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Effect of umbilical cord milking on the incidence of Intraventricular haemorrhage in very preterm infants

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Abstract
Objective: Intraventricular hemorrhage (IVH) is an alarming complication in preterm infants. The present study was aimed to evaluate the effect of umbilical cord milking and non-milking technique on the incidence of IVH in very preterm neonates (28+1 – 31+6).
Methods: This was a prospective comparative study conducted on 59 very preterm (28+1 – 31+6) neonates. The neonates were divided into two groups non milking group (n=31) and umbilical cord milking [UCM] (n=29). The primary outcome measured was the incidence of IVH and secondary outcome was neonatal mortality, significant jaundice, respiratory distress syndrome (RDS) and need for blood transfusions.
Results: In this study, there was no significant difference in the perinatal demographics between the groups. The incidence of IVH was significantly (p=0.027) decreased in UCM group as that of that of the non-milking group (3.8 vs 27.6%). Further, the mortality, RDS, need for ventilation support blood transfusion was decreased in UCM groups but not statistically significant as that of the non-milking group.
Conclusion: UCM significantly decreased the incidence of IVH in very preterm infants without showing any adverse effects to mother and the newborn.

Keywords: very preterm infants, Intraventricular hemorrhage, Umbilical cord milking, early cord clamping, blood transfusion

Introduction
Globally prematurity is prime factor for the neonatal mortality and it is the second major cause of mortality after pneumonia in children below 5 years. Babies delivered less than 32 weeks period of gestation are termed as very preterm neonates, have increased risk of mortality and morbidity during the first year of life [1]. Intraventricular hemorrhage (IVH) is the most prevalent neonatal intracranial hemorrhage, which may lead to adverse neurological outcomes. The clinical manifestations include cerebral palsy, seizures and during advancement of age it may impose disabilities in learning, visual and hearing problems [2]. Early cord clamping (ECC) is the clamping of umblical cord within 30 seconds of delivery and it is still the widely used technique among the obstetricians [3]. Delayed cord clamping (DCC, ≥30s) is a method, which aids higher placental transfusion and elevates blood volume in newborns [4]. Further, a meta-analysis study reveals that exposure of DCC in preterm infants showed minimal requirement of blood transfusion and decreased the risk of IVH and necrotizing enterocolitis [5]. However, delayed clamping elicits complications like hypervolemia, hyper viscosity, polycythemia, respiratory depression and jaundice but still lacks proper clinical evidence [6]. Meanwhile, Cochrane review shows that DCC increases the risk of jaundice in infants requiring phototherapy [7].
An alternative technique is umbilical cord milking (UCM) performed by gently holding the undissected umbilical cord and slightly pressing the cord from the placenta multiple periods towards the infant. However in UCM elicts placental transfusion without delaying resuscitation and shall be completed swiftly as like clamping method. Mounting reports shows that in term infants cord milking effectively maintains blood pressure, hematocrit, and hemoglobin levels during initial period of life and iron stores upto to 6 months of neonatal period [8, 9, 10]. Further, in preterm infants UCM displays increased blood pressure, hemoglobin, urine output, cerebral oxygenation, decreased risk of IVH of all grades and reduced the need for transfusions [11, 12]. In this study, extreme preterm neonates (< 28 weeks) were excluded, as per the study conducted by Katheria *et al*. showing increased risk of severe IVH after exposure to UCM [13]. However, studies related to UCM in very preterm infants are limited. In this backdrop, the present study was conducted to compare the effect of umbilical cord milking versus standard care in very preterm babies on incidence of Intraventricular Haemorrhage in neonatal period.

Materials and Methods
This prospective comparative study was conducted over a period of 12 months and included 59 very preterm babies (28+1 -31+6weeks) admitted to neonatal ICU of of tertiary care hospital.

Inclusion Criteria
All very preterm neonates (28+1 -31+6weeks) born and admitted at neonatal intensive care unit of tertiary care hospital were enrolled into study after obtaining informed consents from parents.

Exclusion Criteria
Monochorionic diamniotic twin pregnancy, IUGR in antenatal scans (<10th centile), hydrops fetalis, congenital Anomalies, Cord prolapse or Cord anomalies and refered out twins and preterms were excluded from the study.

Study design
All the neonates were recruited as per inclusion criteria and divided into two groups. Non-milking (standard care) and umblical cord milking group (UCM) respectively.
In non-milking group, the cord was clamped immediately after the delivery of neonate. In umblical cord milking group (UCM), the baby was positioned close to the mother's leg at or was held below the level of placenta for caesarean section and for vaginal delivery, was held below the level of placenta. About 30cm length of the cord was held towards the placental side and cord was milked towards the baby at approximately 10cm/sec speed. The process for performed for three times followed by cord clamping. Neurosonogram was done during the early neonatal period. Other data was conducted using prepared questionnaire, by interview of parents, by physical examination of neonates, routine investigation done in the unit and monitoring for the development of complications.

Outcomes
Incidence of Intraventricular Haemorrhage in early neonatal period was the primary outcome. Incidence of neonatal deaths, significant jaundice, respiratory distress syndrome, hypotension, and need for blood transfusions were secondary outcomes.

Grading of IVH
IVH diagnosis was done by cranial ultrasound and grading of IVH was done using Volpe classification of IVH, Grade 1-GMH with no or minimal IVH; Grade 2-IVH occupying 10%-50% of ventricular area on parasagittal view; Grade 3-IVH occupying >50% of ventricular area on parasagittal view separate notation-Periventricular echodensity (location and extent)

Statistical analysis
The data were represented as mean ± SD. Results on categorical measurements were presented in number and percentage. The association of study variables (IVH, jaundice, respiratory distress syndrome, PRBC transfusion, mortality, respiratory support, surfactant-ionotropic requirement) within groups Chi-Square test or Fisher Exact test was applied. To compare mean values of PCV independent 2 sample t test were used.

Results
In the present study, out of 59 recruited babies 31 neonates were non milking group and 29 neonates were milking group.
Out of 59 neonates 17(28.8%) neonates were between gestational age of 28+1 to 29+6 and 42(71.2%) neonates between 30+1 to 31+6 gestational age.
Regarding sex there was a male preponderance in this study. Out of 59 neonates, 34(57.6%) were males and 25(42.4%) babies were females.
In this study, majority of neonates was having weight >1.25kg. 32(54%) babies were having weight >1.25kg with 16 babies each in both groups.21(35%) babies were having birth weight between 1kg-1.25kg and 6(10.1%) babies were having weight <1kg.
Among 59 babies 55 babies were undergone neurosonogran for the evaluation of IVH, rest 4 babies expired before the evaluation. Out of 55 neonates, 9 (16.4%) had IVH and the remaining 46 (83.7%) babies were not showed the evidence of IVH. Further, among 9 neonates having IVH 8(89%) were in non-milking group and 1 (11%) was in milking group and it was found to be statistically significant [p=0.027*] (Table 1).

Table 1: Prevalence of IVH among the groups in the study

Groups	No of subjects	Presence of IVH	Absence of IVH	P-Value
Non-Milking	29	8 (27.6%)	21(72.4%)	0.027*; Significant
Milking (UCM)	26	1 (3.8%)	25 (96.2%)	

Among the 8 (27.6%) babies having IVH in non-milking group 4 (13.8%) babies were having grade 1 IVH, 2 (6.9%) babies grade 2 IVH and 2 (6.9%) babies grade 3 IVH. Meanwhile, 1 baby with IVH in milking group had grade I (3.8%).
The mean Hematocrit (PCV) values in milking and non-milking group was found to be 38.9 and 37.34 respectively and it was found to be non-significant (p=0.43). However, the PCV was higher in milking group.
In the present study the neonatal mortality was higher in non-milking group 7 out of 31 cases (22%) as compared to milking group only 2 out of 28 cases (7.1%) and found to be non-significant (p=0.13).
Respiratory Distress Syndrome (RDS) was observed in 30 (96.7%) out of 31 babies in non-milking group and in all babies (28-100%) of milking group and the value was found to be non-significant (p=1).
Surfactant administration for RDS was done in 28(90.3%) out of 31 babies in non-milking group and in all babies (28-100%) of milking group and the value was found to be non-significant (p=0.239).
In this study out of 59 neonates they required different mode of ventilation. 14 and 13 babies in non-milking and milking group required conventional invasive ventilation. 1 baby in each group required High Frequency Ventilation (HFO). Further, 13 and 9 babies in non-milking and milking group requires CPAP support. Furthermore, 8 babies required other modes of non-invasive ventilation ie 2 babies were on nasal HFO, 5 babies were on non-invasive positive pressure ventilation, and 1 neonate was on High flow Nasal Cannula(HFNC).The results were displayed table 2.

Table 2: Ventilation support requirement among the groups

Ventilation support	Non-Milking	Milking (UCM)
Conventional invasive ventilation	14	13
High Frequency Ventilation	1	1
CPAP support	13	9

Regarding packed RBC (PRBC) transfusion, out of 59 neonates, 22 (37.3%) requires PRBC transfusion. However most number of cases in non-milking group (12-54.5%)

requires PRBC transfusion as compared to the milking group(10-45.5%), but the value was not found to be significant (p >0.05).

In this study out of 59 neonates, 54 (91.6%) affected with neonatal jaundice and requires phototherapy. However, higher number of neonates was affected with jaundice in non-milking (28-51.8%) and requires phototherapy as compared to milking group only 25 cases (48.2%) required phototherapy, but the value was not found to be significant (p >0.05).

In this study out of 59 neonates, 6 neonates required ionotropic support, 3 in each group.

Discussion

IVH is the prime factor related to neonatal and neurological complication like disability in preterm infants [14]. Studies indicate that sufficient blood volume is cardinal for normal fetal to neonatal circulatory transition [15]. Earlier reports elicited that, occurrence of IVH is associated with cerebral hypoxia and perfusion leading to hemodynamic instability instantly after delivery [16]. In the case of umbilical cord clamping before a sufficient placental transfusion has been done a considerable blood volume might be accumulated leading to hypoperfusion. Previous studies highlights that preterm infants with IVH, displayed a period of low superior vena cava flow which preludes to reduced upper body perfusion including cerebral blood flow within the first 48 h of life [17]. Mounting clinical reports and meta-analysis displays beneficial effects of UCM in decreasing the risk of IVH as compared to non-milking method and minifies the risk of adverse neurocognitive outcome [18, 19, 20, 14]. Studies indicate that preterm infants subjected to UCM displayed effective systemic blood flow as that of DCC [21]. So the present study was evaluated the effect of UCM in reducing the prevalence of IVH as that standard care in very preterm neonates.

In this study higher number of cases was in the gestational age between 30+1 to 31+6 weeks and weight more than 1.25 kg and the reports were consistent with the previous study done Song *et al*. [11]. In the study male preponderance was seen among the neonates which are in line with the earlier reports [22].

Further, the prevalence of IVH was significantly higher in non-milking group (89%) as that of the milking group (11%). Similar results were seen in the study conducted by Toledo *et al*. where only 12 % were affected with IVH in UCM and 33% were observed with IVH in immediate cord clamping underwent neonates [23]. In the present study the PCV is in higher range in milking group as that of the non-milking group (38.9 vs 37.34%). In a study done by Upadhyay *et al*. the PCV is significantly higher in UCM as that of the ECC [41.2 vs 37.2] [22]. Further, the mortality is higher in milking group as that of the non-milking group (22 vs 7.1%). Previous clinical study and Meta-analysis showed a significantly lower mortality with UCM compared with ECC [11, 20]. In this study, the clinical outcome like RDS, surfactant administration, various ventilation supports like invasive ventilation, HFO and CPAP and ionotropic support was not influenced by UCM, which is in agreement with earlier reports [11, 23].

Further, in UCM group only fewer neonates requires (48.2%) PRBC transfusion, as compared to the non-milking group (51.8%). In a study done by Toledo *et al*. only 30% of UCM neonates needs blood transfusion, but in ECC neonates 56% needed the same and it was found to be statistically significant [23]. However, in our study no significant association was observed regarding the need of blood transfusion between the two groups.

Meanwhile, in this study there was no statically significant association in the need of phototherapy for the treatment of neonatal jaundice between the milking and non-milking neonates (48.2 vs 51.8 %), which is in accordance with the previous reports [22].

Thus in conclusion, Umbilical cord milking is a reliable method and decrease the incidence of IVH in very preterm neonates. Further, the UCM increased hematocrit levels, decreased the mortality rate, need for ventilation support, RDS, surfactant administration and ionotropic support. Further UCM subjected neonates need less PRBC transfusion and phototherapy. However, future studies with large cohort are highly warranted to evaluate the safety and efficacy of UCM in very preterm neonates.

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