Effect of Kangaroo Mother Care on Cerebral Hemodynamics in Preterm Neonates Assessed by Transcranial Doppler Sonography in Middle Cerebral Artery

ANAL J CHAUDHARI,[1] SOMASHEKHAR M NIMBALKAR,[1,2] DIPEN V PATEL,[1] AJAY G PHATAK[2]
[1]*Department of Neonatology, Pramukhswami Medical College, Bhaikaka University, Karamsad, Gujarat.*
[2]*Central Research Services, Charutar Arogya Mandal, Bhaikaka University, Karamsad, Gujarat.*
Correspondence to: Dr Somashekhar M Nimbalkar, Professor and Head, Department of Neonatology, Pramukhswami Medical College, Bhaikaka University, Karamsad, Gujarat. somu_somu@yahoo.com
Received: June 06, 2022; Initial review: July 06, 2022; Accepted: August 04, 2022.

Objective: To study the effect of KMC in premature newborns on cerebral hemodynamics in the middle cerebral artery (MCA) using transcranial doppler sonography.

Methods: In this descriptive study, 40 clinically stable preterm neonates admitted to the neonatal intensive care unit of our institute and undergoing Kangaroo mother care (KMC) were enrolled. Physiological and cerebral blood flow parameters of MCA were obtained by using transcranial doppler sonography at baseline, at 60 minutes of KMC, and after 60 minutes of stopping KMC.

Results: Of the 40 enrolled neonates (24 males), the mean (SD) birth weight, gestation age, and postnatal age were 1698.25 (495.44) g, 33.00 (1.67) wk, and 6.80 (4.51) days, respectively. The mean (SD) cerebral blood flow velocities increased (peak systolic velocity (PSV), *P*=0.03; end diastolic velocity, *P*<0.001; mean velocity, *P*<0.001) and doppler indices decreased (resistive index, *P*=0.001; pulsatility index, *P*<0.001) significantly; whereas, heart rate (*P*<0.001) decreased but SpO2 (*P*=0.001) and mean blood pressure (*P*=0.003) increased significantly at 60 minutes of KMC as compared to baseline. Sixty minutes after stopping KMC, all parameters (except PSV) were higher than baseline, indicating post KMC effect.

Conclusion: KMC improves cerebral hemodynamics in clinically stable preterm neonates.

Keywords: *Benefit*, *Cerebral blood flow, Neonatal care, Outcome*.

Published online: October 29, 2022; ***PII:*** S097475591600466

Premature neonates, born across the globe, spend their first few weeks of life in the neonatal intensive care unit (NICU) [1], where they are subjected to an abnormal environment and multiple invasive procedures. The neonatal period is the critical period of brain development and maturation [2]. Preterm neonates are especially susceptible to brain injury as they have immature cerebral vasculature and ineffective cerebral autoregulation, leading to the marked fluctuation in cerebral blood flow [3,4]. This results in cerebrovascular events like intraventricular hemorrhage and ischemic injury to periventricular white matter, which have long-term adverse neurodevelopmental problems in cognitive, motor, and behavioral domains [5].

Globally, during the last two decades, there has been significant improvement in the survival of extremely preterm neonates due to advanced perinatal and neonatal intensive care practices. Increased survival has also resulted in increased neuro-morbidity among the survivors. Hence, neuroprotective strategies are required to improve cerebral hemodynamics [6]. Kangaroo mother care (KMC), an evidence-based standard of care for preterm neonates [7-10], positively influences the premature brain networks, facilitates the formation of neural connections, and leads to better long-term neurodevelopmental outcomes [11].

Invited Commentary: Pages 13-14

Most studies on KMC have focused on thermoregulation, pain control intervention, physical growth, mortality and sepsis reduction, success with breastfeeding, and improvement in cardiorespiratory parameters. However, the effect of KMC on cerebral blood flow and its dynamics in preterm has not been studied well. Transcranial color Doppler sonography is an excellent, non-invasive modality for real-time assessment of cerebral blood flow in newborns [12]. Color Doppler imaging of the middle cerebral artery (MCA) displays various cerebral blood flow parameters, which helps to evaluate alterations in cerebral hemodynamics [13]. The current study aims to evaluate the changes in cerebral blood flow patterns and velocities in MCA by using transcranial color Doppler before and after KMC in clinically and hemodynamically stable preterm neonates.

METHODS

A single- arm interventional study was conducted between September, 2020 to May, 2021 at Level 3 NICU in a Medical college in Anand, Gujarat, India, enrolling all clinically and hemodynamically stable preterm neonates (28 0/7 to 36 6/7 weeks gestational age) admitted to NICU or KMC ward. Exclusion criteria were neurological impairment (perinatal depression and hypoxic-ischemic encephalopathy, intra-ventricular hemorrhage, hydrocephalus, stroke, seizure or congenital malformation of the central nervous system), congenital heart disease, critical illness rendering the babies unstable (needing invasive mechanical ventilation and/or inotropes), administration of pain control/sedative medications within 24 hours before study interventions, and neonatal abstinence syndrome.

In the absence of any regional estimates of the standard deviation of outcome variables, it was not possible to calculate the exact sample size. The study period was planned for around nine months expecting to enrol around 35 participants.

After obtaining written informed consent from parents, the baseline physiological parameters [heart rate (HR), oxygen saturation (SpO_2), and blood pressure (BP)] and cerebral blood flow parameters of MCA were obtained by using transcranial color Doppler ultrasonography in a supine position under a radiant warmer. After that, neonates were given KMC for the first time as per standard positioning technique, for a minimum of 60 minutes. All cerebral blood flow parameters and physiological parameters were obtained at 60 min of KMC and 60 minutes after stopping KMC. All neonates were examined in a calm and resting state without any sedation. Cerebral blood flow parameters were obtained by Doppler imaging evaluation of the middle cerebral artery using Transcranial color Doppler (TCD) ultrasonography machine (Sonosite, Model-EDGE-Fifth generation portable ultrasound, Sr. no-03P565) with a high resolution phased array transducer (Model P10x) of 8-4 MHz. All cranial ultrasound examinations were performed by a Neonatology fellow having expertise in neonatal cranial ultrasound. Color Doppler imaging with pulsed wave Doppler (PWD) was used to identify MCA from the temporal window. The cerebral blood flow velocities (CBFVs) and Doppler indices (RI and PI) measured included *i*) Peak systolic velocity (PSV): Highest velocity in the cardiac cycle; *ii*) End diastolic velocity (EDV): Lowest velocity at the end of the cardiac cycle; *iii*) Mean velocity (MV): Calculated over a series of cardiac cycles; *iv*) Resistive Index (RI): (PSV-EDV)/PSV; and *v*) Pulsatility index (PI): (PSV-EDV)/MV.

Statistical analysis: Paired *t* test was used to compare physiological and cerebral blood flow Doppler parameters at baseline (before KMC), at 60 min KMC and after 60 min of KMC. Pearson correlation coefficient was used to correlate cerebral blood flow parameters with gestational age and birth weight. The analysis was performed using STATA (14.2). A *P* value of less than 0.05 was considered significant.

RESULTS

Of a total of 152 preterm neonates admitted in NICU, 93 neonates did not meet the inclusion criteria, mothers of 15 eligible neonates were not available to provide KMC as they were COVID-19 positive and sick, and mothers of four neonates refused to participate. So, 40 (24 (60%) males) clinically stable preterm neonates were enrolled in the study, with 27(67.5%), 11(27.5%) and 24 (60%) being appropriate for gestation age (AGA), small for gestation age (SGA) and late preterm babies, respectively. The mean (SD) gestational age, birth weight, and postnatal age of the participants was 33.05 (1.68) weeks, 1698.25 (495.44) g, and 6.8 (4.52) days, respectively.

All the mean cerebral blood flow parameters of MCA Doppler viz., PSV, EDV, MV, RI and PI improved significantly at 60 minutes of KMC compared to baseline

Table I Cerebral Blood Flow Parameters of Middle Cerebral Artery Doppler at Different Durations of Kangaroo Mother Care (KMC) (*N*=40)

Parameters	*Before KMC (Baseline)*	*At 60 min of KMC*	*MD (95% CI)[a]; P value*	*60 min after stopping KMC*	*MD (95% CI)[b]; P value*
PSV (cm/s)	43.9 (3.76)	44.8 (3.94)	-0.90 (-1.70,-0.90); 0.030	43.8 (3.45)	0.12 (-0.59,0.82); 0.74
EDV (cm/s)	10.8 (1.30)	11.8 (1.33)	-0.97 (-1.41,-0.54); <0.001	11.4 (1.1)	-0.66 (-0.96,-0.36); <0.001
MV (cm/s)	21.8 (1.90)	22.8 (1.91)	-0.92 (-1.39,-0.46); <0.001	22.2 (1.64)	-0.38 (-0.73,-0.03); 0.032
RI	0.7 (0.02)	0.7 (0.03)	0.02 (0.01,0.03); 0.001	0.7 (0.023)	0.16 (0.01, 0.020); <0.001
PI	1.5 (0.09)	1.4 (0.11)	0.07 (0.03,0.11); <0.001	1.4 (0.09)	0.06 (0.04,0.09); <0.001

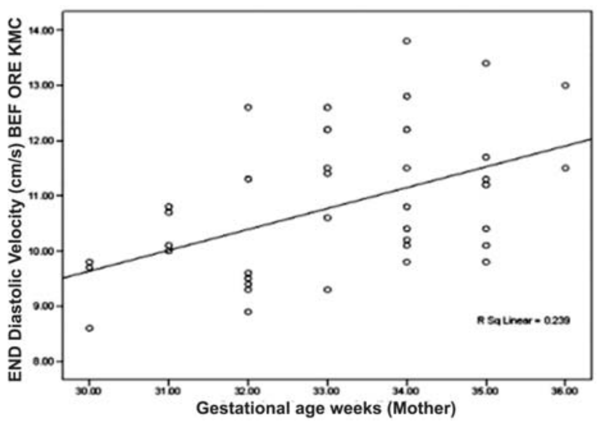
All values in mean (SD). MD-mean difference. [a]before KMC–at 60 min of KMC. [b]before KMC–60 min after stopping KMC. SpO2-oxygen saturation; BP-blood pressure; PSV-peak systolic velocity; EDV-end diastolic velocity; MV-mean velocity; RI- resistive index; PI-pulsatility index.

values. The values were higher than baseline at 60 minutes after stopping KMC except for PSV (**Table I**). Similarly, the physiological parameters viz. SpO2, heart rate, and mean blood pressure showed significant improvement at 60 minutes of KMC from baseline, whereas systolic and diastolic blood pressure remained similar. The effect was sustained only for mean blood pressure after 60 minutes of stopping KMC (**Table II**).

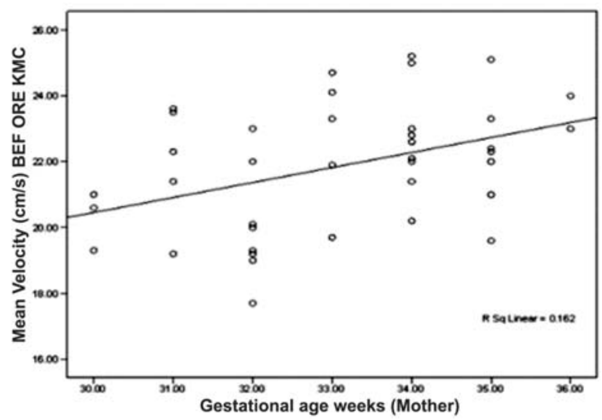
Table II Physiological Parameters of Middle Cerebral Artery Doppler at Different Durations of Kangaroo Mother Care (*N*=40)

Parameters	*Before KMC (Baseline)*	*At 60 min of KMC*	*MD (95% CI)[a]; P value*	*60 min after stopping KMC*	*MD (95% CI)[b]; P value*
Heart rate (per min)	148.8 (10.42)	143.6 (11.24)	5.23 (2.95,7.50); <0.001	146.1 (10.55)	2.65 (-0.05, 5.35); 0.05
SpO2 (%)	95.7 (1.40)	96.5 (1.50)	-0.88 (-1.38,-0.37); 0.001	95.8 (1.82)	-0.18 (-0.76, 0.41); 0.55
Systolic BP(mmHg)	64.0 (7.81)	64.6 (8.73)	-0.63 (-1.84, 0.59); 0.31	63.9 (8.38)	0.05 (-1.34, 1.44); 0.94
Diastolic BP (mmHg)	42.2 (6.96)	43.3 (6.75)	-1.05 (-2.44, 0.34); 0.14	43.3 (6.83)	-1.08 (-2.69, 0.54); 0.19
Mean BP (mmHg)	45.1 (7.59)	46.9 (8.32)	-1.73 (-2.81,-0.64); 0.003	47.1 (7.81)	-1.93 (-3.11,-0.74); 0.002

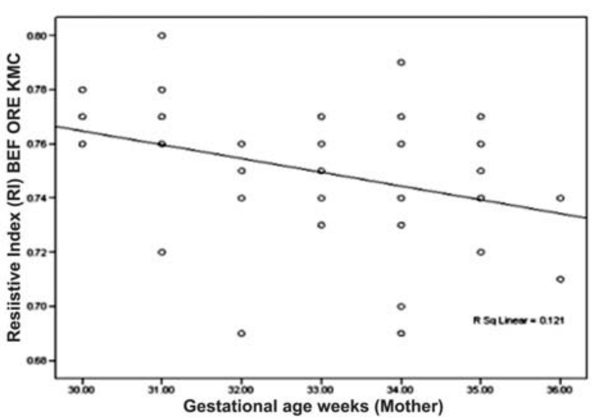
All values in mean (SD). KMC-kangaroo mother care; MD-mean difference, [a]before KMC–at 60 min of KMC, [b]before KMC–60 min after stopping KMC. SpO2-oxygen saturation; BP-blood pressure.



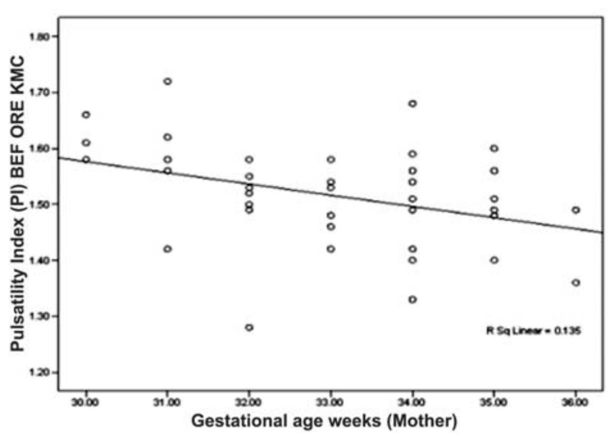
a) Correlation between GA and EDV



b) Correlation between GA and MV



c) Correlation between GA and RI



d) Correlation between GA and PI

EDV: end diastolic velocity, MV: mean velocity, RI: resistive index, PI: pulsatility index.

Fig. 1 Correlation between gestational age (GA) and cerebral blood flow (CBF) parameters in preterm infants undergoing kangaroo mother care (KMC).

Table III Correlation Between Birth Weight and Cerebral Blood Flow (CBF) Parameters of Middle Cerebral Artery Doppler at Baseline Before Kangaroo Mother Care (*N*=40)

CBF parameters	*Correlation coefficient*	*P value*
PSV	0.362	0.022
EDV	0.552	<0.001
MV	0.505	0.001
RI	-0.324	0.042
PI	-0.361	0.022

PSV: peak systolic velocity; EDV: end diastolic velocity; MV: mean velocity; RI: resistive index; PI: pulsatility index.

On evaluating the correlation between cerebral blood flow parameters of MCA Doppler at baseline and gestation age (**Fig.1**) and birth weight (**Table III**), it was seen that while EDV (*r*=0.49) and MV (*r*= 0.40) were significantly positively correlated with gestation age, RI (*r* = -0.35) and PI (*r* = -0.37) were significantly negatively correlated with gestation age. Although, PSV (r=0.26) had a positive correlation with gestation age, it was not statistically significant. The correlation between cerebral blood flow parameters of MCA Doppler and gestational age are shown in **Fig. 1**.

DISCUSSION

The current study determined the impact of KMC on cerebral hemodynamics in MCA and physiological parameters. There was a statistically significant improvement in all CBF parameters at 60 minutes of KMC compared to baseline. However, these changes in CBF parameters were within the normal range. The trend of improving CBF parameters was still evident at 60 minutes of stopping KMC except for the PSV, which was closer to the baseline values. As this effect of KMC was studied only up to 60 minutes after stopping KMC, the effect after that is unknown. We also found significant correlation between CBF parameters at baseline and gestation age and birth weight. Further, this study showed a positive impact of KMC on cardiorespiratory parameters, the effect was sustained only for mean blood pressure post 60 minutes of stopping KMC.

KMC has emerged as a safe, feasible, and low-cost intervention for neonates, with significant benefits [14,15]. The beneficial effects of KMC on cerebral hemodynamics in preterm neonates are yet to be fully explored. Neuro-physiological effects of KMC might mediate improvement in cerebral blood flow. Skin-to-skin care by the mother provides multisensory stimulation, including tactile, auditory, and olfactory. All these may have a tranquilizing effect on the baby, allowing physiological parameters to stabilize, facilitating neural connections, enhancing synaptic efficacy and connectivity of cerebral motor pathways. It also enables better quality of quiet sleep and induces non-chaotic sleep patterns and normal sleep cycling [9]. Nelson and Panksept's brain opioid theory of social attachment, based on animal experimentation, postulates that maternal touch, smell, and milk release endogenous opiates, which are known to promote affiliative behavior [16]. Oxytocin is the primary hormone promoting affiliation and appears to have anti-nociceptive effects. Activation of slow-conducting unmyelinated afferents by pleasant touch stimulates the cortex to produce various vasodilatory mediators and induces nitric oxide-mediated smooth muscle relaxation of cerebral microvasculature [17,18]. Hence, KMC might positively influence cerebral hemodynamics in the preterm brain by these various proposed mechanisms.

Korraa, et al. [19], in a similar study in Egypt, recruited 60 clinically stable preterms and measured CBF parameters in MCA before and after 30 min of KMC. This study demonstrated a significant increase in CBFVs (EDV and MV) and a significant decrease in Doppler indices (RI and PI) after 30 minutes of KMC, indicating improvement in CBF following KMC application. Other authors [20-22] also observed a correlation between all CBFVs and gestational age. Thus, the current study results are concordant with these previously published studies.

Similar to the study by Seibert, et al. [23], Doppler indices (RI and PI) showed a significant decrease with increasing gestational age in the current study. Nourian, et al. [24] suggested that the effect of KMC on the physiological parameters remains sustained. Azeez, et al. [25] also found that the majority of babies who received KMC showed significant improvement in vital parameters. Pezzati, et al. [22] generated normal reference data for MCA CBF parameters in preterm infants and demonstrated association with GA and BW. The current study additionally helped in the establishment of a normative database for MCA cerebral Doppler measurements in stable preterm infants.

The residual effect on many parameters even after 60 minutes suggests that KMC may be working through the release of various hormones or neurotransmitters which have a half-life of more than 60 minutes. As KMC is a multimodal intervention and achieves its actions through various mechanisms, it is difficult to isolate a single or few hormones/neurotransmitters that are responsible for it. Duration of KMC has a dose-relation-ship effect on the size of the grey matter, especially the left caudate nucleus, as shown by a 20-year follow-up study [11]. We now have some evidence that KMC alters circulatory flow in the

WHAT IS ALREADY KNOWN?

- Most of the studies on Kangaroo Mother Care have focused on thermoregulation, pain control intervention, physical growth, breastfeeding, mortality, and sepsis reduction.

WHAT THIS STUDY ADDS?

- KMC improves cerebral hemodynamics response by improving cerebral blood flow in hemodynamically stable preterm neonates.

brain, which might ensure appropriate growth of neurons and thus their function [26]. The residual effect following stopping KMC, as shown in the current study, suggests that short breaks between KMC sessions due to change in KMC providers/KMC provider fatigue may not deprive preterm neonates of the beneficial effects of KMC. A recently published i-KMC trial showed that low birth weight babies who were provided continuous KMC initiated immediately after birth experience a reduced risk of mortality compared with a similar group in whom KMC is initiated only after clinical stabilization [27].

The pre-requisite of enrolling only hemodynamically stable newborns in this study limited the application of KMC to other newborns. The sample size was also small across gestations, and we do not have data on the long-term neurodevelopmental follow up.

The current study showed a positive impact of KMC on cerebral hemodynamic response by improving cerebral blood flow in hemodynamically stable preterm neonates. It also shows it stabilized cardiorespiratory para-meters and thus positively influences the physiological stability of preterm neonates**.** Further research could compare cerebral blood flow Doppler parameters between babies who were initiated on KMC after birth and those in whom KMC is initiated after clinical stabilization.

Ethics clearance: IEC, HM Patel Centre for Medical Care and Education; No. IEC/HMPCMCE/123/Faculty/2/246120, dated Oct 22, 2020.
Contributors: AC: conceptualized and designed the study, undertook data collection, and reviewed and revised the manuscript; SN: conceptualized and designed the study, coordinated and supervised the analysis, and substantially reviewed and revised the manuscript; DP: conceptualized the study, contributed to the data collection, and reviewed and revised the manuscript; AP: conceptualized the study, conducted the analysis, and reviewed the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.
Funding: None; *Competing interests*: None stated.

REFERENCES

1. World Health Organization. Preterm Birth. WHO fact sheet on preterm birth providing key facts and information on solution, geographical distribution and WHO response. Accessed July 26, 2022. Available from *https://www.who.int/news-room/fact-sheets/detail/preterm-birth*
2. Anand KJ, Scalzo FM. Can adverse neonatal experiences alter brain development and subsequent behavior? Neonatology. 2000;77:69-82.
3. Brew N, Walker D, Wong FY. Cerebral vascular regulation and brain injury in preterm infants. Am J Physiol Regul Integr Comp Physiol. 2014;306:R773-86.
4. Rhee CJ, Rios DR, Kaiser JR, Brady K. Cerebral hemodynamics in premature infants. Neonatal Med. 2018;25:1-6.
5. Volpe JJ. Brain injury in the premature infant–from pathogenesis to prevention. Brain Dev. 1997;19:519-34.
6. Lien R. Neurocritical care of premature infants. Biomed J. 2020;43:259-67.
7. Sharma D, Farahbakhsh N, Sharma S, et al. Role of kangaroo mother care in growth and breastfeeding rates in very low birth weight (VLBW) neonates: A systematic review. J Matern Fetal Neonatal Med. 2019;32:129-42.
8. Conde-Agudelo A, Díaz-Rossello JL. Kangaroo mother care to reduce morbidity and mortality in low birthweight infants. Cochrane Database Syst Rev. 2016;2016: CD002771.
9. Feldman R, Eidelman AI. Skin to skin contact (kangaroo care) accelerates autonomic and neurobehavioural maturation in preterm infants. Dev Med Child Neurol. 2003; 45:274-81.
10. Bera A, Ghosh J, Singh AK, et al. Effect of kangaroo mother care on vital physiological parameters of the low birth weight newborn. Indian J Community Med. 2014;39:245-9.
11. Charpak N, Tessier R, Ruiz JG, et al. Twenty-year follow-up of kangaroo mother care versus traditional care. Pediatrics. 2017;139:e20162063.
12. Kalyani R, Patil CB. Utility of cranial color Doppler sonography in preterm and term neonates. Int J Radiol Diagn Imaging 2020;3:09-17.
13. Rhine WD, Blankenberg FG. Cranial ultrasonography. NeoReviews. 2001;2:3.
14. Nimbalkar SM, Patel VK, Patel DV, et al. Effect of early skin-to-skin contact following normal delivery on incidence of hypothermia in neonates more than 1800 g: Randomized control trial. J Perinatol. 2014;34:364-8.
15. Nimbalkar SM, Chaudhary NS, Gadhavi KV, Phatak A. Kangaroo mother care in reducing pain in preterm neonates on heel prick. Indian J Pediatr. 2013;80:6-10.
16. Nelson EE, Panksepp J. Brain substrates of infant–mother attachment: contributions of opioids, oxytocin, and norepinephrine. Neurosci Biobehav Rev. 1998;22:437-52.

17. Olausson H, Lamarre Y, Backlund H, et al. Unmyelinated tactile afferents signal touch and project to insular cortex. Nat Neurosci. 2002;5:900-4.
18. Joannides R, Richard V, Haefeli WE, et al. Role of nitric oxide in the regulation of the mechanical properties of peripheral conduit arteries in humans. Hypertension. 1997;30:1465-70.
19. Korraa AA, El Nagger AA, Mohamed RA, Helmy NM. Impact of kangaroo mother care on cerebral blood flow of preterm infants. Ital J Pediatr. 2014;40:83.
20. Horgan JG, Rumack CM, Hay T, et al. Absolute intracranial blood-flow velocities evaluated by duplex Doppler sonography in asymptomatic preterm and term neonates. AJR Am J Roentgenol. 1989;152:1059-64.
21. Forster DE, Koumoundouros E, Saxton V, et al. Cerebral blood flow velocities and cerebrovascular resistance in normal-term neonates in the first 72 hours. J Paediatr Child Health. 2018;54:61-8.
22. Pezzati M, Dani C, Biadaioli R, et al. Early postnatal doppler assessment of cerebral blood flow velocity in healthy preterm and term infants. Dev Med Child Neurol. 2002; 44:745-52.
23. Seibert JJ, McCowan TC, Chadduck WM, et al. Duplex pulsed Doppler US versus intracranial pressure in the neonate: clinical and experimental studies. Radiology. 1989;171:155-9.
24. Nurian M, Mashdberdi Y, Yaghmaei F, Akbarzadeh Baghban AR. Effects of kangaroo and routine care on physiologic parameters of low-birth-weight infants. Advances in nursing and midwifery (faculty of nursing of midwifery quarterly). 2009;19:19-24.
25. Azeez AH, Azize PM. The Effect of Kangaroo Mother Care Intervention on the newborns health outcome delivers at Sulaymaniyah Maternity Teaching Hospital. Erbil J Nurs Midwifery. 2020;3:178-92.
26. Schneider C, Charpak N, Ruiz-Peláez JG, Tessier R. Cerebral motor function in very premature-at-birth adolescents: A brain stimulation exploration of kangaroo mother care effects. Acta Paediatr. 2012;101:1045-53.
27. WHO Immediate KMC Study Group. Impact of continuous Kangaroo Mother Care initiated immediately after birth (iKMC) on survival of newborns with birth weight between 1.0 to <1.8 kg: Study protocol for a randomized controlled trial. Trials. 2020;21:280.