RESEARCH PAPER

Randomized Control Trial Comparing Pain Control Interventions in Preterm Neonates

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ABSTRACT

Objectives: To compare individual efficacy and additive effects of pain control interventions in preterm neonates.

Design: Randomized controlled trial

Setting: Level-3 University affiliated neonatal intensive care unit.

Participants: 200 neonates (26-36 weeks gestational age) requiring heel-stick for bedside glucose assessment. Exclusion criteria were neurologic impairment and critical illness precluding study interventions.

Intervention: Neonates were randomly assigned to Kangaroo mother care with Music therapy, Music therapy, Kangaroo Mother care or Control (no additional intervention) groups. All groups received expressed breast milk with cup and spoon as a baseline pain control intervention.

Main outcome measure: Assessment of pain using Premature Infant Pain Profile (PIPP) score on recorded videos.

Results: The mean (SD) birth weight and gestational age of the neonates was 1.9 (0.3) kg and 34 (2.3) weeks, respectively. Analysis of variance showed significant difference in total PIPP score across groups (P<0.001). Post-hoc comparisons using Sheffe's test revealed that the mean (SD) total PIPP score was significantly lower in Kangaroo mother care group ([7.7 (3.9) *vs*. 11.5 (3.4), 95% CI(-5.9, -1.7), P<0.001] as well as Kangaroo mother care with Music therapy group [8.5 (3.2) *vs*. 11.5 (3.4), 95%CI (-5.1, –0.9), P=0.001] as compared to Control group. PIPP score was not significantly different between Control group and Music therapy group.

Conclusions: Kangaroo mother care with and without Music therapy (with expressed breast milk) significantly reduces pain on heel-stick as compared to expressed breast milk alone. Kangaroo mother care with expressed breast milk should be the first choice as a method for pain control in preterm neonates.

Keywords: Kangaroo mother care, Music therapy, Neonatal pain.

Trial registration: Clinical trial registry of India (CTRI/2016/06/007028)

INTRODUCTION

Neonates receiving intensive care are subjected to multiple painful procedures as a part of their intensive care management. Preterm neonates have immature nociceptive circuitry [1,2]. Pain is linked with abnormal neurodevelopment [3-5], so it is extremely important to treat and reduce pain. Multiple studies have shown the benefits of individual pain control interventions [6-11]. There are no randomized control trials comparing effects of the simultaneous application of different pain control interventions as compared to theirs individual application on pain control.

The objective of the study was to compare the efficacy of pain control interventions and interaction effects (if any) through randomized control trial.

METHODS

We conducted the study from January 2016 to May 2016 at a level 3 NICU of Shree Krishna Hospital a University affiliated teaching hospital, Anand, Gujarat, India. Hospital research ethics committee approved the trial protocol.

We enrolled preterm neonates (28 to 36 weeks gestational age) admitted to the NICU after written and informed consent from their parents. Study interventions were done on babies expected to have heel-stick procedure for bedside glucose assessment as per the routine medical management. Key exclusion criteria were neurologic impairment (perinatal depression and HIE≥stage 2 of Sarnat classification [12], Grade 3/4 IVH [13], stroke, seizures or congenital malformations of the central nervous system, those who received pain control medications in 12 hours before study interventions, those with neonatal abstinence syndrome) and those with critical illness unstable to undergo study interventions (those requiring mechanical ventilation, inotropes). The SD of PIPP score [14] was found to be about 3.5 from the previous study in the same setting [7]. Considering 2-point difference in PIPP score as clinically important between any two groups, a sample of size 50 per group was required at 5% alpha error and 80% power. Considering the study design, we did not expect dropouts from the study.

Randomization was performed with the use of WINPEPI software by the statistician and the assignment was placed in sealed opaque envelopes. The resident involved in the study enrolled the participants and obtained consent. Neonatologist involved in the study opened the sealed opaque envelopes and allocated the intervention. Eligible participants were randomly assigned, in a 1:1 ratio, to Kangaroo mother care (KMC) with Music therapy (MT) group, Music therapy group, KMC group or

Control (no additional intervention) group (***Fig.*1**). We provided 2 mL of mother's expressed breast milk (EBM) with cup and spoon as baseline pain control measure to all study participants 2 minutes prior to heel-stick in addition to the study interventions. Study intervention was provided 10 min prior to heel-stick procedure, and music therapy continued for at least 5 min and KMC was continued post heel-stick procedure as per institutional protocol. We adhered to the pain control protocol of the study institute to use EBM for procedural pain control as a baseline.

In music therapy group, the music was provided from mobile devices at a distance of 2 feet, and the sound level was between 35 to 45 dBA as measured at the level of ear of the newborn with the help of Sound Meter PRO, Googletm Playstore application from mobile phone. Efforts were made to minimize noise level in the NICU during music therapy. The music that was played was instrumental-Indian classical flute music. In the control group no additional pain control intervention was provided except for baseline 2 mL of EBM 2 minutes prior to the heel-stick procedure, they were then swaddled following the video recording. Video recording of the neonate's facial expression and pulse-oximetry monitor which was required for PIPP score calculation was recorded for 5 minutes before and after the intervention. PIPP scoring was done at 30 seconds after the heel-stick procedure. In KMC group infant's face was turned to side; care was taken to capture only the facial expression of the neonate without revealing study interventions, and muted video was taken for blinded PIPP score assessment. Two Neonatology Fellows trained in measuring PIPP score independently assessed the videos for PIPP score assessment. If the discrepancy was more than 2 points on total PIPP score, it was resolved through discussion involving the Neonatologist. Otherwise, the average of the PIPP scores was considered.

Statistical analysis: Descriptive statistics were used to depict the baseline characteristics of the study population. Analysis of variance (ANOVA) was employed to compare the total PIPP score across groups. Scheffe's test was used for post-hoc comparison to tease out the significant differences between groups. The analysis was performed using STATA version 14.1.

RESULTS

Parents of all eligible participants were contacted, and all consented for the study. One neonate who was allotted to music therapy could not be provided music therapy due to technical problem (instrument failure) hence was allocated to control group. ***Fig.* 1** provides the study flow.

Out of 200 participants, 104 (52%) were females. The mean (SD) birth weight and gestational age of the neonates was 1.91 (0.34) Kg. and 33.97 (2.32) weeks, respectively. The mean (SD) [IQR] age of the

neonates was 8.24 (7.35) [3–11] days. The baseline characteristics were comparable across groups ***(Table* I).**

Analysis of variance revealed that there was significant difference in total PIPP score across groups (P<0.001). A significant difference was also observed in all the individual components of PIPP score across groups except Behavioral State (P=0.65). Post-hoc comparisons using Sheffe's test revealed that the mean (SD) total PIPP score was significantly lower in KMC group ([7.67 (3.93) *vs*. 11.49 (3.37), 95% CI of difference: (-5.90, -1.73), P<0.001] as well as KMC with Music therapy group ([8.50 (3.23) *vs*. 11.49 (3.37), 95% CI of difference: (-5.06, –0.92), P=0.001] as compared to control group. However, it was similar between control group and music therapy group (p=0.18). Similar observation was noted for individual components of PIPP score ***(Table* II)** .

No study intervention related side effects were encountered in any participants.

DISCUSSION

Preterm neonates admitted to NICU receive 10-15 painful procedures as a part of their medical management and care every day. It is extremely important to treat and reduce neonatal pain as it has been shown to be associated with many short-term complications and long-term consequences [3-5,15]. Research till date has been focused on individual pain control interventions (Kangaroo mother care [6,7, 16-18], music therapy [8,9,19,20] and expressed breast milk [10,11,21]) but they have not been studied for comparison and additive effects. The results of present study revealed that pain control interventions have different efficacy individually and when combined on total PIPP score as well as on majority of its individual components. KMC with EBM was found to be the most efficacious method in reducing neonatal pain. In our study flute based Music therapy had no additive benefit when combined with KMC and EBM.

Flute-based music therapy was not shown to have additive benefit when combined with KMC and EBM. It is however possible that different kind of music may give different results albeit it is difficult to test it with current research design that contained only one type of music. We chose flute-based music as it has been shown to have pain-modifying effect in adults [22,23]. Being a single center study can be considered a limitation; nonetheless, we tried to include adequate number of participants for ensuring adequately powered study results. Because of ethical considerations expressed breast milk was provided as baseline for all study participants. Because of this baseline intervention individual efficacy of study interventions might have been impacted. We included neonates born 28 to 36 weeks of gestational age for increasing the generalizability of the study results across extended gestational age group; however the individual efficacies of interventions in particular gestational age may be different and was not studied, as

that was not the focus of present research.

Sucrose although routinely used for pain control in neonates has not been adequately studied for long-term side effects. Concerns have been raised about neurodevelopmental effects of sucrose when used in preterm babies for multiple doses [24]. Given that preterm neonates receive multiple painful procedures it would be imperative to use non-pharmacological methods like Kangaroo mother care, music therapy and expressed breast milk. KMC and EBM would have additional benefits of promoting breastfeeding and mother infant bonding.

Within the current study setting scenarios, KMC with expressed breast milk should be offered to all neonates undergoing painful procedures and this should be practiced whenever feasible. Increased efficacy of pain control for preterm neonatal pain on heel-stick when kangaroo mother care was combined with expressed breast milk should be investigated further in different settings for enhanced generalizability. Additional studies for assessing effects of different music types on neonatal pain should be pursued.

KMC and KMC with music therapy (with EBM for baseline pain control) significantly reduces pain on heel-stick as compared to control (EBM alone). Increased efficacy of KMC and EBM should be investigated further in different study settings to enhance generalizability and should be practiced in current study settings considering KMC and EBM provides additional benefits of promoting breastfeeding and mother infant bonding. KMC with EBM should be the first choice as a method for pain control in preterm neonates. Further studies comparing pain control interventions for confirming the present findings and to assess long-term neurodevelopmental outcome implications with better pain control are warranted.

WHAT IS ALREADY KNOWN?

* Kangaroo mother care, music therapy and expressed breast milk are individually effective interventions for pain control in preterm neonates.

WHAT THIS STUDY ADDS?

* Kangaroo mother care has an additive effect when combined with expressed breast milk or with expressed breast milk and music therapy, showing significantly better pain control as compared to expressed breast milk alone.

Contributors: VS: conceptualized and planned the study, drafted the proposal and manuscript, and supervised data collection; SB: planned the study design, and revised the manuscript for important

intellectual points; AN: conceptualized and devised the study, analyzed the data, and contributed to manuscript writing; AC: contributed to data collection, analysis of study, and drafting the manuscript;; AP: contributed to study design, analyzed the data, provided important intellectual inputs to the manuscript; DP: contributed to study design, supervised the study, and contributed to manuscript writing; SN: conceptualized, planned and supervised the progress of the study, analyzed the data, and provided important intellectual inputs to the manuscript. All authors approved the final version of manuscript.

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TABLE I *BASELINE CHARACTERISTICS OF THE STUDY PARTICIPANTS*

Particulars	*KMC (N=50)*	*Music Therapy (N=49)*	*KMC + Music (N=50)*	*Control (N=51)*	*Overall (N=200)*
Gestational age (weeks) [Mean (SD)]	33.90 (2.22)	33.59 (2.20)	33.82 (2.87)	34.55 (1.84)	33.97 (2.32)
Birth Weight (Kg). [Mean (SD)]	1.85 (0.37)	1.87 (0.32)	1.94 (0.33)	1.96 (0.33)	1.91 (0.34)
Age (days) [Mean(SD)[IQR]]	9.02 (8.09) [3.0–13.25]	8.12 (8.21) [3.0–9.5]	9.32 (7.94) [4.0–12.0]	6.51 (4.38) [3.0–9.0]	8.24 (7.35) [3–11]
Female Gender (%)	23 (46)	23 (46.90)	27 (54)	31 (60.80)	104 (52)
Small for gestational age (SGA)	21.0 (42.00)	19.0 (38.80)	28.0 (56.00)	23.0 (45.10)	91.0 (45.50)

TABLE II *COMPARISON OF PIPP SCORES ACROSS GROUPS*

PIPP Components	*KMC (N= 50)*	*Music Therapy (N=49)*	*KMC + Music (N=50)*	*Control (N=51)*	*Overall (N=200)*
Gestational age Mean (SD)	0.8 (0.8)	0.9 (0.7)	0.8 (0.8)	0.5 (0.6)	0.8 (0.8)
Behavioral State Mean (SD)	2.5 (0.9)	2.4 (0.9)	2.3 (1.1)	2.3 (0.9)	2.3 (0.9)
Heart Rate Mean (SD)	0.9 (0.8)	1.1 (0.7)	0.9 (0.7)	1.5 (0.7)	1.1 (0.77)
Oxygen Saturation (SPO2) Mean (SD)	0.3 (0)	0.6 (0.6)	0.4 (0.6)	0.8 (0.7)	0.57 (0.66)
Brow Bulge Mean (SD)	1.2 (1.2)	1.8 (1.1)	1.6 (1.1)	2.3 (0.9)	1.72 (1.15)
Eye Squeeze Mean (SD)	1.1 (1.2)	1.6 (1.1)	1.3 (1.0)	2.2 (1.1)	1.55 (1.15)
Naso-Labial Furrow Mean (SD)	0.8 (1.0)	1.4 (1.1)	1.1 (1.0)	1.9 (1.1)	1.32 (1.14)
Total PIPP score [Mean (SD)]	*7.7 (3.9)*	*9.9 (4.2)*	*8.5 (3.2)*	*11.5 (3.4)*	*9.40 (3.95)*

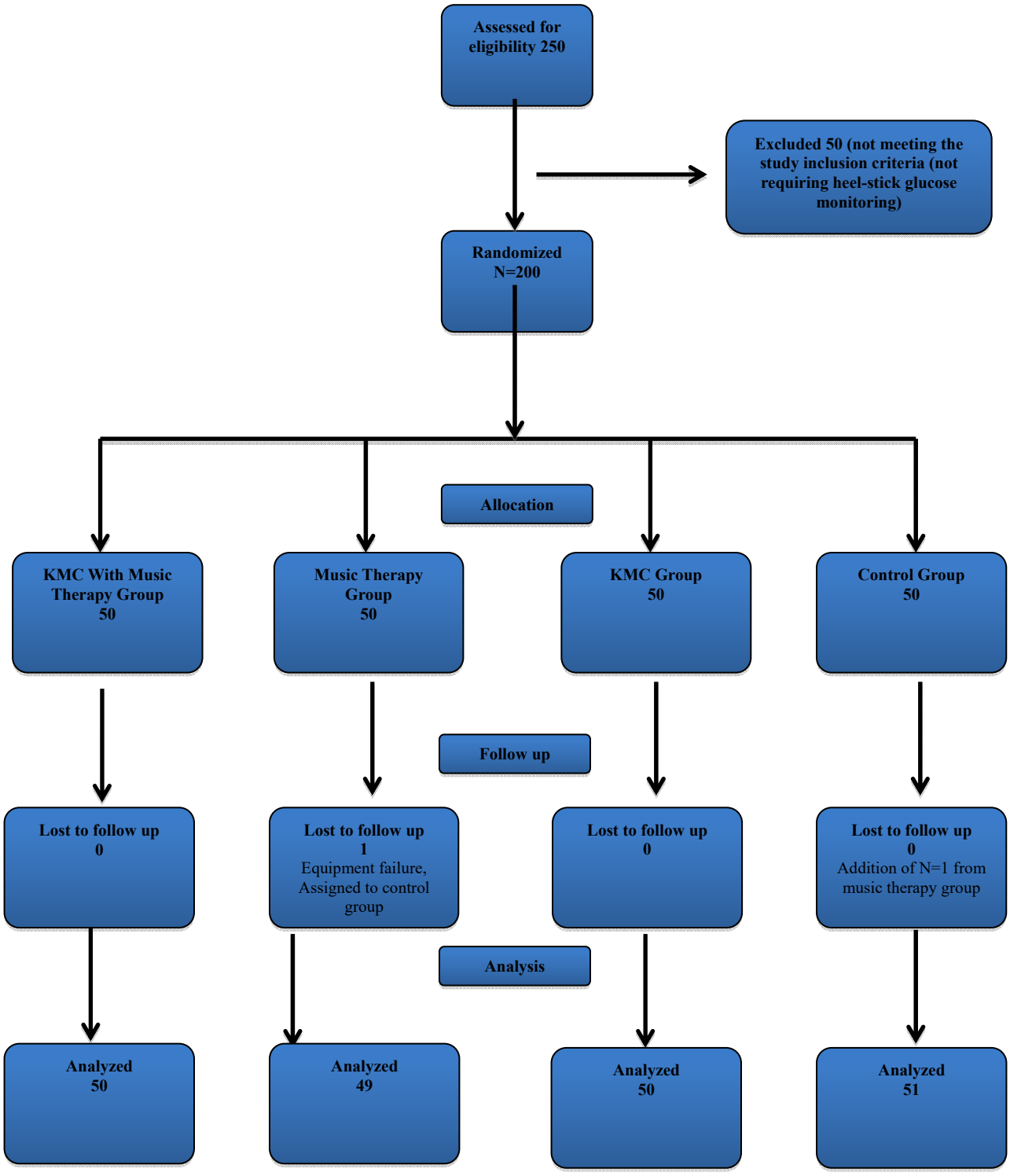

***Fig.* 1.** Study Flow