonatal intensive care.ti,ab,kw.

22. pediatric intensive care.ti,ab,kw.

23. or/1-12

24. or/13-22

25. 23 and 24

26. limit 25 to humans

Appendix IV: Relevance Assessment Form

Relevance Assessment for Inclusion

Efficacy of music on sedation/analgesia and delirium in critically ill patients

Reviewer: _____ Paper Reference # Date |__|__|__|__|__|__|
D D M M Y Y

Instructions: Please complete the form on each study. If you reach a "NO" response, exclude the study.

A. Criteria	**Yes**	**No**	**Unclear**
1. Study Design			
a. Randomized Controlled Trial	[ ]	[ ]	[ ]
2. Population			
a. Critically ill patients	[ ]	[ ]	[ ]
3. Intervention			
a. Did at least one patient group receive/use music?	[ ]	[ ]	[ ]
b. Did all the patients in the intervention group receive/use a co-intervention?	[ ]	[ ]	[ ]

Potential study interventions

Live Music
Recorded music

B. Decision of Reviewer

Include [ ] Exclude [ ] Unsure [ ]

C. Final Decision

Include [ ] Exclude [ ] Unsure [ ]

Appendix V: Data Collection Form

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

First author	Journal/Protocol, etc	Year

Additional Reference to single trial

Choose 1 publication as the main reference (the one with the earliest publication date) and the rest will be additional references to the main one and should be listed below. All references to a trial should be linked under one *Study ID* in RevMan.

Code each publication	Author(s)	Journal/Conference Proceeding/Protocol, etc	Year
A			
B			
C			

Trial and participant characteristics

(when necessary indicate "not reported" or not applicable", please do not leave blanks)

Trial characteristics	
	Details
Country/Countries	
Multicenter	
Trial registry ID	
Trial registration document/protocol available?	(If yes , append to study)
Intervention arms studies	
Number of participants randomized to music arm	
Number of participants randomized control arm	
Number of participants randomized third arm (_____)	
Number of participants randomized to a co-intervention arm	

Control group	[ ] Standard of care [ ] Quite time [ ]Transitions] Headphones with no music [ ] Other
Type of music (check all that apply)	[ ] Classic [ ] Lullaby [ ] Instrumental [ ] Natural sounds [ ] Other:
Did the music included human voice?	[ ] yes [ ] no
Other details on the music played	
How was the music played (check all that apply)	[ ] Live [ ] Recorded played in the room [ ] Recorded played with headphones [ ] Other:_____
Who selected the music? (check all that apply)	[ ] Music Therapist [ ] Family member [ ] Nurse [ ] Patient [ ] Patient from a list [ ] Physician [ ] Child Life specialist [ ] Other:
Duration of each intervention (minutes)	
How many times per day?	
Wash out time between interventions? (for cross-over designs)	
How many days?	
Night time	[ ] yes [ ] no [ ] not reported
Day time	[ ] yes [ ] no [ ] not reported
Was the intervention before or around a procedure?	[ ] No [ ] Yes, which?
Number of drop-outs and reasons in intervention arm	
Number of drop-outs and reasons in control arm	

Analysis type	[ ] ITT [ ] Per protocol [ ] Other _____
Study Funding	[ ] Industry [ ] Government [ ] Other _____

Participant characteristics	
	Details
Age (years)	Mean (SD): days Range:
Age group (Neonate: < 30 days of age, Children: 31 days -17 years of age, Adults ≥18 years of age) (check all that apply)	[ ] Neonates [ ] Children [ ] Adults Preterm infants: weight 800 to 2430 Gram, GA 29-36 weeks. APGAR range: 5-10
Sex of participants N(%)	Male: Female:
Type of ICU	[ ] NICU [ ] PICU [ ] PCICU [ ] Adult ICU [ ]Adult CICU [ ] Other [ ] Premature
Mechanically ventilated Yes N (%)	
Sedated N (%)	[ ] no [ ] yes. If yes, [ ] only PRNs or [ ] continuous
Days in ICU between admission and enrollment. Mean (SD) or Median (IQR)	

Appendix VI: Music Use for Sedation in Critically ill Children (MUSiCC trial): study protocol for a pilot randomized controlled trial

Abstract

Background

Stress induced by pain and anxiety is common in pediatric intensive care unit (PICU) patients. Sedation/analgesia in PICU is usually achieved through various analgesics and sedatives. Excessive use of these drugs can put patients at risk for hemodynamic/respiratory instability, prolonged ventilation, withdrawal, delirium, and critical illness polyneuromyopathy.
The use of non-pharmacologic interventions has been recommended by sedation guidelines. However, non-pharmacologic measures in PICU, including music and noise reduction, have been inadequately studied.

Methods

The Music Use for Sedation in Critically ill Children (MUSiCC trial) pilot study is an investigator-initiated, three arm, randomized controlled trial (RCT) on the use of music for sedation in PICU. The main goal of the study is to demonstrate feasibility of a music trial in PICU and to obtain the necessary information to plan a larger trial. The study compares music versus noise cancellation versus control in sedated and mechanically ventilated children admitted to PICU. In the music group, children receive the music (modified classical music) three times a day for 30 minutes at a time. Music is delivered with noise cancellation headphones. The noise cancellation group receives the same intervention but with a no music (sham playlist). The control group receives usual care with no specific intervention. Children remain in the study until extubation or a maximum of 7 days. The primary outcomes of the study are feasibility and

sedation/analgesia requirements. Secondary outcomes include change in vital signs before and during the intervention, ICU delirium and adverse effects related to the intervention. The estimated sample size is 20 subjects per group for a total 60 children.

Discussion

Despite being recommended by current guidelines, evidence to support the use of music in PICU is lacking. Music has the potential to reduce sedation requirements and their negative side effects. This pilot RCT will demonstrate feasibility and provide the necessary information to plan a larger trial focusing on the effectiveness of the intervention.

Trial Registration

The study was registered at ClinicalTrials.gov (NCT03497559) on April 13th, 2018.

Key words: sedation, analgesia, intensive care, pediatric, music.

Background

Stress induced by pain and anxiety is common in pediatric intensive care unit (PICU) patients and can impede the care to children as well as their recovery. [1] Children in PICUs experience pain and anxiety for a wide variety of reasons. [2] In PICU sedation/analgesia are not important just for comfort, but also for safety. Children with inadequate sedation/analgesia are at risk for loss of vascular access, extubation, self-injury, post-traumatic stress, etc. Sedation/analgesia in PICU is usually achieved through various analgesics and sedatives. However, excessive use of these drugs can put patients at risk for hemodynamic/respiratory instability, prolonged ventilation, withdrawal, delirium, and critical illness polyneuromyopathy. These negative consequences can lead to prolonged PICU stay and increase health care costs. [2] [3] [4] [5]

Non-pharmacologic measures for analgesia/anxiolysis are interventions that do not involve drugs, and thus may reduce the total medication requirement and their side effects.[5] The use of non-pharmacologic interventions has been recommended by published international sedation guidelines. [72] [7] However, none of these guidelines state how these interventions should be provided. A survey conducted by our group showed that Canadian PICUs do not use them routinely. [143] Non-pharmacologic measures in PICU, including music and noise reduction, have been inadequately studied. [9] Even more, the need for research around non-pharmacologic interventions in PICU has been recently identified. [143] In our survey, 85% of the respondents stated that non-pharmacologic interventions in PICU should be formally studied.

Music and medicine, mechanism of action

Although music has been used for years in healthcare, the exact mechanisms by which it can reduce pain/anxiety are not well understood. It is known that music can modify emotional

state by releasing anti-stress hormones and by activating the limbic system of the brain. [14] According to the gate control theory of pain, distracters such as music can block certain neural pathways and diminish the amount of perceived pain. [14] [15] [137] [17] [23]

Music in Adult Intensive Care Units

A systematic review on the use of music in mechanically ventilated adults found that music was associated with lower levels of anxiety, lower sedation requirements, and improved vital signs suggesting relaxation. [22] A randomized controlled trial (RCT) on patient-directed music demonstrated that music was associated with a reduction in anxiety, and in sedation requirements in critically ill adults. [23] A recent study showed that music can also improve sleep in adult ICU patients. [26]

Music in the Pediatric setting

A systematic review demonstrated that music can reduce procedural pain in a variety of clinical settings. [15] Another review showed that music was associated with lower pain scores and anxiety in children going for surgery. [9] Other studies have found similar results showing that music can be used to treat pain in pediatric clinical settings. [17] [27] [35]However, none of these studies explored the use of music for sedation/analgesia in the intensive care unit setting other than during a single painful procedure.

Music in Pediatric Intensive Care

In newborns, music has been shown to be effective in reducing pain and stress behavior during procedures. Music is also associated with more stable vital signs, increased weight gain, shorter length of stay, and increased parental satisfaction with neonatal intensive care. [35] [29] [36] [37] [38] A large RCT confirmed that music is associated with better vital signs, improved feeding behaviour, and prolonged time remaining settled. [45] Except for studies conducted in

neonatal intensive care units, there is only one RCT on music in critically ill children that evaluated the effects of music on vital signs and pain scores, which demonstrated that music improved these clinical signs. [27] However, this trial used music only once for 30 minutes in the first 24 hours after surgery and did not investigate effects on sedation requirements. Whether these benefits would be observed with repeated use over several days in PICU is not known.

Potential Concerns in Critically Ill Children

Although music can have positive effects, the contrary is also possible. [46] There is evidence that pleasant music can alleviate pain perception, but unpleasant music had no significant effect. [47] [48] Music, especially with the use of headphones, can pose a challenge for patient communication. [17] As communication is already limited in PICU patients, close monitoring while applying this type of interventions may be required. As recommended by the American Academy of Pediatrics, volume should be kept $\leq$ 45 dB. [49] Music may reduce pain and anxiety, but patients should not receive music as the sole source of sedation as it is not likely to be adequate in isolation. [152]

Rationale for the study and study hypothesis

Despite the recommendations from current guidelines on the use of music in critical care, a recent systematic review conducted by the authors (unpublished data) demonstrated that there are no published or ongoing RCTs investigating the effect of music on sedation and analgesia requirements in critically ill children. [72] [7] Hence the effect of music in sedated and mechanically ventilated children and the optimal administration of such an intervention is unknown. Previous studies, especially in adult ICU, have led the way on the use of music to provide sedation/analgesia in the critical care setting. However, the optimal administration of music (type, mode, and frequency) and its effectiveness in PICU needs to be established. The

aim of the MUSiCC pilot trial is to determine the feasibility of a pediatric music trial, to study the effects of music on sedation/analgesia requirements and in the incidence of delirium in children admitted to PICU. We hypothesize that an RCT of music in critically ill children will be feasible. Further, the pilot study will allow us to collect pediatric data on sedation and analgesia requirements, which will be necessary to calculate the sample size for a future, larger, trial. A survey conducted by this research group found that reduction in sedation requirements is a meaningful and clinically relevant outcome for a trial on non-pharmacologic interventions in PICU. [143] The study is currently being conducted in the PICU and Pediatric Cardiac Intensive Care Unit (PCICU) of the Stollery Children's Hospital (Edmonton, AB, Canada).

Methods

Study Design

The MUSiCC trial pilot study is an investigator-initiated, three arm RCT examining the use of music for sedation in PICU. A parallel three-group design including a noise cancellation group was included based on adult data showing that noise cancellation can reduce sedation requirements as well as pediatric evidence that noise levels are associated with sedation requirements in PCICU. [23] [141]

Patient eligibility – Inclusion Criteria

Upon admission to the PICU or PCICU, all critically ill children are screened for eligibility and inclusion in the MUSiCC pilot trial by research nurses. All non-eligible patients, identified by the investigators, are logged. All children admitted to the Stollery Children's Hospital PICU or PCICU, with an age of 1 month to 16 years of age, receiving invasive

mechanical ventilation for > 24 hours, are eligible and approach for consent by our research nurses.

Exclusion criteria

Patients meeting one or more of the following criteria are excluded:

- Known hearing deficit
- Infants < 1 month old and/or < 3 kilograms (as the headphones will not fit)
- Major Cranial-facial abnormalities (as the headphones will not fit)
- Traumatic Brain Injury (could cause pain in cranial fractures and risk of displacing intracranial catheters)
- Not receiving any sedation and/or analgesia drugs
- Receiving paralytic agents
- Expected to die in the next 48 hours
- On Extracorporeal Membrane Oxygenation (ECMO) with neck cannulation (difficulty fitting the headphones and risk of cannula displacement)
- Enrolled in another sedation intervention study

Data collection at study entry

At baseline the following variables are being recorded: demographic variables (sex, weight, age, diagnosis), unit of admission, operative status, pediatric risk of mortality score (PRISM) and whether the patient was on sedation and/or analgesia drugs prior to ICU admission. At the time of enrollment we are also collecting information on the following variables: Pediatric Logistic Organ Dysfunction score (PELOD2), inotrope score, need for invasive procedures, presence of invasive lines and tubes. [144] Variables are recorded in an anonymized database

using REDCap, Research Electronic Data Capture. [51] The data collection case report form is attached as Appendix VIII.

Randomized treatment allocation

Randomization procedure and treatment allocation

Randomization is done by a computer-based program to ensure allocation concealment and is being performed by the Epidemiology Coordinating and Research Centre (EPICORE), a clinical trials unit at the University of Alberta. A total of 60 patients are being consecutively randomly assigned in a 1:1:1 ratio to receive music, noise cancellation or control.

Blinding

In order to blind the intervention, the research nurse provides the portable music player (Apple iPod^{TM} touch, California, US).) with music or silent recording based on group allocation and does not disclose this information to the healthcare team or the family. The iPods assigned to the noise cancellation group have a sham playlist with a silent recording that displays in the iPod screen as if music were being played. Each 30 minutes playlist (music and sham) start with 1 minute of silent recording in an attempt to maintain blinding of the intervention. The volume in the iPods is set at approximately 45 to 55 dB. Based on the nature of the intervention, it is impossible to blind the use of headphones vs. control. However, collection of outcome data is blinded to group allocation. The statistician analyzing the data will also be blinded to the group allocation.

Randomized interventions

After consent and randomization, patients are started on the assigned intervention (music/noise cancellation/control) 24-48 hours after admission to the PICU. In the music and noise cancellation groups, the intervention is delivered three times a day for 30 minutes at a time. The bedside nurse determines the exact time of each intervention so that it doesn't interfere with care, e.g., avoiding times when clinical interventions are taking place. However, the bedside nurse is asked to deliver each intervention within the following time windows: 7am-12 pm (morning intervention), 12-4pm (afternoon intervention), and 4pm-8pm (evening intervention). The control group receives usual care. Music is delivered with the use of noise cancellation headphones (PURO® Sound Labs Kids BT2200 and BT5200, California, US) and an iPod touch. Puro Sound Labs headphones have an intrinsic volume restrictor of 85dB and 82% ambient noise cancellation and have two different sizes that allow to deliver the intervention across a wide range of ages. Music selection was performed by our music therapist (KH) and consists of short pieces of classical music with a tempo of around 60 beats per minute with preference for major keys and with attention to avoid dramatic moments, unsettling chords, and minor keys, as they can be associated with sadness. We created four different music playlists of 30 minutes each to add variation to the intervention. In the *noise cancellation* group, the intervention is provided with the same headphones connected to an iPod with a sham playlist with silent recording as described above. Children are assessed with the Sedation Behavior Scale (SBS) before and during the intervention. [56] Signs of agitation or an increase in the SBS by two points indicate failure of the intervention. Patients are to remain on protocol as long as they are receiving invasive mechanical ventilation or for a maximum of 7 days, whichever comes first.

Concomitant interventions

Other than the music/noise cancellation interventions, clinical care is not protocolized and is according to usual management. Sedation and analgesia management is not directed by the study protocol; it is up to the attending PICU physician to decide the drugs, dose and intervals to provide comfort and analgesia to enrolled patients. Assessment of the patients' sedation status and withdrawal symptoms is conducted every 6 hours by the bedside nurse as part of the routine care. Sedation status is assessed with the use of the SBS and withdrawal is assessed with the Withdrawal Assessment Tool (WAT-1) score; both are well validated tools . [56] [57] [58]

Handling of re-admissions to the PICU

Patients re-admitted to the PICU are considered eligible for enrollment as long as they required invasive mechanical ventilation and the use of sedation and/or analgesia upon their re-admission. Patients and families are re-approached for consent and randomization, and started on the new assigned intervention (music/noise cancellation/control) within 24-48 hours of their new admission.

Outcome measures

Primary endpoints

The primary outcomes of this trial are feasibility and sedation requirements. In order to determine feasibility of a music trial in critically ill children we are collecting information on: number of eligible patients, number of patients enrolled, rate of enrollment, time to complete participation, protocol adherence and reasons for protocol deviation. Feasibility is defined as a protocol adherence of 80%, and consent rate of 70%, with an average enrolment rate of 5

patients per month. Protocol adherence is defined as receiving the allocated intervention for 30 minutes 3 times/day during the time patient remains in the study.

Information on sedation and analgesia requirements will allow the appropriate sample size calculations for a larger trial if this study demonstrates that a music intervention in critically ill children is feasible. A survey conducted by this research group found that reduction in sedation requirements is a meaningful and clinically relevant outcome for a trial on non-pharmacologic interventions in PICU. [143] Sedation requirements will be captured as a daily intensity score and intermittent dose (PRN) frequency. [23] The sedative drug intensity score aggregates the amount of sedation/analgesia from different drug classes using a weight-adjusted dose of each sedative administered during 4 hour-time blocks. [23] Every sedation amount, for each drug is then placed in quartiles created by using the patients' data during the time the patients are involved in the study. The values are then summed over the six 4-hours blocks to obtain the daily score. Dose frequency will be captured by the administration of a (PRN) dose of any of the sedatives drugs. This way of capturing sedation requirements allows to account for the administration of different and non-equivalent types of drugs. [23] This will be expressed as the average number of PRN doses/4 hours.

Secondary endpoints

This study will also explore the effects of music on ICU delirium. Delirium is assessed twice a day (per usual care) with the Cornell Assessment of Pediatric Delirium (CAPD) instrument. [55] Those patients with a score > 9 in two consecutive measurements will be considered to have PICU delirium. Vital signs including heart rate, systolic blood pressure, diastolic blood pressure, respiratory rate and oxygen saturation are being collected prior to the intervention, at 15 minutes during the intervention, at the end of the intervention and 30 minutes

after the intervention. This information is being obtained to assess physiologic effects of music in critically ill children and also to monitor adverse effects of this intervention. Other adverse events such as intolerance to the intervention and skin and/or ear problems (e.g., pressure injuries) thought to be associated with the use of headphones are being monitored. Tolerance is being assessed with the use of the SBS as described above.

We are also collecting daily information of possible sources for discomfort or pain including the following: insertion, removal and/or presence of intravenous lines, arterial line, central venous line, chest tubes, urinary catheter, nasogastric tube, endotracheal tube; dressing changes, sternotomy closure and/or wound vacuum changes. Duration of invasive mechanical ventilation, PICU stay and PICU mortality are also being recorded.

Parents survey

As part of our family centered care approach, we are including parents' perspective on the use of music for sedation in critically ill children. Parents' opinions on the intervention are being explored with a survey conducted at the end of the intervention and prior to the patient's discharge from the ICU (Appendix VII). Parents interested in the study results will be contacted and informed of the study outcomes by email.

Data handling

Data are being collected using an electronic case report (eCRF) form using REDCap, Research Electronic Data Capture. [51] Monitoring on data collection and consistency checks are being performed by the research coordinator. Original records, including consent, eCRF, parent's surveys will be archived as per local regulations. See Figure 1 for the schedule of data collection and interventions.

Sample size justification

Our primary outcome is protocol adherence. Assuming a protocol acceptance/completion of 80%, 60 patients will be needed to estimate the rate within 10% of the true rate with 95% confidence. Also, this number of participants per group follows the recommended rules for pilot trials' sample size when the standardized effect size is unknown but expected to be small. [59] With 20 patients in each group, we will obtain pediatric-specific information to calculate a sample size for a future definitive trial.

Analysis

Baseline characteristics will be presented by descriptive statistics and graphs to show the distribution of the variables. Feasibility outcomes will be presented as percentage and 95% confidence intervals. Analysis of outcomes will be conducted using both intention to treat and per protocol. Linear regression and mixed-effects models will be used to analyze the primary effect of the music on sedation requirements and treatment effect differences between groups. Mixed-effects models will be implemented to accommodate the correlation and inconstant variance between sedation requirements measurements among various time points. Additionally, using mixed-effects models for repeated measurement data analysis will improve the statistical power and decrease biases due to missing data in compare to using any imputation method which could under- over estimate treatment effects and standard errors. When feasible all analysis will be presented with 95% CI to inform the precision of the results. Since the analysis of preliminary pilot data is not usually recommended, this will be preliminary and should be treated with caution. We will use R version 5.3.0 statistical software for the analysis. [153]

Research Ethics Approval

Research ethics approval for this study was obtained from the University of Alberta Health Research Ethics Board (Pro00073775). Informed consent is given in writing by the parents or legal guardians after providing study information orally and in writing after admission to the PICU or PCICU (Appendix VIII). The study has been registered at ClinicalTrials.gov (NCT03497559).

Discussion

While music appears to be a promising intervention, there is presently no evidence that it decreases use of pharmacologic therapies for sedation and analgesia in critically ill children. This pilot study is a necessary first step toward the conduct of a future definitive music trial in critically ill children. In order to design and conduct a larger trial, we need to demonstrate the tolerability and feasibility of a music intervention. This pilot study will also allow formal sample size calculation for a larger trial and will allow us to obtain feedback from major stakeholders, including families.

Trial status

The study was initiated on March 27th, 2018 and finished enrollment on April 11th, 2019. We are currently finalizing data collection and we expect to complete the study by June 1st, 2019.

List of abbreviations

CAPD, Cornell assessment of pediatric delirium; ECMO, extracorporeal membrane oxygenation; eCRF, electronic case report; EPICORE, epidemiology coordinating and research centre; ICU, intensive care unit; PCICU, pediatric cardiac intensive care unit; PELOD, pediatric logistic organ dysfunction score; PICU, pediatric intensive care unit; PRN, intermittent dose; REDCap, research electronic data capture; RCT, randomized controlled trial; SBS, sedation behavior scale; WAT-1, withdrawal assessment tool 1.

Declarations

Ethics approval and consent to participate

Ethics approval for this study was obtained from the University of Alberta Health Research Ethics Board (Pro00073775). Informed consent is given in writing by the parents or legal guardians.

Consent for publication

Not applicable.

Availability of data and material

Not applicable

Competing interests

The authors declare that they have no competing interests

Funding

This study is funded by the Women and Children's Health Research Institute (WCHRI); HARD Manufacturing and the World Federation of Pediatric Intensive and Critical Care Societies (WFPICCS). WCHRI has funded this project through a building capacity Grant that supports our research coordinator and nurses in the conduction of several research projects within our ICUs.

HARD Manufacturing and WFPICCS funded this project through the HARD Manufacturing Pediatric Critical Care Research Grant. None of the funding agencies have any involvement on the design of the study and neither will be involved the analysis nor the interpretation of the results.

Authors' contributions

GGG: participated in the design of the study, the analysis plan and drafted the manuscript; AJ: participated in the design of the study, the analysis plan and reviewed the manuscript; CS: participated in the design of the study, and reviewed the manuscript; KH: participated in the design of the study and the music selection for the intervention; ID: participated in the design of the study, the analysis plan and reviewed the manuscript; AdeC: participated in the design of the study, the analysis plan and reviewed the manuscript; HJ: participated in the design of the study, the analysis plan and reviewed the manuscript; LH: participated in the design of the study, the analysis plan and reviewed the manuscript; SV: participated in the design of the study, the analysis plan and reviewed the manuscript; CCCTG: provided input in the design of the study, the analysis plan and reviewed the manuscript. All authors read and approved the final manuscript.

Appendix VII: Parent's Survey

1) In your opinion, how helpful was the use of the intervention while your child was in the intensive care unit:
    a. Very helpful
    b. Somewhat helpful
    c. Neutral
    d. Not helpful
    e. Not helpful at all
    f. I don't know

2) To what extent do you agree with the following statement: "The use of the intervention reduced my child's **anxiety** while he/she was in the intensive care unit."
    a. Strongly agree
    b. Agree
    c. Neutral
    d. Disagree
    e. Strongly disagree
    f. Don't know

3) To what extent do you agree with the following statement: "The use of the intervention reduced my child's **pain** while he/she was in the intensive care unit."
    a. Strongly agree
    b. Agree
    c. Neutral
    d. Disagree
    e. Strongly disagree
    f. Don't know

    g. Strongly disagree
    h. Don't know

4) To what extent do you agree with the following statement: "The use of the intervention reduced my child's need for **sedatives** while he/she was in the intensive care unit."
    a. Strongly agree
    b. Agree
    c. Neutral
    d. Disagree
    e. Strongly disagree
    f. Don't know

5) To what extent do you agree with the following statement: "The use of the intervention reduced my child's need for **pain** medications while he/she was in the intensive care unit."

a. Strongly agree
b. Agree
c. Neutral
d. Disagree

6) How comfortable do you think the headphones used were for your child:
    a. Very uncomfortable
    b. Uncomfortable
    c. Neutral
    d. Comfortable
    e. Very comfortable
    f. Don't know

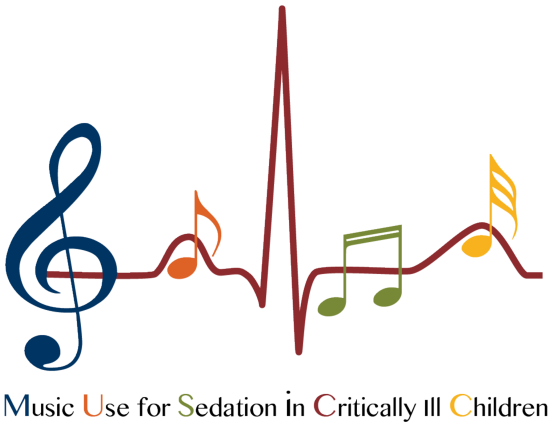
7) How would you describe your child's most common reaction when the intervention was used?
    a. Was more settled and remained awake
    b. Was more settled and slept
    c. Was more agitated
    d. Was more agitated with more crying
    e. No difference
    f. Don't know

8) Would you like to leave some comments about the use of the intervention in intensive care?

Appendix VIII

Pilot randomized controlled trial on Music Use for Sedation In Critically ill Children.

MUSiCC



CASE REPORT FORM

Patient Information

Please complete and return to:

MUSiCC Project Manager
Stollery Children's Hospital University of Alberta

Case Report Forms: Procedure Manual Notes

General Instructions

- At the top of each page, enter the patient study **Number**
- Enter dates in the format dd / mm / yyyy (i.e. October 22, 1998 is 22 / Oct / 1998)
- Enter times according to the 24 hour clock in the format HH:MM (i.e. 4 pm is entered 16:00)
- Do not write in shaded areas
- If data is not applicable, not known, illegible, or incorrect, enter N/A. There should be no blank spaces. If data is missing use the letter M.
- Use only **black ink**

Source Document

Complete the information on this page and file it separately in the Patient Source Document Binder.

The document is to be used as reference for patient follow-up. It may also be necessary to access the patient's medical record in the future for auditing purposes. This information will allow for accurate case identification.

SOURCE DOCUMENT

Once this page is completed it has to be detached from the CRF and has to be kept in a separate binder with all the rest of the Source Document forms.

Patient initials: _____

Patient study number: _____

Age in years: |__|__|

FORM 1: INCLUSION/EXCLUSION CRITERIA:

1.1 Inclusion Criteria:

Check "**yes**" for each inclusion criteria present.
NOTE: all inclusion criteria must be checked "yes" in order for the patient to be eligible for the study.

FORM 1. INCLUSION/EXCLUSION CRITERIA

1.1 INCLUSION CRITERIA: (all inclusion criteria must be answered "YES" to include patient)

YES	NO	
□	□	1. Admitted to PICU or PCICU
□	□	2. Age ≥ 1 months and < 17 years old
□	□	3. Mechanically ventilated for > 24 hours but not more than 48 hours
□	□	4. Parental or legal guardian consent

FORM 1: INCLUSION/EXCLUSION CRITERIA :

1.2 Exclusion Criteria: Check "**no**" for each exclusion criteria NOT present. **NOTE**: all exclusion criteria must be checked "no" in order for the patient to be eligible for the study.

FORM 1 cont. INCLUSION/EXCLUSION CRITERIA

1.2 EXCLUSION CRITERIA (all exclusion criteria must be answered "NO" to include patient)

YES	NO	
□	□	1. Known hearing deficit
□	□	2. Major Cranial-facial abnormalities
□	□	3. Traumatic Brain Injury with suspected high intracranial pressure or GCS ≤10
□	□	4. Patients receiving paralytic agents
□	□	5. Patients not expected to survive the next 48 hours
□	□	6. Non-invasive mechanical ventilation
□	□	7. Infants < 1 months of age and/or unable to fit the headphones
□	□	8. Patients not receiving sedation and/or analgesia drugs
□	□	9. Patients enrolled in another sedation intervention study.

Form 2 – ADMISSION AND DEMOGRAPHICS:

2-1 Sex: Check either male or female

2-2 Weight on admission: This is the weight at admission in Kg with one decimal.

2-3 Age on admission: Age in years (If less than 1 year, divide the number of months by 12).

2-4 Pediatric Risk of Mortality Score (PRISM)

2-5 Admission to PCICU or PICU: Record if the patient was admitted under PCICU or PICU team. Please note that this may not exactly coincide with physical unit location: for example, a PICU team patient may be cared for by the PICU team in the PCICU location.

2-6 Sedation and/or analgesia drugs pre-admission to ICU: State if the patient was receiving sedation/analgesia drugs prior to the admission to PICU or PCICU. This does not include anesthetics for a surgical procedure just prior to the admission. If the answer is "Yes" specify the number of days the patient was on sedation or analgesia medications.

2-7 Admission post-operatively: Please record if the patient was admitted to ICU after a surgical procedure.

2-8 Cardiac diagnosis: Please check "Yes" if the patient has a congenital and/or acquired heart disease. Check "No" otherwise.

2-9 Diagnosis: Please report the patient diagnosis on admission. **Use the following categories for diagnosis**:

1. Post-operative	Patient recovering from surgical procedure (non-cardiac): 1a. general surgery, 1b. neurosurgery, or 1c. ENT
2. Shock:	2a. Septic shock, 2b. hypovolemic shock (dehydration, bleeding), 2c. vasodilatory shock (anaphylaxis, overdose, spinal trauma)
3. Respiratory:	Respiratory distress/failure (3a. pneumonia, 3b. bronchiolitis, 3c. aspiration, 3d. acute respiratory distress syndrome, 3e. other, e.g., croup)
4. Gastrointestinal:	Gastrointestinal 4a. bleed, or 4b. liver failure, or 4c. liver transplant
5. Neurologic:	Coma, seizures, encephalitis, meningitis, encephalopathy, Guillain-Barre syndrome, Asphyxia (e.g., hanging)
6. Trauma:	6a. Multitrauma [e.g., liver or spleen injury, bowel injury, fractures], 6b. Traumatic brain injury, 6c. Burn
7. Cardiac arrest	Admitted after a cardiac arrest
8. Renal failure	Admitted for primary kidney disease needing dialysis
9. Other	If not captured in above

2-10 Admission to Stollery Children's PICU/PCICU date and time: This is the date and time the patient arrives at the Stollery PICU/PCICU.

2-11 Date and time of enrolment: Date and time when the patient was included in the study.

2-12 Arterial line: Please check "Yes" if the patient has an arterial line at the time of enrollment

2-13 Central line: Please check "Yes" if the patient has a central line (including PICC lines) at the time of enrollment

2-14 Chest tube: Please check "Yes" if the patient has a chest tube at the time of enrollment

2-15 Mediastinal tube: Please check "Yes" if the patient has a mediastinal tube at the time of enrollment

2-16 Inotrope score: record the highest inotrope score for the day of enrolment. Inotrope Score is calculated as follows: Dopamine dose (μg/kg/min) + Dobutamine dose (μg/kg/min) +100 × epinephrine dose (μg/kg/min) + 100 X norepinephrine dose (ug/kg/min) + 10 X Milrinone dose (μg/kg/min) +10,000 × Vasopressin dose (U/kg/min).

2-17 PELOD2 score: record the Pelod score for the day of enrollment. For PELOD scoring consider the following (PELOD scoring tool at the end of the CRF):
a. GCS is that expected without sedation. Only can be abnormal in patients with known or suspected central nervous system disease.

-If a GCS lower than 11 is not due to a brain injury [e.g., not admitted for cardiac arrest, meningitis, head trauma, neurosurgery, seizures, stroke, intracranial bleeding, hydrocephalus] or not due to a chronic brain dysfunction [e.g., not severe developmental delay], then record GCS as normal.
-In intubated patients, sometimes the GCS is scored out of 10 because the patient cannot verbally make sounds with the ETT in. Thus, a GCS of 10/10 is normal.
-check the MD Notes: if when giving CNS note, there is no mention of a concern about level of consciousness, response to stimulus, or seizures, then the GCS is considered normal.
b. Pupils: nonreactive pupils must be >3mm in size to record as nonreactive on PELOD.
c. Pa02 is only on arterial blood gas [not from venous or capillary blood gases].
-if there is no arterial blood gas, then Pa02 is assumed normal.
-PaC02 can be from arterial, venous, or capillary blood gas.
d. Can use worst values for creatinine, WBC, and platelets from 24hr pre- to 4hr post- calorimetry.
-if not measured, then assume these values are normal.

FORM 2. BASELINE AND DEMOGRAPHICS

2-1. Sex: |__| *Male* |__| *Female*

2-2. Weight on admission: |__|__|.|__| Kg

2-3. Age on admission: |__|__| years

2-4. PRISM: |__|__|

2-5. Intensivist team caring for the patient: PCICU |__| PICU |__|

2-6. Sedation and/or analgesia drugs pre-admission to PICU/PCICU: Yes |__| No |__| If yes, how many days |__|__|

2-7. Admission post-operatively: Yes |__| No |__|

2-8. Cardiac diagnosis: Yes |__| No |__|

2-9. Diagnosis on admission: |__|__|

2-10. Admission to Stollery Children's Hospital PICU/PCICU date:|__|__| |__|__|__| |__|__|__|__|
D D / M M M / Y E A R

Admission to Stollery Children's Hospital PICU/PCICU time: |__|__|*HH :* |__|__| *MIN*

2-11 Enrolment date:|__|__| |__|__|__| |__|__|__|__|
D D / M M M / Y E A R

Enrolment time: |__|__|*HH :* |__|__| *MIN*

2-12 Arterial line: Yes |__| No |__|

2-13 Central line: Yes |__| No |__|

2-14 Chest tube: Yes |__| No |__|

2-15 Mediastinal tube: Yes |__| No |__|

2-16 Inotrope score at enrolment: |__|__|

2-17 PELOD 2 at enrolment: |__|__|

……

FORM 3: Sedation and analgesia daily information.

This should be recorded for every day the patient was ventilated in the ICU and while the study is being conducted (maximum of 7 days, enrollment date is day 1; any part of a day is recorded as one day, and days are according to our charting from 0700 to 0659 hrs [e.g., if admitted at 2300 on May 1, then May 1 is day 1, May 2 is day 2 starting at 0700hrs).

3-0. Date: This is the date of the patient stay (i.e. If we are collecting information of the sedation the patient received on March 12th, we should enter 12/Mar/2017)

3-1. Continuous sedation and analgesia drugs: Enter the name and dose per kilogram of all the sedation and analgesia drugs the patient received as a continuous infusion in each 4 hour block for that day. For example: if the patient is receiving at 7:00h a morphine infusion at 30 mcg/kg/hour and at 9:00h the dose is changed to 40 mcg/kg/hour, the dose enter for the 7am -11am block is = 30 x 2 + 40 x 2 = 140 mcg/kg.

3-2. Sedation and analgesia intermittent and PRNs doses given: Enter the drug, dose per kilogram and the time when these doses were given, and if they were given for a particular procedure (intubation, IV start, CVL, arterial line, dressing change, chest closure, chest tube removal, etc).

3-3. Sedation/pain scores: Enter the type of score performed, the number scored and the time of the scoring. State Behavior Scale: +2 to -3. Goal is usually 0 to -1. FLACC: 0 to 10. Score >3 needs treatment. In non-ventilated children can use Faces or Numeric score instead; if so, record the value in the FLACC entry space. If a score is not recorded, check: "not done".

3-4. Withdrawal scores: Enter the type of score performed, the number scored and the time of the scoring. WAT-1: 0 to 12. Score >3 indicates possible withdrawal. If a score is not recorded, check: "not done".

3-5. Delirium scores: Enter the type of score performed, the number scored and the time of the scoring. CAP-D: 0 to 32. Score >9 indicates delirium. If a score is not recorded, check: "not done".

FORM 3. Sedation and analgesia daily information

Day |__|

3-0. Date: |__|__| |__|__|__| |__|__|__|__|
D D / M M M /Y E A R

3-1. Continuous sedation and analgesia drugs:

Dose of Morphine:	**07:00 to 11:00**	|__|__|.|__|__| mcg/kg
	11:00 to 15:00	|__|__|.|__|__| mcg/kg
	15:00 to 19:00	|__|__|.|__|__| mcg/kg
	19:00 to 23:00	|__|__|.|__|__| mcg/kg
	23:00 to 03:00	|__|__|.|__|__| mcg/kg
	03:00 to 07:00	|__|__|.|__|__| mcg/kg
Dose of Midazolam:	**07:00 to 11:00**	|__|__|.|__|__| mcg/kg

	11:00 to 15:00	|__|__|.|__|__| mcg/kg
	15:00 to 19:00	|__|__|.|__|__| mcg/kg
	19:00 to 23:00	|__|__|.|__|__| mcg/kg
	23:00 to 03:00	|__|__|.|__|__| mcg/kg
	03:00 to 07:00	|__|__|.|__|__| mcg/kg
Dose of Hydromorphone:	**07:00 to 11:00**	|__|__|.|__|__| mcg/kg
	11:00 to 15:00	|__|__|.|__|__| mcg/kg
	15:00 to 19:00	|__|__|.|__|__| mcg/kg
	19:00 to 23:00	|__|__|.|__|__| mcg/kg
	23:00 to 03:00	|__|__|.|__|__| mcg/kg
	03:00 to 07:00	|__|__|.|__|__| mcg/kg
Dose of Dexmedetomidine:	**07:00 to 11:00**	|__|__|.|__|__| mcg/kg
	11:00 to 15:00	|__|__|.|__|__| mcg/kg
	15:00 to 19:00	|__|__|.|__|__| mcg/kg
	19:00 to 23:00	|__|__|.|__|__| mcg/kg
	23:00 to 03:00	|__|__|.|__|__| mcg/kg
	03:00 to 07:00	|__|__|.|__|__| mcg/kg
Dose of Propofol:	**07:00 to 11:00**	|__|__|.|__|__| mg/kg
	11:00 to 15:00	|__|__|.|__|__| mg/kg
	15:00 to 19:00	|__|__|.|__|__| mg/kg
	19:00 to 23:00	|__|__|.|__|__| mg/kg
	23:00 to 03:00	|__|__|.|__|__| mg/kg
	03:00 to 07:00	|__|__|.|__|__| mg/kg
Dose of Fentanyl:	**07:00 to 11:00**	|__|__|.|__|__| mcg/kg
	11:00 to 15:00	|__|__|.|__|__| mcg/kg
	15:00 to 19:00	|__|__|.|__|__| mcg/kg
	19:00 to 23:00	|__|__|.|__|__| mcg/kg
	23:00 to 03:00	|__|__|.|__|__| mcg/kg
	03:00 to 07:00	|__|__|.|__|__| mcg/kg

Study day |__|
Date: |__|__| |__|__|__| |__|__|__|__|
D D / M M M /Y E A R

Dose of ketamine:

07:00 to 11:00	|__|__|.|__|__| mcg/kg
11:00 to 15:00	|__|__|.|__|__| mcg/kg
15:00 to 19:00	|__|__|.|__|__| mcg/kg
19:00 to 23:00	|__|__|.|__|__| mcg/kg
23:00 to 03:00	|__|__|.|__|__| mcg/kg
03:00 to 07:00	|__|__|.|__|__| mcg/kg

Other:……(name)

07:00 to 11:00	|__|__|.|__|__| ___/kg
11:00 to 15:00	|__|__|.|__|__| ___/kg
15:00 to 19:00	|__|__|.|__|__| ___/kg
19:00 to 23:00	|__|__|.|__|__| ___/kg
23:00 to 03:00	|__|__|.|__|__| ___/kg
03:00 to 07:00	|__|__|.|__|__| ___/kg

3-2. Sedation and analgesia intermittent (PRNs) doses given:

Morphine:

07:00 to 11:00 Number doses: |__|__|	**Cumulative dose**|__|__|.|__|__| mg/kg
11:00 to 15:00Number doses: |__|__|	**Cumulative dose**|__|__|.|__|__| mg/kg
15:00 to 19:00Number doses: |__|__|	**Cumulative dose**|__|__|.|__|__| mg/kg
19:00 to 23:00Number doses: |__|__|	**Cumulative dose**|__|__|.|__|__| mg/kg
23:00 to 03:00Number doses: |__|__|	**Cumulative dose**|__|__|.|__|__| mg/kg
03:00 to 07:00Number doses: |__|__|	**Cumulative dose**|__|__|.|__|__| mg/kg

Lorazepam:

07:00 to 11:00 Number doses: |__|__|	**Cumulative dose**|__|__|.|__|__| mg/kg
11:00 to 15:00Number doses: |__|__|	**Cumulative dose**|__|__|.|__|__| mg/kg
15:00 to 19:00Number doses: |__|__|	**Cumulative dose**|__|__|.|__|__| mg/kg
19:00 to 23:00Number doses: |__|__|	**Cumulative dose**|__|__|.|__|__| mg/kg
23:00 to 03:00Number doses: |__|__|	**Cumulative dose**|__|__|.|__|__| mg/kg
03:00 to 07:00Number doses: |__|__|	**Cumulative dose**|__|__|.|__|__| mg/kg

Chloral hydrate:

07:00 to 11:00 Number doses: |__|__|	**Cumulative dose**|__|__|.|__|__| mg/kg
11:00 to 15:00Number doses: |__|__|	**Cumulative dose**|__|__|.|__|__| mg/kg
15:00 to 19:00Number doses: |__|__|	**Cumulative dose**|__|__|.|__|__| mg/kg
19:00 to 23:00Number doses: |__|__|	**Cumulative dose**|__|__|.|__|__| mg/kg
23:00 to 03:00Number doses: |__|__|	**Cumulative dose**|__|__|.|__|__| mg/kg
03:00 to 07:00Number doses: |__|__|	**Cumulative dose**|__|__|.|__|__| mg/kg

Study day |__|
Date: |__|__| |__|__|__| |__|__|__|__|
D D / M M M /Y E A R
Clonidine:

07:00 to 11:00 Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
11:00 to 15:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
15:00 to 19:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
19:00 to 23:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
23:00 to 03:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
03:00 to 07:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg

Propofol:

07:00 to 11:00 Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
11:00 to 15:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
15:00 to 19:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
19:00 to 23:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
23:00 to 03:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
03:00 to 07:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg

Fentanyl:

07:00 to 11:00 Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
11:00 to 15:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
15:00 to 19:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
19:00 to 23:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
23:00 to 03:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
03:00 to 07:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg

Ketamine:

07:00 to 11:00 Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
11:00 to 15:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
15:00 to 19:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
19:00 to 23:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
23:00 to 03:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
03:00 to 07:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg

Other:……
Name

07:00 to 11:00 Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
11:00 to 15:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
15:00 to 19:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg

19:00 to 23:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
23:00 to 03:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg
03:00 to 07:00Number doses: |__|__| **Cumulative dose**|__|__|.|__|__| mg/kg

3-3. Sedation scores:

|__| **SBS:** |__|__| score Time scored:|__|__|.|__|__| Hs.

|__|__| score Time scored:|__|__|.|__|__| Hs.

|__|__| score Time scored:|__|__|.|__|__| Hs.

|__|__| score Time scored:|__|__|.|__|__| Hs.

Not done |__|

|__| **FLACC:** |__|__| score Time scored:|__|__|.|__|__| Hs.

|__|__| score Time scored:|__|__|.|__|__| Hs.

|__|__| score Time scored:|__|__|.|__|__| Hs.

|__|__| score Time scored:|__|__|.|__|__| Hs.

Not done |__|

3-4. Withdrawal scores:

|__| **WAT-1:** |__|__| score Time scored:|__|__|.|__|__| H

|__|__| score Time scored:|__|__|.|__|__| H

|__|__| score Time scored:|__|__|.|__|__| H

|__|__| score Time scored:|__|__|.|__|__| H

Not done |__|

3-5. Delirium scores:

|__| **CAPD:** |__|__| score Time scored:|__|__|.|__|__| H

|__|__| score Time scored:|__|__|.|__|__| H

|__|__| score Time scored:|__|__|.|__|__| H

|__|__| score Time scored:|__|__|.|__|__| H

Not done |__|

FORM 4: Intervention daily information:

This should be recorded for every day the patient stays ventilated in the ICU and while the study was being conducted (maximum of 7 days since enrollment).

4-0. Date: This is the date of the patient stay (i.e. If we are collecting information of the sedation the patient received on March 12th, we should enter 12/Mar/2017)

4.1 Time of intervention: The corresponding intervention should be performed for 30 minutes 3 times a day: morning (M) between 07:00h and 12:00h, afternoon (A) between 12:00h and 16:00h, and evening (E) between 16:00h and 20:00h. The bedside nurse will decide the exact time of the intervention based on the patient status and procedures. Each intervention will take place for a minimum 30 minutes. For each intervention please record:

a) Time: Record the time when the intervention was started and discontinued during that day. Write N/A if patient was in the control arm.
b) Duration (in minutes)
c) Discontinuation: If the intervention was stopped prior to 30 minutes, please record the reason.

4.2 Heart rate: Record the HR

a) Prior to the intervention
b) 15 minutes after the start of the intervention
c) At the end of the intervention
d) 30 minutes after the completion of the intervention

4.3 Respiratory rate: Record the RR

a) Prior to the intervention
b) 15 minutes after the start of the intervention
c) At the end of the intervention
d) 30 minutes after the completion of the intervention

4.4 Systolic Blood pressure: Record SBP only if patient has an arterial line

a) Prior to the intervention
b) 15 minutes after the start of the intervention
c) At the end of the intervention
d) 30 minutes after the completion of the intervention

4.5 Diastolic Blood pressure: Record DBP only if patient has an arterial line

a) Prior to the intervention
b) 15 minutes after the start of the intervention
c) At the end of the intervention
d) 30 minutes after the completion of the intervention

4.6 Oxygen Saturation: Record O2Sats

a) Prior to the intervention
b) 15 minutes after the start of the intervention
c) At the end of the intervention
d) 30 minutes after the completion of the intervention

FORM 4: **Daily Information:**

Study Day |__|

4.0 Date: |__|__| |__|__|__| |__|__|__|__|
D D / M M M /Y E A R

4.1M Intervention

Morning (M): Done? Yes |__| No |__| If no, why_____?

a) **Time started**:|__|__|.|__|__| H **Time stopped**:|__|__|.|__|__| H
b) **Duration** |__|__| minutes
c) **Discontinuation prior to 30 minutes**
No |__| Yes |__| If yes, why: |__| Patient in OR |__| Patient too unstable

|__| Procedure being done to the patient |__| Family asked not to do it

|__| Patient gone for CT or other diagnostic test/intervention

Other _____

4.2.M Heart Rate:

a) Prior to the intervention |__|__|__|
b) At 15 minutes of the intervention |__|__|__|
c) At the end of the intervention |__|__|__|
d) 30 minutes after the intervention |__|__|__|

4.3.M Respiratory rate:

a) Prior to the intervention |__|__|
b) At 15 minutes of the intervention |__|__|
c) At the end of the intervention |__|__|
d) 30 minutes after the intervention |__|__|

4.4.M Systolic Blood pressure:

a) Prior to the intervention |__|__|__|
b) At 15 minutes of the intervention |__|__|__|
c) At the end of the intervention |__|__|__|
d) 30 minutes after the intervention |__|__|__|

4.5.M Diastolic Blood pressure

a) Prior to the intervention |__|__|
b) At 15 minutes of the intervention |__|__|
c) At the end of the intervention |__|__|
d) 30 minutes after the intervention |__|__|

4.6.M Oxygen Saturation

a) Prior to the intervention |__|__|__|
b) At 15 minutes of the intervention |__|__|__|
c) At the end of the intervention |__|__|__|
d) 30 minutes after the intervention |__|__|__|

FORM 4: **Daily Information*:***

Study Day |__|

4.0 Date: |__|__| |__|__|__| |__|__|__|__|
D D / M M M /Y E A R

4.1A Intervention

Afternoon (A): Done? Yes |__| No |__| If no, why_____?

a) **Time started**:|__|__|.|__|__| H **Time stopped**:|__|__|.|__|__| H
b) **Duration** |__|__| minutes
c) **Discontinuation prior to 30 minutes** No |__| Yes |__| If yes, why_____?

4.2.A Heart Rate:

a) Prior to the intervention |__|__|__|
b) At 15 minutes of the intervention |__|__|__|
c) At the end of the intervention |__|__|__|
d) 30 minutes after the intervention |__|__|__|

4.3.A Respiratory rate:

a) Prior to the intervention |__|__|
b) At 15 minutes of the intervention |__|__|
c) At the end of the intervention |__|__|
d) 30 minutes after the intervention |__|__|

4.4.A Systolic Blood pressure:

a) Prior to the intervention |__|__|__|
b) At 15 minutes of the intervention |__|__|__|
c) At the end of the intervention |__|__|__|
d) 30 minutes after the intervention |__|__|__|

4.5.A Diastolic Blood pressure

a) Prior to the intervention |__|__|
b) At 15 minutes of the intervention |__|__|
c) At the end of the intervention |__|__|
d) 30 minutes after the intervention |__|__|

4.6.A Oxygen Saturation

a) Prior to the intervention |__|__|__|
b) At 15 minutes of the intervention |__|__|__|
c) At the end of the intervention |__|__|__|
d) 30 minutes after the intervention |__|__|__|

FORM 4: **Daily Information*:***

Study Day 1

4.0 Date: |__|__| |__|__|__| |__|__|__|__|
D D / M M M /Y E A R

4.1E Intervention

Evening (E): Done? Yes |__| No |__| If no, why_____?

a) **Time started**:|__|__|.|__|__| H **Time stopped**:|__|__|.|__|__| H
b) **Duration** |__|__| minutes
c) **Discontinuation prior to 30 minutes** No |__| Yes |__| If yes, why_____?

4.2.E Heart Rate:

a) Prior to the intervention |__|__|__|
b) At 15 minutes of the intervention |__|__|__|
c) At the end of the intervention |__|__|__|
d) 30 minutes after the intervention |__|__|__|

4.3.E Respiratory rate:

a) Prior to the intervention |__|__|
b) At 15 minutes of the intervention |__|__|
c) At the end of the intervention |__|__|
d) 30 minutes after the intervention |__|__|

4.4.E Systolic Blood pressure:

a) Prior to the intervention |__|__|__|
b) At 15 minutes of the intervention |__|__|__|
c) At the end of the intervention |__|__|__|
d) 30 minutes after the intervention |__|__|__|

4.5.E Diastolic Blood pressure

a) Prior to the intervention |__|__|
b) At 15 minutes of the intervention |__|__|
c) At the end of the intervention |__|__|
d) 30 minutes after the intervention |__|__|

4.6.E Oxygen Saturation

a) Prior to the intervention |__|__|__|
b) At 15 minutes of the intervention |__|__|__|
c) At the end of the intervention |__|__|__|
d) 30 minutes after the intervention |__|__|__|

FORM 5: **Other daily Information*:***

5.1 Procedures: record which procedures and at what time were conducted that day. Procedures include: intubation, central venous line insertion, arterial line insertion, chest tube insertion (including mediastinal tubes), chest tube removal (including mediastinal tubes), nasogastric(NG) or naso-jejunal(NJ) tubes, foley catheter, dressing changes, wound vacuum changes, intubation, IV insertion or other major procedures that required sedation within the unit.

5.2 Major sources of discomfort: check if the patient has already any of the following in place: central venous line, arterial line, chest tube (including mediastinal tubes), Foley catheter.

FORM 5: **Other daily Information*:***

5.1 Procedures: Central venous line |__| Arterial line|__| Intubation|__|

Chest tube insertion|__| Chest tube removal|__| NG/NJ insertion|__|

Foley catheter|__| Dressing change|__| Wound vacuum|__|

Intubation |__| IV Insertion|__|
Other:…….. |__|

5.2 Major source discomfort: Central venous line |__| Arterial line|__| Endotracheal tube|__|

Chest tube|__| NG/NJ insertion|__| Foley catheter|__|

Other:…….. |__|

FORM 6: MORBIDITY AND MORTALITY:

6-1 MORBIDITY:

6-1.1 Date invasive mechanical ventilation discontinued: Record the date according to the date format listed. This is defined as the date the patient is able to breathe spontaneously with no mechanical ventilation or endotracheal tube (with or without tracheostomy). The patient must remain spontaneously breathing for at least 24 hours without reintubation to satisfy this endpoint.

6-1.2 Length of mechanical ventilation: Record total number of days of mechanical ventilation during PICU stay after surgery. **Note:** Any portion of a day is considered a full day. For example, a patient is intubated at 2200h on Jan 10th (day 1) and extubated on January 17th (day 8). The length of mechanical ventilation is 8 days.

6-1.3 Date of discharge from PICU: Record the date according to the date format listed above. Transfer to NICU or another hospital would be considered discharge from PICU/PCICU.

6-1.4 Length of PICU/PCICU stay: Record total number of days in PICU after admission. **Note:** Any portion of a day is considered a full day. One day extends from 0700 until 0659 the following day.

FORM 6: MORBIDITY, MORTALITY:

6-1 MORBIDITY

6-1.1 Date invasive mechanical ventilation discontinued:|__|__| |__|__|__| |__|__|__|__|
D D / M M M / Y Y Y Y

6-1.2 Total duration of mechanical ventilation during PICU/PCICU stay: |__|__|__| days

6-1.3 Date of discharge from PICU/PCICU: |__|__| |__|__|__| |__|__|__|__|
D D / M M M / Y Y Y Y

6-1.4 Total length of PICU/PCICU stay since admission: |_____| days

6-2 MORBIDITY, MORTALITY CONT

6-2.1 PICU/PCICU Survival Status: Check yes or no to indicate if the patient survived to PICU/PCICU discharge

6-2.2 Date of death: Record this in the date format specified.

6-2.3 Number of days from inclusion to death: record number of days from inclusion to death.

6-2.4 Cause of Death: Select the primary cause of death. Please discuss the most probable cause of death with the attending physician. You may select more than one cause.
Established MODS = MODS occurring and persisting after 48 hours of presentation of shock.
Refractory shock = Hypotension not responding to maximum medical therapy.
Dysrhythmia = Heart rhythm other than sinus that because it is too fast or too low leads to death
Neurologic sequelae = severe brain injury.

FORM 6: MORBIDITY, MORTALITY (cont.)

6-2 MORTALITY:

6-2.1 Survival to discharge from PICU |__| *Yes* |__| *No*

6-2.2 Date of death |__|__| |__|__| |__|__|__|__|
D D / M M / Y Y Y Y

6-2.3 Number of days from inclusion to death |_____| *days*

6-2.4 Cause of death

Refractory Shock	|__| *yes*	|__| *no*
Established MODS	|__| *yes*	|__| *no*
Severe myocardial dysfunction	|__| *yes*	|__| *no*
Dysrhythmia |__| *yes*	|__| *no*	

Withdrawal of life sustaining therapy	|__| *yes*	|__| *no*
Other(s): _____	|__| *yes*	|__| *no*

FORM 7: WITHDRAWAL FROM THE STUDY:

WITHDRAWAL FROM THE STUDY: Check "yes" if the patient has been withdrawn from the study within 7 days after the randomization, and check the appropriate reason.

FORM 7: WITHDRAWL FROM THE STUDY

Withdrawal from study	|__| yes|__| no
If yes, check the appropriate reason	
7-1 Parents asked to withdraw the child from the trial: (*Justification:*_____)	|__| yes|__| no
7-2 Physician asked to withdraw the child from the trial: (*Justification:*_____)	|__| yes|__| no
7-3 Other cause of withdrawal: (*Specify:*_____)	|__| yes|__| no
7-4 Date of withdrawal	|__|__| |__|__|__| |__|__ |__|__| *DD M M M Y Y Y Y*

FORM 8: SUSPENSION OF COMPLIANCE WITH PROTOCOL:

8.1 WAS THERE SUSPENSION OF COMPLIANCE WITH THE STUDY PROTOCOL?

If there was a suspension with compliance with the study protocol, check yes.

Suspension of compliance is defined as not receiving the allocated intervention 2 times or more per day.

8.2 Suspected intervention related adverse event

If compliance with the study protocol is suspended because of a suspected adverse event, mark "yes" and specify reason in form 8.

8.3 Other

If the suspension was not suspected to be because of an intervention related adverse event, specify the reason.

8.4 Date of suspension of compliance to study protocol.

Record the date according to the date format listed above

FORM 8: SUSPENSION OF COMPLIANCE WITH PROTOCOL:

Was there a suspension of compliance with study protocol?	|__| *yes* |__| *no*
***If yes**, check the appropriate reason(s)*	
8-1 Suspected study intervention related adverse event *(see form on page 46)*:	|__| *yes* |__| *no*
8-2 Other – specify:_____	|__| *yes* |__| *no*
8-3 Date of suspension of compliance to study protocol:	|__|__| |__|__|__| |__|__ |__|__| *DD M M M Y Y Y Y*

FORM 9: SERIOUS ADVERSE EVENTS:

Serious Adverse Event Information:
Record all serious adverse events that occurred to the patient from the date of admission, until the *first* of the following events: death, PICU discharge, 7 days after enrolment or successful extubation.

Date and Time: Using the most applicable units (i.e. minutes, hours, days) indicate the time that the adverse event began.

Duration: Using the most applicable units (i.e. minutes, hours, days) indicate the duration of the adverse event.

Intervention Relationship: Indicate with the appropriate number the degree of relationship of the intervention to the adverse event according to the scale provided. **Please review with the Site Investigator/attending intensivist.**

Treatment Required: Indicate with the appropriate number the treatment required for the adverse event according to the scale provided, more than one option may be selected.

Patient Outcome: Indicate with the appropriate number, the outcome of the adverse event according to the scale provided.

Date of resolution: Record the date that the adverse event stopped, or was resolved. If the patient died, enter the date of death. **Please review with the site investigator or the attending intensivist.**

Definition of a Serious Adverse Event (SAE)

An event is considered "serious" if any of the following situations occur:

- Death
- Life-threatening: refers to an event in which the patient was, in the view of the investigator, at risk of death from the event if medical intervention had not occurred.
- Prolonged Patient In-hospitalization: if a complication prolongs a patient's hospitalization, the event is considered "serious".
- Resulting in Persistent or Significant Disability/Incapacity: a substantial disruption of a person's ability to conduct normal life functions.
- Other medically important condition (specify)

FORM 9: SERIOUS ADVERSE EVENTS:

Serious Adverse Event Information

Description of event	**Date** (dd/mmm/ yyyy) **Time** (H H)	**Duration (mins, hours)**	**Study intervention relationship** 1 = none 2 = possible 3 = probable 4 = definite 5 = insufficient data	**Treatment required (enter all that apply)** 1 = none 2 = medication 3 = surgery 4 = other therapy 5 = Stop Protocol	**Patient outcome** 1 = no sequelae 2 = sequelae 2 = death **3** = ongoing	**Date of Resolution** (dd/mmm/yyyy)

FORM 7: SIGN OFF SHEET:

Sign Off Sheet

This sheet must be completed. By signing this page the parties state that the forms have been reviewed and are deemed complete and accurate

FORM 8: SIGN OFF SHEET

Case Report Form to be signed off when the data has been checked as accurate and complete.

Research Assistant:

_____**Date:**_____

Site Investigator:

_____**Date:**_____

Appendix IX: Consent Form

DEPARTMENT OF PEDIATRICS

FACULTY OF MEDICINE AND DENTISTRY

Title of Research Study **MUSiCC: Pilot randomized controlled trial on Music Use for Sedation In Critically ill Children.**

Principal Investigator(s): Gonzalo García Guerra MD MSc

Co-Investigator(s): Ari Joffe, Allan de Caen MD, Lisa Hartling PhD, Hsing Jou MD, Sunita Vohra MD.

Background: Your child has been admitted to the intensive care unit (PICU) because of the severity of his/her illness and/or to recover after surgery. Very sick ("critically ill") children admitted to the PICU commonly suffer from discomfort, pain and stress, related to their illness or to the interventions that will help them to recover (catheters, chest tubes, and breathing tubes for mechanical ventilation). Management of pain and stress is extremely important in PICU as it provides comfort and prevents children from accidentally removing equipment that is necessary for their recovery. Pain and agitation are usually treated with narcotics and/or sedatives. However, these drugs can have significant side effects, including low blood pressure, weakness, confusion, breathing problems, and withdrawal symptoms upon discontinuation. Interventions that don't involve medications, decreasing noise/lights and listening to music, can provide comfort without the side effects of narcotics and sedatives. Music has been successfully used as a sedative in children undergoing surgical procedures and in critically ill adults. We have also found that noise in the PICU is associated with discomfort and the need for extra doses of sedation. Whether music and noise cancellation can also provide comfort to critically ill children is unknown. We want to find out if music can provide comfort and reduce (not avoid) the use of sedatives and narcotics, and reduce these medication's side effects. In our proposed study, children will be assigned to one of three groups: standard care (no music), music provided with headphones, and headphones with no music (noise cancellation). The music provided will be chosen by a pediatric music therapist. The music or noise cancellation will be provided 3 times a day. The amount of sedatives and narcotics used in each group will be recorded and compared. The need for these medications will be up to the doctors and nurses treating these children and will not depend on the study.

Purpose: We are asking you to allow your child to participate in a research study to find out if music and noise cancellation can provide comfort, help to reduce the need for sedatives and narcotics, and reduce medication side effects in critically ill children.

Procedures: Participating in this study will involve:

a) Your child will be randomized to the one of the "intervention groups" or the "control group" of the study. Randomization is like flipping a coin; this means that your child has an equal chance of being in one of the "intervention groups" or the "control group". One of the intervention groups will receive *music* with the use of headphones, while the second intervention group will receive *noise cancellation* headphones but without music; the "control group" will not receive headphones (*standard of care*). Neither you nor your physician can choose or know which group your child is randomized to. This "blinding" is necessary to fairly test the intervention. In an emergency, your physician can immediately find out which of the study groups your child has been assigned to.
b) 24-48 hours after admission to the PICU your child will be started on the assigned intervention (music/noise cancellation/control).
c) In the *music* and *noise cancellation* groups the intervention will be delivered during 30 minutes three times a day.. The control group will receive usual care. Children will be assessed with the Sedation Behavior Scale (SBS) before and during the intervention. Signs of agitation or an increase in the SBS will indicate failure of the intervention. Patients will remain on protocol for a maximum of 7 days as long as they are on invasive mechanical ventilation. A parent survey will be conducted at the end of the study.
d) *Music* will be delivered with the use of noise cancellation headphones and an iPod Touch. Music selection will consist on classic music chosen by a music therapist based on the patient's age. The music volume will be limited to 45-65 dB. The headphones used in the study also have a maximum volume limit of 85dB to provide extra safety.
e) N*oise cancellation* will be provided with the same headphones connected to an iPod with a silent recording.
f) The iPods provided will contain music (music group) and a sham music list (noise cancellation group) so you and the medical team do not know which group your child is in. This "blinding" is done to make sure that the results of the study are not being affected by knowing who gets the intervention. Only the research nurse will know which group your baby is in.
g) If your child appears upset or uncomfortable during the intervention (music or noise cancellation) the bedside nurse will remove the headphones.
h) The study will last 7 days or until your child is discharged from the PICU. During this time we will record some clinical information from your child's hospital chart. This information is on the hospital chart, and will not need any extra interventions or blood work. This study will not affect any of the care your child receives in the PICU.
i) At the end of the study we will provide you with a short survey (5 minutes) so we can obtain your opinion about the intervention.

Possible Benefits: There may not be any direct benefit to your child for taking part in this study. New information about the use of music and noise cancellation in PICU will be obtained from your child's participation in this study. This new information may benefit other children in the future.

Possible Risks: Your child may have some discomfort during the intervention, and if so, the intervention will be discontinued by the bedside nurse. Regardless of which group your child is assigned to, he/she will receive the standard of care for his/her illness and we do not expect any

side-effects due to the study. This study will not affect any of the treatments or care given by the doctors and nurses to your child during the PICU stay.

Confidentiality: Personal health records relating to this study will be kept confidential. Any research data collected about your child during this study will identify your child only by his/her initials and a coded number. Your child's name will not be disclosed outside the research clinic. Any report published as a result of this study will not identify your child's name.

For this study, the study doctor may need to access your child's personal health records for health information such as past medical history and test results. He/she may also need to contact your child's pediatrician and your child's other health care providers to obtain additional medical information. The health information collected as part of this study will be kept confidential unless release is required by law, and will be used only for the purpose of the research study. By signing the consent form you give permission to the study staff to access any personally identifiable health information which is under the custody of other health care professionals as deemed necessary for the conduct of the research. In addition to the investigators(s), people from the Health Research Ethics Board or University of Alberta may have access to your child's personal health records to monitor the research and verify the accuracy of study data.

By signing the consent form you give permission for the collection, use and disclosure of your child's medical records. At the University of Alberta, study information is required to be kept for 5 years. Even if you withdraw your child from the study, the medical information which is obtained from your child for study purposes will not be destroyed. You have a right to check your child's health records and request changes if your child's personal information is incorrect.

Voluntary Participation: If you agree to participate, you are free to withdraw your child from the research study at any time, and your child's continuing medical care will not be affected in any way. If the study is not undertaken or if it is discontinued at any time, the quality of your child's medical care will not be affected. If any knowledge gained from this or any other study becomes available which could influence your decision to continue your child in the study, you will be promptly informed.

Compensation for Injury: If your child becomes ill or injured as a result of being in this study, he/she will receive necessary medical treatment, at no additional cost to you. By signing this consent form you are not releasing the investigator(s), institution(s) and/or sponsor(s) from their legal and professional responsibilities.

Contact Names and Telephone Numbers:
If you have concerns about your or your child's rights as a study participant, you may contact the University of Alberta Research Ethics Office, at 780 492-2615. This office has no affiliation with the study investigators.

Please contact any of the individuals identified below if you have any questions or concerns:

DEPARTMENT OF PEDIATRICS
FACULTY OF MEDICINE AND DENTISTRY

Title of Research Study **MUSiCC: Pilot randomized controlled trial on Music Use for Sedation In Critically ill Children.**

Principal Investigator(s): Gonzalo García Guerra MD, 780-407-1673, 780-445-5963 (pager)
Co-Investigator(s): Ari Joffe, Allan de Caen MD, Lisa Hartling PhD, Hsing Jou MD, Sunita Vohra MD.

	Yes	No
Do you understand that you have been asked to have your child in a research study?	☐	☐
Have you read and received a copy of the attached Information Sheet?	☐	☐
Do you understand the benefits and risks involved in your child taking part in this research study?	☐	☐
Have you had an opportunity to ask questions and discuss this study?	☐	☐
Do you understand that you are free to withdraw from the study at any time, without having to give a reason and leaving the study will not affect your child's future medical care?	☐	☐
Has the issue of confidentiality been explained to you?	☐	☐
Do you understand who will have access to your child records, including personally identifiable health information?	☐	☐
Do you wish to be contacted at the end of the study so we can provide you with information regarding the study results as well as letting you know which intervention group your child was randomized to?	☐	☐

If so, please provide your email or postal address:

_____

_____

Who explained this study to you? _____

I agree for _____ (child's name) to take part in this study.

_____

Parent/Guardian name Parent/Guardian signature Date

I believe that the person signing this form understands what is involved in the study and voluntarily agrees to participate.

Signature of the person who obtained consent Date

THE INFORMATION SHEET MUST BE ATTACHED TO THIS CONSENT FORM AND A COPY GIVEN TO THE RESEARCH PARTICIPANT.