

Pain Control Interventions in Preterm Neonates: A Randomized Controlled Trial

VIVEK V SHUKLA¹, SATVIK BANSAL², ARCHANA NIMBALKAR³, APURVA CHAPLA², AJAY PHATAK⁴, DIPEN PATEL² AND SOMASHEKHAR NIMBALKAR²

From ¹Division of Neonatology, The Hospital for Sick Children, Toronto, Canada; Departments of ²Pediatrics and ³Physiology, Pramukhswami Medical College, Karamsad, Anand, Gujarat, India; and ⁴Central Research Services, Charutar Arogya Mandal, Karamsad, Anand, Gujarat, India.

Correspondence to: Dr Vivek Shukla, Division of Neonatology, The Hospital for Sick Children, 555 University Avenue, Toronto, ON M5G 1X8. viveks3985@gmail.com

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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 wk gestational age) requiring heel-prick 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) wk, 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-prick 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: CTRI/2016/06/007028

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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 their individual effect on pain. The objective of this study was to compare the efficacy of two pain control interventions and interaction effects (if any).

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.

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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-prick procedure for bedside glucose assessment as per the routine medical management. Exclusion criteria were neurologic impairment (perinatal depression and HIE \geq 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 a 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-prick in addition to the study interventions. Study

intervention was provided 10 min prior to heel-prick procedure, and music therapy continued for at least 5 min and KMC was continued post heel-prick 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 (Google 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 2 mL of EBM 2 minutes prior to the heel-prick 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-prick procedure. In KMC group infant's face was turned to side; care was taken to capture only the facial expression of the neonate

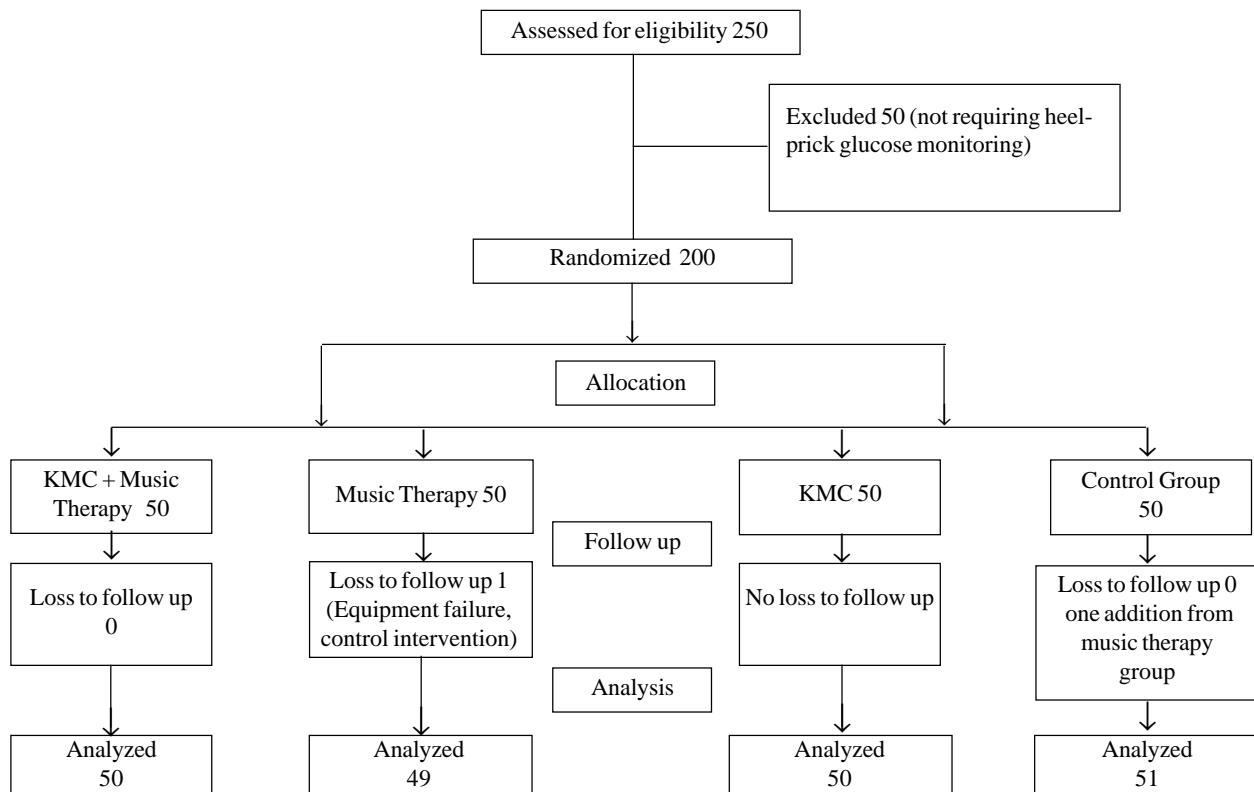


FIG. 1 Study flow.

without revealing study interventions, and muted video was taken for blinded PIPP score assessment. Two fellows in neonatology, 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: Analysis of variance (ANOVA) was employed to compare the total PIPP score across groups. Scheffe's test was used for post-hoc comparison to find 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. **Fig. 1** provides the study flow. Out of 200 participants, 104 (52%) were females. The mean (SD) birthweight and gestational age of the neonates was 1.91 (0.34) kg and 34.0 (2.32) weeks, respectively. The mean (SD) age of the neonates was 8.2 (7.35) days. The baseline characteristics were comparable across groups (**Table I**).

Analysis of variance revealed that there was a 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 Scheffe'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

Pain research in preterms, till date, has been focused on individual pain control interventions (Kangaroo mother care [6,7,15-18], 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.

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]. Because of ethical considerations expressed breast milk was provided as baseline for all study participants. Due to this baseline intervention, individual efficacy of study interventions might have been impacted. We included neonates born at 28 to 36 weeks of gestational age for increasing the generalizability of the study results across extended gestational age group; however, the individual efficacy of interventions in particular gestational ages 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 in multiple doses [24]. Given that preterm neonates receive multiple painful procedures, it is imperative to use non-pharmacological methods like Kangaroo mother care, music therapy and expressed breast milk.

KMC and KMC with music therapy (with EBM for baseline pain control) significantly reduces pain on heel-

TABLE I BASELINE CHARACTERISTICS OF PRETERM NEONATES RECEIVING PAIN-CONTROL INTERVENTIONS

Particulars	KMC (n=50)	Music Therapy (n=49)	KMC +Music (n=50)	Control (n=51)	Overall (n=200)
Gestational age, wk	33.9 (2.22)	33.6 (2.20)	33.8 (2.87)	34.6 (1.84)	34.0 (2.32)
Birthweight, kg	1.85 (0.37)	1.87 (0.32)	1.94 (0.33)	1.96 (0.33)	1.91 (0.34)
Age, d	9.0 (8.09)	8.1 (8.21)	9.3 (7.94)	6.5 (4.38)	8.2 (7.35)
Female gender*	23 (46)	23 (46.9)	27 (54)	31 (60.8)	104 (52)
SGA*	21(42.0)	19 (38.8)	28 (56.0)	23 (45.1)	91 (45.5)

Values in mean (SD) or *No.(%); SGA: small for gestational age.

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.

TABLE II COMPARISON OF PIPP SCORES ACROSS GROUPS (N=200)

<i>PIPP Components</i>	<i>KMC (n= 50)</i>	<i>Music Therapy (n=49)</i>	<i>KMC + Music (n=50)</i>	<i>Control (n=51)</i>	<i>Overall (n=200)</i>
Gestational age	0.8 (0.8)	0.9 (0.7)	0.8 (0.8)	0.5 (0.6)	0.8 (0.8)
Behavioral state	2.5 (0.9)	2.4 (0.9)	2.3 (1.1)	2.3 (0.9)	2.3 (0.9)
Heart rate	0.9 (0.8)	1.1 (0.7)	0.9 (0.7)	1.5 (0.7)	1.1 (0.77)
Oxygen saturation (SpO ₂)	0.3 (0)	0.6 (0.6)	0.4 (0.6)	0.8 (0.7)	0.57 (0.66)
Brow bulge	1.2 (1.2)	1.8 (1.1)	1.6 (1.1)	2.3 (0.9)	1.72 (1.15)
Eye squeeze	1.1 (1.2)	1.6 (1.1)	1.3 (1.0)	2.2 (1.1)	1.55 (1.15)
Naso-labial furrow	0.8 (1.0)	1.4 (1.1)	1.1 (1.0)	1.9 (1.1)	1.32 (1.14)
Total PIPP score	7.7 (3.9)	9.9 (4.2)	8.5 (3.2)	11.5 (3.4)	9.40 (3.95)

PIPP: Premature infant pain profile; All values in mean (SD).

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.

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