Tehran University of Medical Sciences

**Nursing Practice Today**

*2025; Volume 12, No 1, pp. 85-97*

**Original Article**

# The effects of kangaroo care on delirium management in neonates under non-invasive mechanical ventilation: A randomized control trial

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ARTICLE INFO

Received 14 August 2024
Accepted 01 December 2024

Available online at:
http://npt.tums.ac.ir

**Keywords:**
infant;
delirium;
mechanical ventilation;
neonatal intensive care unit;
kangaroo mother care method

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**DOI:** 10.18502/npt.v12i1.17528

ABSTRACT

**Background & Aims:** Little is known about managing delirium in neonates admitted to Neonatal Intensive Care Units. The current study investigated whether kangaroo mother care can affect neonates' delirium under non-invasive mechanical ventilation.
**Materials & Methods:** In this randomized control trial, a total of 50 term neonates who were under non-invasive mechanical ventilation were allocated to intervention and control groups (n=25 in each group) using block randomization. Utilizing "Cornell Assessment of Pediatric Delirium", and "ACoRN respiratory sequence protocol", the data were gathered at baseline, 24, 48, and 72 hours after. The intervention group received 30 minutes of kangaroo mother care daily.
**Results:** There was a statistical delirium mean scores difference between the two groups on day 2 ($p < 0.045$) but not on other days. Repeated measures modeling (linear mixed models and generalized linear mixed models) indicated significant differences in change curves for both Cornell Assessment of Pediatric Delirium scores and the incidence of delirium.
**Conclusion:** Implementing kangaroo mother care for a 30-minute duration each day for neonates under non-invasive mechanical ventilation may markedly decrease delirium occurrence.

## Introduction

Despite the well-described nature of delirium in adults and pediatric intensive care units, little is known about this phenomenon in hospitalized neonates. Hospitalization, especially in intensive care units, may increase delirium occurrence in adults. Neonatal Intensive Care Units (NICUs) have similar characteristics and may increase the risk that neonates also experience delirium. Furthermore, recent studies suggest that up to one-quarter of infants in NICUs may experience delirium (1). Several factors have been identified to be associated with the occurrence of delirium. These include patient-related variables such as the severity of the illness, the age of the patient, and the presence of significant comorbidities. Additionally, environmental conditions, characterized by extreme sensory experiences involving light and sound, play a role. The use of invasive ventilation (2) and pharmacological influences, including the administration of multiple medications and certain specific drugs, are also pertinent factors (3). Considering the mentioned risk factors, neonates admitted to the NICUs have the potential to develop delirium; they usually are critically ill, have prolonged stay in a highly

Please cite this article as: Mirnia K, Osborne J.W, Sharif-Nia H, Sánchez-Teruel D, Khoshnavay Fomani F, Mirzaei N. The effects of kangaroo care on delirium management in neonates under non-invasive mechanical ventilation: A randomized control trial. Nursing Practice Today. 2025; 12(1):85-97.

medicalized environment, may be subject to invasive ventilation, and are often treated with multiple drugs, including benzodiazepines (1, 2, 4). Furthermore, they mostly meet the pathophysiological criteria, including neuronal activity dysregulation, for delirium development during the NICU stay. Critically ill neonates may suffer from systemic inflammation and illness stress that elevates the levels of cytokines in the brain and disrupts the integrity of the blood-brain barrier, resulting in the dysfunction of neurons and synapses. It also leads to glucocorticoid elevation as well as melatonin production disruption. Melatonin plays a crucial role in various physiological processes, including the scavenging of free radicals, as well as exhibiting anti-apoptotic and anti-inflammatory properties. The stress of illness and systemic inflammation also may be comorbid with central nervous system (CNS) hypoperfusion periods. It causes CNS energy failure and consequently impairs the toxic metabolic clearance. This condition ultimately affects neurotransmitters' synthesis and metabolism, and terminates the inability to maintain ion gradients. Decreased levels of acetylcholine and dopamine, and an increase in the level of glutamine, are a consequence of neurotransmitter imbalances proposed as another mechanism of delirium occurrence in ill neonates (1, 5).

Neonatal delirium is typically identified by a range of symptoms including agitation, hyperactivity, diminished attention span, disruptions in the sleep-wake cycle, and persistent inconsolability even when sedative doses are escalated. Newborns may exhibit resistance to mechanical ventilation, continuous crying, heightened spontaneous and aimless movements, irritability characterized by facial grimacing, and frequent flailing of limbs. Additionally, affected newborns often show an inability to recognize or respond to their parent's face or voice, despite having previously demonstrated such recognition (6). The neonates who suffer from delirium may be categorized as hyperactive, hypoactive, or a mixed condition (3). While the hypoactive type is challenging to identify due to its insidious nature, neonates who suffer from hyperactive delirium attract the caregivers' attention easily due to the clear manifestation.

Although a few case studies focused on describing delirium in neonates, there are several published papers discussing the delirium burden in NICUs (2, 6-8). This suggests that many cases may go undiagnosed and subsequently untreated due to a lack of delirium recognition by neonatologists or NICU nurses (2). Therefore the incidence and prevalence of delirium in neonatal intensive care units cannot be accurately estimated.

Most delirium screening tools depend on verbal communication with the patient and therefore, are not appropriate for assessing delirium in neonates. Currently, only the Cornell Assessment of Pediatric Delirium (CAPD) has been validated for this purpose (2, 9). Regular screening is important as early identification and treatment of delirium in neonates may minimize its long-term consequences. Given the significant implications of delirium, early diagnosis and treatment or prevention of delirium should lead to reduced hospital costs and better patient outcomes (2).

More importantly, there are known interventions to improve delirium prevention or management. These include reducing exposure to factors that can trigger delirium (1). Kangaroo care (KC), a non-pharmacological measure, focuses on skin-to-skin contact of neonates with mothers (Kangaroo Mother Care, or KMC) or other caregivers while the neonates are carried with well-documented benefits (10). Taking into account the various factors that contribute to delirium in neonates, as well as the roles of KMC intervention, it is plausible that KMC may serve as an effective strategy for managing neonatal delirium. KMC facilitates physiological equilibrium, enhances respiratory regularity, reduces energy expenditure for thermoregulation, accelerates weight gain, improves sleep patterns that support brain development, optimizes cerebral oxygenation, regulates gastrointestinal hormones more effectively, lowers the likelihood of infections, and diminishes pain sensitivity (11). Notwithstanding these remarkable capabilities, the influence of this intervention on the management of neonatal delirium remains to be explored.

The failure to recognize and manage this condition promptly can lead to both short-term and prolonged complications for affected neonates. Among different interventions, Kangaroo Mother Care (KMC), which is increasingly being adopted in various healthcare settings, has theoretical foundations suggesting its potential efficacy in managing delirium as a non-pharmacological intervention. Nevertheless, despite the acknowledged advantages of KMC, there is currently a lack of empirical evidence to substantiate its effectiveness in addressing neonatal delirium. The current study aims to investigate the effects of Kangaroo Mother Care (KMC) on delirium management in neonates under non-invasive mechanical ventilation.

## Methods

### *Study design and participants*

In this parallel two-group randomized clinical trial, a total of 50 neonates who were admitted to one hospital affiliated with the X University of Medical Sciences and who met the inclusion criteria were recruited for the study. Based on the inclusion criteria, all neonates were term ( gestational age more than 37 weeks) at the time they were evaluated for inclusion in the study, were under non-invasive mechanical ventilation (NIV) for at least 72 hours (12), didn't receive sedative and antiepileptic drugs included in the study. The NIV modes included Nasal continuous positive airway pressure (NCPAP), Non-invasive positive pressure ventilation (NIPPV), and High-flow nasal cannula (HFNC). Mothers in both the control and intervention groups expressed their willingness to participate in this study, and as an inclusion criterion, the parents needed to sign the informed consent form. In the intervention group, mothers were instructed to engage in Kangaroo Mother Care (KMC) for a continuous duration of 30 minutes each day for their newborns. To be eligible for participation, mothers were required to express their willingness and readiness to undertake this intervention. The 50 neonates were randomly assigned to intervention (n=25) and control groups(n=25) using block randomization. Any neonate who received sedative or antiepileptic drugs due to convulsion or any other condition, invasive mechanical ventilation, who were under NIV for less than 72 hours, or whose mothers were unavailable to continue KMC were excluded from further participation in the study.

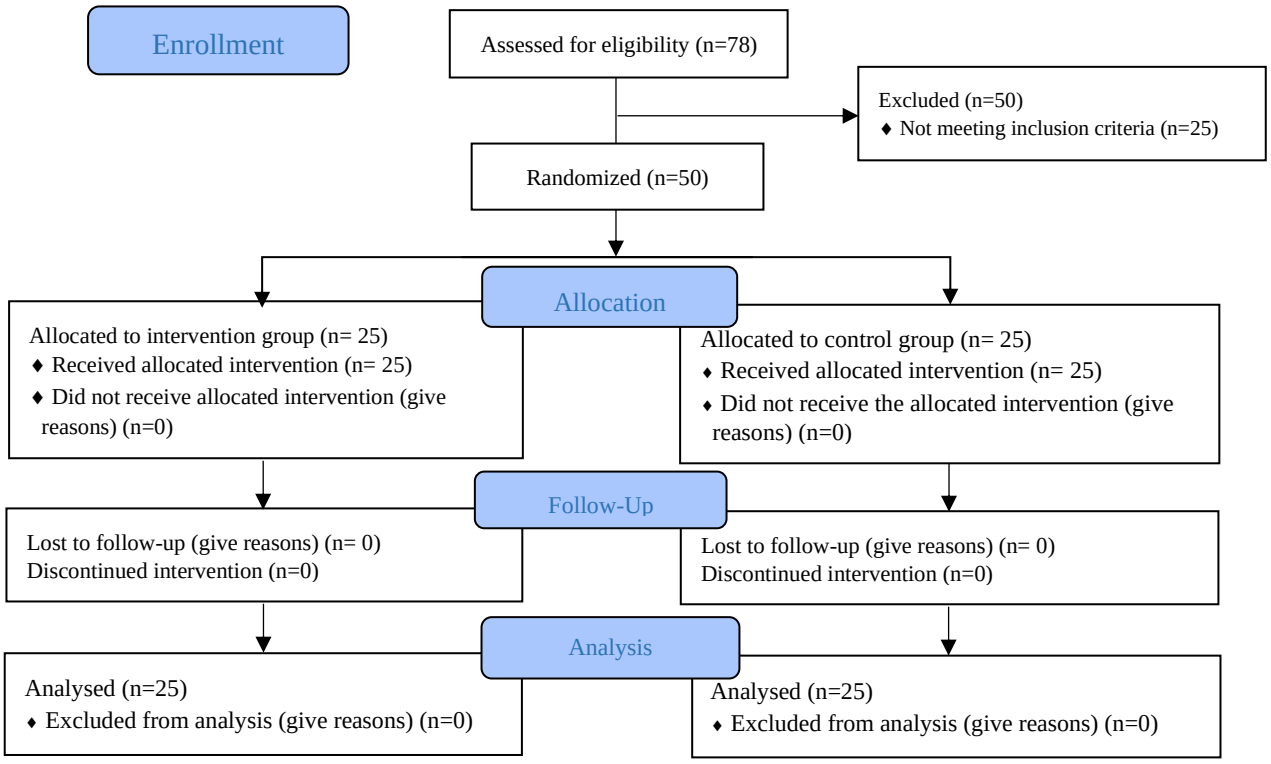


**Diagram 1.** CONSORT Diagram of the study

***Sampling and procedure***

Considering the limitation of previous studies to indicate the effects of KMC on neonates' delirium, a prior pilot study (total sample size of 20) was conducted to assess the feasibility of conducting the current study, investigating the study questionnaires' validity and reliability, and determining the sample size. Based on the pilot study, which estimated effect size (*d*) of 0.80, a power calculation concluded that we needed at least 45 neonates to complete the study to allow for an alpha of 0.05 and a power of 80%. Considering a projected attrition rate of 10%, our goal was to recruit fifty neonates for the current study.

After obtaining the hospital's principals' agreements, the researchers went to the NICU at different shift times during the study. When neonates were admitted to the NICU during these times, the research team introduced themselves to the mothers in each group and explored the study aims how mothers were expected to participate, and the potential benefits and risks. Randomization was conducted using a computer-generated permuted block randomization sequence with block sizes of four in a 1:1 ratio to either the control ($n$ = 25) or intervention group ($n$ = 25) to ensure equal representation of both groups in each block. Due to the nature of the intervention, mothers, physicians, nurses, and study investigators were not blinded to treatment allocation.

To prepare documentation, the study process was discussed in a face-to-face meeting with the parents, and after signing the informed consent form, baseline data was collected for all neonates upon enrollment (i.e., when she/he went under the non-invasive mechanical ventilation). This baseline assessment included neonates' demographic characteristics (e.g., biological sex gender, age, birth weight, gestational age, congenital heart disease), respiratory distress syndrome (RDS) scores, non-invasive mechanical ventilation mode after extubating, NICU stay duration, nutrition status, and delirium score.

Delirium screening was performed for both groups of neonates during evening shifts for 72 hours using the Cornell Assessment of Pediatric Delirium (CAPD; 9). During each evening shift, from 2:00 PM to 7:00 PM, neonates' behaviors, sleep, and wakefulness status were recorded on video using a camera that was placed near the infants' incubator. Videos were recorded for the first fifteen minutes of each hour for the duration of the shift. The procedure persisted for an additional 15 minutes each hour, contingent upon the neonate remaining asleep during the initial 15 minutes. This approach was implemented to guarantee the precision of the assessment during the neonate's sleep and wake cycles. Both neonatologists and the first researchers contributed in this procedure. The video data was then evaluated and scored according to the CAPD (13). The research team decided to collect data in the evening shift because usually the unit was not very crowded at that time, and gathering the data was more feasible, providing a representative sample of data for each neonate without interfering with or being distracted by the activities of the daytime shift.

The camera was strategically positioned in proximity to the neonates' incubator to ensure minimal disruption to the caregiving environment, thereby allowing for unobstructed nursing and medical intervention for the neonates. The researchers ensured the privacy of parents and neonates was protected. Video files were not shared elsewhere and were deleted at parents' request in each study stage. To protect the personal privacy of mothers and their preferences, recording videos wasn't conducted during KMC and was intended exclusively for data collection, videos were recorded. The whole process of data gathering lasted for eleven months from May 2021 to April 2022.

***Intervention: Kangaroo Mother Care (KMC)***

The mothers in the intervention group conducted intermittent Kangaroo Mother Care (KMC) for a single 30-minute block during each 24-hour day (14). Performing skin-to-skin contact in an infant undergoing noninvasive mechanical ventilation can be challenging and mothers may be anxious and worried due to experiencing fear and uncertainty before

starting KMC for their unstable neonates. To reduce anxiety and protect the neonates, both the primary researcher and a neonatologist who was responsible for treating the neonate were present in the unit before and during the KMC intervention.

Before the KMC intervention, the procedure was explained in detail, and all questions raised by the mothers were answered carefully. The mother's seat was placed next to the neonate's incubator to prevent issues with the equipment connected to the neonate. The main researcher then transferred the neonate to the mother's chest under the supervision of a neonatologist, who observed all the precautions and took care of the neonate's safety. The neonate's head was covered with a cotton cap and placed vertically between the two bare breasts of the mother. The neonate was covered with a sheet, and none of the monitoring devices, respiratory support, intravenous line, or other equipment were removed from the neonate. The time of skin-to-skin contact was determined with the coordination of the nurse responsible for the neonate so as not to interfere with any patient care or treatment measures. During the entire period of skin-to-skin contact, the neonate was monitored by the nurse and the researcher, and no feeding was given. At the end of the skin-to-skin contact, following all precautions, the neonate was again transferred to the incubator for monitoring and other treatment and care measures.

Conducting KC for neonates admitted to NICUs is not routine care in the current study settings. Therefore, the neonates in the control group did not receive KC during the study but the parents of control group neonates were trained in KMC after the study was completed.

### *Primary and secondary outcomes*

The primary outcome was investigating the changes in delirium under non-invasive mechanical ventilation (NIV) after conducting KMC. The secondary endpoint of the current study was the reduction of neonates' delirium by KMC as a nonpharmacologic measure.

### *Measures*

The data were gathered using three questionnaires including demographic profile, "Cornell Assessment of Pediatric Delirium" (CAPD) along with "Developmental anchor point", and "ACoRN respiratory sequence protocol". Furthermore, items such as the non-invasive mechanical ventilation mode after extubating, NICU stay duration, and nutrition mode were recorded via a demographic data form.

#### *2.5.1. Cornell Assessment of Pediatric Delirium (CAPD) and Developmental Anchor Point*

CAPD is an easy and rapid screening tool that has been developed to help nurses identify delirium in critically ill children of all ages and developmental stages (13, 15). CAPD contains eight items related to the $DSM_5$ domains of awareness and cognition, as well as including psychomotor symptoms. It has been shown that it is very easy to administer by a bedside nurse and requires about two minutes to complete for each patient (9). The CAPD scores derive from assessing the neonate's attention, awareness, actions, and general state. Delirium can be detected with scores of nine or higher, but it should be compared to the baseline data of the patient. A set of developmental anchor points for CAPD allows nurses to apply the scores in a developmentally appropriate manner. The "developmental anchor points" are used as a multifaceted bedside reference chart hand help nurses score CAPD in a validated way (9). The CAPD has been translated and validated in previous studies (13, 16).

#### *Translation and validation*

We used the widely-accepted Beaton et al. (2000) process for translation and back-translation of measures used in this study (17). The questionnaires were translated into Persian by two bilingual translators independently and then the research team members assessed two translated versions for selecting the best items. In the next step, the translated (Persian) version was back-translated into English by another two bilingual translators who were blinded to the

original questionnaires. The expert committee consisting of research team members, two psychologists, two neonatologists, and one methodologist, checked the back-translated version to ensure the accuracy and equivalence between it and the original questionnaire. After the expert panels' consensus about the back-translated and the final translated version, we evaluated the translated questionnaire in a pilot study. The Cronbach's alpha coefficient was estimated to be 0.79, which is acceptable, particularly for clinical diagnostic screening measures like the CAPD. To score each questionnaire for every neonate, the recorded videos were assessed by two research team members (a Certified NIDCAP Professional and a Ph.D. nurse) independently, and they provided their scores for items. In the next stage, all video records were assessed by them in a joint meeting, and the final consensuses for each case were obtained. We calculated the average inter-rater agreement for the CAPD score as an average weighted Kappa of 0.81 (range 0.78 to 0.84) which demonstrates very strong agreement.

Before the implementation of the above-mentioned procedure, the research team contacted the questionnaire developer (Traube C.) for permission to use CAPD and received some recommendations for study design and sampling.

### *Statistical analysis*

Following initial exploratory data analysis, hierarchical multivariate linear modeling (HMLM) was used to analyze the repeated CAPD measures, which are continuous, and generalized linear mixed modeling (GLMM) was used to analyze the repeated delirium measures, which are binary. Both models tested whether change curves over time differed between the two groups of neonates.

### *Ethical consideration*

The Ethics Committee of Tehran University of Medical Sciences approved the Ethical Considerations of this study (Reference No.: IR.TUMS.FNM.REC.1399.181).In addition, all participants were informed of the purpose of the data collection, and questionnaires were distributed to the respondents only after they provided their consent to participate in the survey. Moreover, the respondents were ensured that their participation was voluntary and confidentiality of all collected data was guaranteed. Written informed consent was obtained from all mothers who participated in this study. The current study has been approved by the Iranian Registry of Clinical Trials (IRCT); IRCT20201130049544N1. Available at: https://www.irct.ir/search/result?query=IRCT20201130049544N1

## Results

The characteristics profile of the study participants is presented in Table 1. Nearly one-third (66%) of neonates recruited in the current study were male. The samples were mostly born pre-term and term (96%). All included neonates were term at the time of including the study, but they might have been born term or pre-term. The neonates had a mean weight of more than 2500 grams and were classified as mild or moderate respiratory distress syndrome (RDS). Non-invasive positive pressure ventilation (NIPPV) was the most prevalent NIV mode that was used for 76% of the neonates. The most common diagnosis was respiratory distress (24%).

There were no statistically significant differences between the two groups at the baseline in terms of age, birth weight, gestational age, neonates' age (in days) at the time of including in the study, RDS score, NIV mode, length, delirium scores, and occurrence. We also assessed two groups in terms of nutritional status during 72 hours. The findings indicated that the number of nothing-by-mouth (NPO) cases decreased gradually, but a chi-squared test revealed no significant differences between the two groups.

CAPD scores are summarized in Table 2. These means show that both groups improved (showed decreasing scores) over time. Initial exploratory analyses indicated that the two groups were not significantly different except on Day 2 (48 hours).

**Table 1.** Demographic characteristics of respondents and assessing groups' homogeneity

| Variable | Control group | Intervention group |
|---|---|---|
| **Neonates' gender** | **N(%)** | **N(%)** |
| **Female** | 9(36) | 8(32) |
| **Male** | 16(64) | 17(68) |
| **p = 0.76** | | |
| **Neonates' birth weight (grams)** | **Mean (SD)** | **Mean (SD)** |
| | 2796(654) | 2856(621) |
| **p=0.74** | | |
| **Gestational age** | **N(%)** | **N(%)** |
| **Late Pre-term (32 weeks and lower)** | 0(0) | 2(8) |
| **Pre-term (33-36 weeks)** | 14(56) | 12(48) |
| **Term (37-40 weeks)** | 11(44) | 11(44) |
| | p = 0.31 | |
| **Neonates' age at the time of including the study** | **Median (IQR)** | **Median (IQR)** |
| | 4 ($14_{1-14}$) | 7 ($11_{1-11}$) |
| | p = 0.54 | |
| **RDS[a] score based on ACoRN** | **N(%)** | **N(%)** |
| **mild (scores less than 5)** | 13(52) | 15(60) |
| **moderate (scores 5-8)** | 12(48) | 10(40) |
| | p = 0.77 | |
| **NIV[b] Mode** | **N(%)** | **N(%)** |
| **NCPAP[c]** | 2(8) | 1(4) |
| **NIPPV[d]** | 19(76) | 19(76) |
| **HFNC[e]** | 4(16) | 5(20) |
| | p = 0.79 | |
| **NIV duration** | **Median (IQR)** | **Median (IQR)** |
| | 14 ($24_{8-31}$) | 14 ($15_{10-25}$) |
| | p = 0.90 | |
| **Delirium score based on CAPD[f]** | Mean (SD) | Mean (SD) |
| | 10.36(3.32) | 9.88(3.03) |
| | p=0.59 | |
| **Delirium occurrence based on CAPD** | **N(%)** | **N(%)** |
| **Yes** | 16(64) | 15(60) |
| **No** | 9(36) | 10(40) |
| | p = 0.77 | |

| Nutritional status during the study | Control group | | | | Intervention group | | | |
|---|---|---|---|---|---|---|---|---|
| | **Baseline** | **Day 1** | **Day 2** | **Day 3** | **Baseline** | **Day 1** | **Day 2** | **Day 3** |
| | **N(%)** | | | | **N(%)** | | | |
| **Nothing by mouth (NPO)** | 14(56) | 10(40) | 3(12) | 3(12) | 14(56) | 8(32) | 3(12) | 2(8) |
| **Not NPO** | 11(34) | 15(60) | 22(88) | 22(88) | 11(34) | 17(68) | 22(88) | 23(92) |
| | Baseline: $p$= 0.38<br>Day 1: $p$=0.83<br>Day 2: $p$= 0.73<br>Day 3: $p$= 0.48 | | | | | | | |

*[respiratory] distress syndrome (RDS), [b]Non- invasive mechanical ventilation (NIV), [nasal] continuous positive airway pressure (NCPAP), [d]Non-invasive positive pressure ventilation (NIPPV) , [e]High-flow nasal cannula (HFNC), [f]Cornell Assessment of Paediatric Delirium (CAPD)*

**Table 2.** Comparing the delirium mean score in the four-time assessment of the intervention and control groups

| Assessment day | Baseline (day 0) | Day 1 (24 hours) | Day 2 (48 hours) | Day 3 (72 hours) |
|---|---|---|---|---|
| | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** | **Mean (SD)** |
| **Control group** | 10.36 (3.32) | 9.84 (3.07) | 9.00 (2.59) | 8.08 (1.97) |
| **Intervention group** | 9.88 (3.32) | 8.40 (3.61) | 7.36 (3.02) | 6.96 (2.65) |
| **The variables of neonates' age, NICU stay days, duration of non-invasive mechanical ventilation, and RDS score were adjusted.** | | | | |

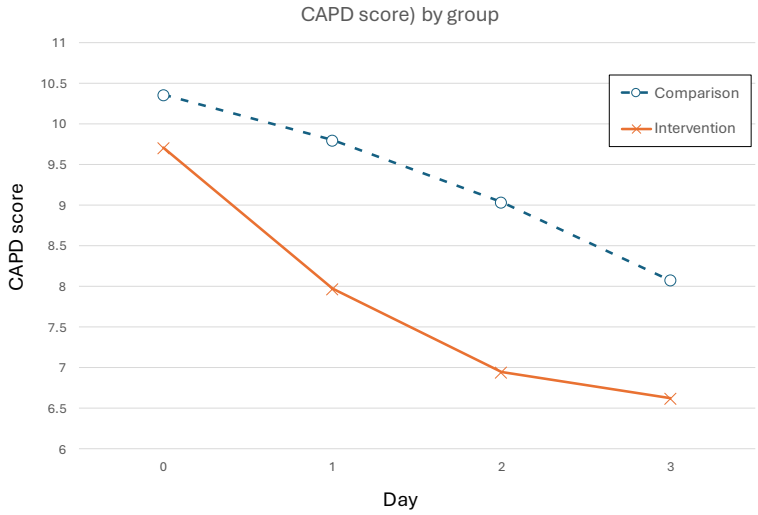


**Figure 1.** Change in CAPD scores over time as a function of group

As mentioned above, linear mixed models (LMM) were utilized to appropriately model the repeated CAPD measures and test whether the respective linear and nonlinear change curves for the two groups were significantly different. For these analyses, an autoregressive (AR) variance structure was modeled for Level 1 (repeated CAPD measures) variance, as an AR variance structure produced a better model fit than homogenous variance ($X^2_{(8)} = 18.44$, $p < .001$). Level 2, the individual level, included group and sex as well as the interaction of the two. Sex and the interaction of sex and group were not significant predictors and were excluded from the final models.

It is a best practice in linear mixed models to center the variables at meaningful points so that intercepts are interpretable. In these analyses, we centered time on the second day, allowing the intercept to reflect the mean of scores at 48 hours. Because there are multiple time points, nonlinear effects are possible, and so a squared time term was also entered into the Level 1 model to test for nonlinear trends. Both individual slopes and intercepts were modeled as random parameters, allowing for Level 2 variables to predict differences (in other words, allowing us to see if the different groups had different means and change curves over time).

Initial analyses indicated that there was significant variability in both the random slopes and the intercepts, providing justification for entering Level 2 variables in an attempt to explain the variation. When group (coded 0=comparison group, 1= intervention group) was entered as a Level 2 variable, the model improved significantly (measured as overall "deviance" in the model, equivalent to lack of fit, from 893.24 with 6 parameters estimated to 884.16 with 9 parameters estimated, yielding $X^2_{(3)} = 9.08$, $p < 0.028$).

In Table 3 we summarize the results of this analysis and Figure 2 graphs the results. Looking at the first set of intercept coefficients, there is a significant difference between group CAPD scores on the second day (as time was centered on the second day, the intercept is the mean for these scores) at $p < 0.006$. As noted above, the intervention group had, on average, scores 2.09 points lower than the comparison group by Day 2.

Looking at the linear time slope, there is a significant change over time ($p < .004$) and this does not differ by group. Looking at the final group of coefficients, the squared (quadratic) effect of time is not significant alone, but there is a near-significant interaction of time squared and group, indicating that the change curves may be different. Figure 2 shows that using these estimates, we can see that the intervention group scores improve more rapidly than the comparison group, and end markedly lower than the comparison group.

**Table 3.** Linear mixed model predicting CAPD from time and group

| Fixed Effect | Coefficient | Standard error | t-ratio | Approx. d.f. | *p*-value |
|---|---|---|---|---|---|
| **For INTRCPT1, $\pi_0$** | | | | | |
| INTRCPT2, $\beta_{00}$ | 9.039095 | 0.507055 | 17.827 | 47 | <0.001 |
| GROUP, $\beta_{01}$ | -2.094336 | 0.724515 | -2.891 | 47 | 0.006 |
| **For TIME slope, $\pi_1$** | | | | | |
| INTRCPT2, $\beta_{10}$ | -0.861811 | 0.298372 | -2.888 | 190 | 0.004 |
| GROUP, $\beta_{11}$ | 0.188828 | 0.426334 | 0.443 | 190 | 0.657 |
| **For TIMESQ slope, $\pi_2$** | | | | | |
| INTRCPT2, $\beta_{20}$ | -0.100000 | 0.187381 | -0.534 | 190 | 0.593 |
| GROUP, $\beta_{21}$ | 0.454167 | 0.267742 | 1.696 | 190 | 0.089 |

Following up on these analyses, each neonate was classified as experiencing delirium or not (coded 1 if so, 0 if not) at each time point. Exploratory analyses showed similar patterns to that of the CAPD analysis above. The percentage of neonates experiencing delirium at each time point is summarized in Table 4, below. It is clear that the percentage of neonates experiencing delirium drops substantially and more quickly in the intervention group than in the control group (as evidenced by the stronger Q in the intervention group than in the comparison group).

**Table 4.** Percent of neonates experiencing delirium

| | Day 0 | Day 1 | Day 2 | Day 3 | Cochran Q |
|---|---|---|---|---|---|
| **Comparison group** | 68.0% | 64.0% | 56.0% | 28.0% | $Q_{(3)} = 14.88$, $p < .002$ |
| **Intervention group** | 72.0% | 44.0% | 20.0% | 20.0% | $Q_{(3)} = 29.5$, $p < .0001$ |

Exploring further, we can sum the number of days that the individuals were classified as experiencing delirium. The average number of days for individuals in the intervention group was 1.56 compared to an average of 2.16 in the comparison group. While not statistically significant ($p < 0.12$), it again reinforces the notion that there were qualitative differences between these two groups' outcomes.

To formally test the hypothesis that the change curves for the two groups differ over time in predicting delirium, a Generalized Linear Mixed Model (GLMM) analysis was created to mirror the CAPD analysis above but account for the binary repeated measures outcome. In logistic regression, the predicted values, the log of the odds of experiencing the outcome, can be complicated to interpret, so following best practices (18), the predicted values were exponentiated and converted to conditional probabilities for ease of interpretation.

As Table 4 shows, the main effect of the group was significant. As the time variable was centered at Day 2, this reflects the mean group difference at that time, indicating that the intervention group was significantly less likely to experience delirium than the comparison group. The significant effect of time reflects the fact that both groups improved significantly over time, and the interaction of group and time-squared (after covarying the linear time effect) indicates that the nonlinear trend is significantly different for the two groups (Table 5). These effects are presented graphically in Figure 2, below.

**Table 5.** A generalized linear mixed model predicting delirium from group and time

| Fixed Effect | Coefficient | Standard error | *z* value | Approx. *d.f.* | *p*-value |
|---|---|---|---|---|---|
| **For INTRCPT1, $\pi_0$** | | | | | |
| INTRCPT2, $\beta_{00}$ | 0.2331 | 0.6725 | 0.347 | 47 | 0.729 |
| GROUP, $\beta_{01}$ | -3.0012 | 1.1256 | -2.666 | 47 | 0.008 |
| **For TIME slope, $\pi_1$** | | | | | |
| INTRCPT2, $\beta_{10}$ | -1.4745 | 0.4443 | -3.318 | 190 | 0.0009 |
| GROUP, $\beta_{11}$ | 0.2959 | 0.6449 | 0.443 | 190 | 0.459 |
| **For TIMESQ slope, $\pi_2$** | | | | | |
| INTRCPT2, $\beta_{20}$ | -0.4694 | 0.2948 | -1.592 | 190 | 0.111 |
| GROUP, $\beta_{21}$ | 1.1517 | 0.4835 | 2.382 | 190 | 0.017 |

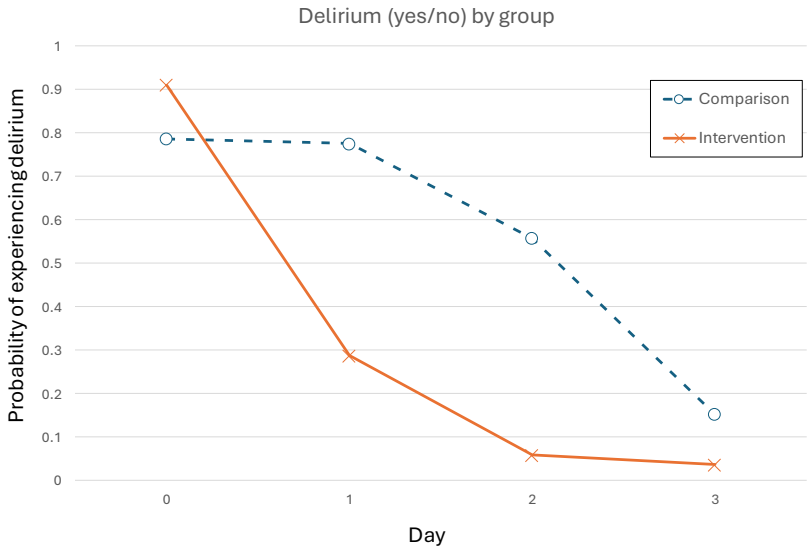


**Figure 2.** Change in the probability of delirium over time by group

As you can see in Figure 2, the probability of experiencing delirium drops much faster for the KC intervention group, essentially flattening after the second day, whereas for the comparison group, the downward trend begins a day later. These predicted conditional probabilities match the observed probabilities trend presented above.

Combined, the different change curves for the KC and intervention groups demonstrate the dramatic difference in the two groups of neonates. Not only do CAPD scores improve more quickly in those experiencing KC, but the probability of experiencing delirium declines to almost zero a full day before the comparison neonates.

## Discussion

The present research examined the impact of Kangaroo Mother Care (KMC) on delirium in neonates receiving non-invasive mechanical ventilation, highlighting its advantages in reducing the occurrence of delirium among this population. Although few studies, which were mostly case reports (6, 7) have been published focusing on neonatal delirium, and this health condition is not always taken seriously by many clinicians, it has affected a wide range of neonates admitted to NICUs and imposed short and long-term consequences on neonates' health. This is the first study we are aware of to examine the potential for KMC to prevent or reduce delirium in neonates. Given that delirium can have significant impacts on health and wellness for a broad range of patients, this study is important in stimulating further investigation and awareness of this topic and this potential intervention.

Limited research has been undertaken to explore the association between demographic variables, including gender, and the incidence of delirium in newborns admitted to neonatal intensive care units. Nevertheless, within the

pediatric demographic, it remains inconclusive whether gender serves as a reliable predictor of delirium (19). Our intervention and control groups were not different statistically in terms of gender, although we did tend to enroll more male neonates, and sex has been identified as an influencing factor in neonatal morbidity and mortality. However, sex was not a significant factor when entered into our analyses, and given there were no significant differences across groups, we did not discuss it further.

The findings displayed in Table 1 indicate that there is no statistically significant difference observed between the intervention and control groups in terms of the number of nothing-by-mouth (NPO) cases across the four measurements. However, poor nutritional status is one underlying factor that can cause delirium occurrences in hospitalized neonates (20). In the current study, the number of NPO cases decreased during the investigation, especially after 24 hours, and ancillary analyses indicated that the decline was more dramatic in the intervention group compared to the control group (declining from 54.2% to 29.2% in the intervention group compared to a decline from 56.0% to 40% in the control group). This aligns with other studies that have identified benefits of implementing KMC in pre-term neonates' nutrition and improving nutritional behavior (21, 22).

The main objective of the current research was to examine the impact of implementing Kangaroo Mother Care (KMC) on delirium in neonates under non-invasive mechanical ventilation. The data analysis indicated that in the intervention group, implementing KMC led to significant and rapid decrease in the number of delirious neonates, and the delirium mean scores difference between intervention and control groups became statistically significant after 48 hours and there was a near-significant curvilinear (quadratic) effect when looking at all four-time points, it appears that this study may have benefitted from more neonates in each group. Studies show that the patients' delirium incidence is higher in the first three days of intensive care unit admission than in other days (15, 23, 24). The current study indicates that neonates can experience significant advantages from Kangaroo Mother Care in mitigating delirium during these crucial initial three days, particularly within the first 48 hours. Consequently, this evidence may prompt the revision of NICU policies to incorporate KMC practices. Furthermore, additional research in this area is essential to expand upon the outcomes observed in this study.

Considering the underlying factors associated with delirium occurrence in neonates (e.g., prematurity, illness severity, medications and inflammation, and illness stress) (1, 25, 26), the effects of implementing KMC can be explored. The activation of the hypothalamus-pituitary–adrenocortical (HPA) axis occurs in response to stress, initiating a multifaceted feedback mechanism that encompasses the hypothalamus, pituitary gland, and adrenal glands. This process results in the release of the glucocorticoid cortisol, which serves as a biomarker for stress, as its plasma concentrations increase in reaction to both psychological and physiological stressors (27). Research suggests that initiating early physical contact with the mother through Kangaroo Mother Care (KMC) influences the neuroendocrine pathways in infants that regulate stress responses. Studies indicated that KMC, even in a short duration of 15 minutes, can reduce neonates' stress (28). KMC, also, is useful for neonates’ autonomic hemostasis by managing their response to painful procedures (29). In this regard, through multisensory stimulation input and modulation of stress regulation, KC can reduce the neonates’ pain and stress (30, 31). Furthermore, it has been suggested that skin-to-skin improves neonates' stabilization by promoting physiological function and attenuating autonomic-neuroendocrine stress responses (32, 33). The secretion of oxytocin occurs during kangaroo care, particularly when the infant is in close contact with the mother. This hormonal release increases the pain threshold and operates in a manner akin to opioids by blocking pain receptor sites. Additionally, it facilitates a transition in brain stem control towards the parasympathetic nervous system, promoting relaxation and a sense of safety (34).

### *Study limitation*

The current study is not without limitations. The first and important limitation of the study is that delirium occurrence in neonates who are admitted to NICU is associated with several factors. Considering the current study findings as well as the limited available evidence on this topic, there is a need for further investigations with different designs, settings, and sample sizes (e.g., mediator/moderator models) to better understand this phenomenon and its underlying factors.

## Conclusion

In conclusion, the current study indicated that implementing KMC for a 30-minute duration each day for neonates under non-invasive mechanical ventilation can rapidly decrease delirium occurrence compared to standard care. The number of delirious cases decreased significantly more rapidly in the KMC intervention group than in the standard care group. This may have important implications for overall outcomes for neonates experiencing these situations and should be addressed further.

### *The implications for clinical practice*

In the first place, the current study makes the nurses working in the NICU more aware of the possibility of delirium occurrence in neonates. In addition, considering the well-known benefits of kangaroo care, this non-pharmacological measure can be used to manage delirium in neonates and prevent its short and long-term health consequences.

## Acknowledgment

We express our gratitude to all the mothers who took part in the current study. Also, we would like to express our sincere gratitude to all nurses and hospital principals who contributed to providing a study setting for us.

## Conflict of interests

The authors declare that they have no competing interests.

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