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COMPARISON OF EFFECT OF EARLY CORD CLAMPING WITH UMBILICAL CORD MILKING ON THYMIC SIZE AMONG PRE-TERM INFANTS

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Abstract:

Objectives: *The research objective is the comparison of early cord clamping and umbilical cord milking effect on the thymic size, and neonatal morbidity/mortality among preterm infants.*

Methods: *The study method is a controlled randomised, prospective and double-blind that we conducted in Mayo Hospital, Lahore (September 2018 to March 2019). We divided women, who delivered in less than 32 weeks, into two groups, Group-A (umbilical cord milking) and Group-B (early cord clamping). Our experienced radiologist performed Ultrasonographic evaluation in each new-born within the first day of life. We estimated thymic size in-line with literature. We analyzed all data using SPSS.*

Results: *There were 38 and 37 patients in Group-A and Group-B respectively with insignificant (P=0.213) higher Haemoglobin level in Group-A. In Group-A, the absolute neutrophil count was lower than Group-B with P= 0.017 however the difference between neonatal mortality/morbidity was insignificant (P> 0.05).*

Conclusion: *We did not find any association of UCM with TS within the first 24-hours of newborn's life.*

Keywords: *Thymic Size (TS), Umbilical Cord Milking (UCM), Umbilical Cord (UC), Acute Thymic Involution (ATI), Early Cord Clamping (ECC), Premature Infant (PI), Full-Term Infants (FTI), Pre-Term Infant (PTI), and Placental Transfusion (PT).*

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INTRODUCTION:

In maturing thymus lymphocytes or T-lymphocytes, thymus plays a vital role. Moreover, TS extends its association with functions of the immune system and thymic. According to Aaby et al., infant mortality and TS has an association [1]. With the TS size increased, the mortality rate decreases. During the neonatal period, TS is the largest but later it decreases [2]. We can measure thymus volume through a reliable measurement of calculating thymic index (TI) [3]. Many factors like prenatal toxin exposure, feeding behaviour, infections, weight at birth, and environment can affect TS. Genetic factors, perinatal and gestational environment determines the TS at birth [4 – 7]. Stress hormones cortisol can increase cell death of T-Lymphocytes leading to Acute Thymic Involution in the thymic cortex [7]. ATI can affect the function of cellular immune for long-term during malnutrition and infection [8]. Among new-borns, especially pre-matures, the immune system is under-development with the functional capacity of the cells decreased. Factors involved in immune-deficiency among infants are inadequate production of cytokines, insufficient quantity of fibronectin, phagocytosis, adhesion molecules, and phagocytosis, intracellular killing function, monocyte chemotaxis and leukocyte in neonates, inadequate antigen recognition, antibodies' low synthesis, and Inadequate polymorph-nuclear [9]. Recent studies favour UCM to be beneficial among FTIs PTIs. A study shows a better haemoglobin level without jaundice and polycythaemia among full and late PTIs of Placental Transfusion group [10]. According to an analysis report, there was less necrotising enter-colitis, intraventricular haemorrhage (all stages), and blood transfusion among UCM-group than ECC-group [11]. Umbilical cord blood includes a huge number of haematopoietic stem-cells instead of immature T-cells and nucleated blood cells. Infants born at (23 to 31) weeks gestations have haematopoietic progenitor cells of three-fold among FTIs [12]. Migrating haematopoietic stem-cells to different organs, bone marrow niches, and across endothelial vasculature through blood is called Homing process, which requires active navigation. The purpose of our study was to test whether UCM improves the function of the immune system through homing and might affect TS positively, decreasing neonatal morbidity in comparison of ECC.

SUBJECTS AND METHODS:

The study method is a controlled randomised, prospective and double-blind that we conducted in Mayo Hospital, Lahore (September 2018 to March 2019). We took approval from the institutional review board with written informed consent from parents of our subject infants. We included PTIs of ≤32 weeks gestational age and excluded infants with foetal/maternal bleeding, conotruncal heart disease, dysmorphic features and twin-to-twin transfusion syndrome. We divided the admitted pregnant women into two random groups. We used armbands, serially numbered, to differentiate between UCM and ECC group patients and identify that these women are the study participants. To keep UCM technique standardised, we briefed each physician and ensured double-blinding so that neither the radiologist nor the women know about the group they belong to. We used a UC of an extended hand's size (20±2 cm) as standard. We put UCM-Group infants at placenta level if delivered through Caesarean Section and at or below the placenta level if born vaginally. Before clamping the cord, we milked umbilical cord (20±2 cm) gently toward umbilicus three times [13]. We did not give any oxytocin before obstetrician clamped UC. However, we clamped UC within 10 seconds of delivery and cut it immediately in the ECC-Group. We used no double-blinding for paediatric support staff and neonatologists as they were present at delivery time. We used OpenEpi v.3.0 calculator to calculate sample size. We assumed level (0.05) of two-sided α level, therefore we needed forty-two infants in each group to get 80% power [14]. Our aim was enrolling forty-five women to compensate for any ineligibility due to congenital anomalies or bleeding. We collected maternal data like age, IUGR (Intrauterine Growth Restriction), preeclampsia, antenatal steroid administration, PPROM (Preterm Premature Rupture of Membranes), and delivery mode. We also collected data of infants' birth, with gender, gestational age, RDS (), hsPDA (Haemodynamic Significant Patent Ductus Arteriosis), IVH (Intra-ventricular Haemorrhage), peak serum bilirubin, hospital stay duration, and frequency of sepsis from medical record of the hospital. We performed ultrasound examinations by the same radiologist (blinded), on the same equipment, and within 24-hours of life. All infants were on nCPAP (Nasal Continues Positive Airway Pressure) while we performed measurements. TS was in-line to literature 3 description. We measured TTD (Thymic Transverse Diameter) twice while infants were in the supine position to avoid intra-observer variability. We measured maximum TSA (Thymus Sagittal Area) of the largest lobe, vertical to thymus diameter. To get TI, we multiplied the mean of two diameter and two area measurements. We estimated TIWR (Thymus Index Weight Ratio) by dividing TI by infant's weight in kilograms. We used a transportable ultrasound and a linear transducer (7.5 MHz), both Hitachi, Tokyo, Japan made, for examination. We represented descriptive variables as Mean ± SD (Standard Deviation) or median. We used 2-independent Student's t-test and Mann-Whitney U-test for normally and non-normally distributed values respectively while comparing clinical and demographic continuous

variables. To compare categorical variables, we used Fisher's exact test. The statistical significance level was (P=0.05) for all tests. We analyzed data using SPSS.

RESULTS:

Among 90 enrolled women, the number of women in UCM-Group and ECC-Group was 49% (44) and 51% (46) respectively. In UCM-Group and ECC-Group, 86.36% (38) and 80.43% (37) subjects respectively completed the study. The number of new-borns in UCM-Group and ECC-Group was 51% (38) and 49% (37) respectively out of 75.

We did not find any significant differences in birth weight, gestational age, IUGR, PPROM, or antenatal steroid administration. Similarly, there was no difference in TSA, TTD, TI/WR, and TI. The level of mean ANC (Absolute Neutrophil Count) was significantly low (P=0.017) among UCM-Group however the whole blood-cells levels were almost similar in both groups with (P> 0.05) each. UCM-Group has slightly higher mean haemoglobin and serum bilirubin level than ECC-Group with (P= 0.23) and (P= 0.18) respectively. The differences in IUGR, sepsis, RDS, IVH, and hsPDA were not significant (P> 0.05) between groups. The mortality and born-rate (at the gestation of <30 weeks) were significantly higher in UCM-Group than in ECC-Group with (P= 0.027) and (P= 0.02) respectively. Antenatal steroid administration, gender, IUGR, PPROM, and Pre-eclampsia had an insignificant effect on TSA, TI, TI/TW, or TTD with (P > 0.05). Gravidity increased with no correlation with TI, TTD, or TSA. The increase in TI was insignificant (P= 0.66). We found a significant difference (P= 0.001) between TIWR and Gestational age (<30 weeks). We find no relation among hsPDA, IVH, TIWR, TI, TTD, TSA, sepsis, weight at discharge, and hospital stay duration (P> 0.05). In a group where RDS existed, we found significantly higher TI/WR (P= 0.03). Infants having IVH, sepsis, and hsPDA had higher mortality rates.

Table – I: Infants' Features

Variables	ECC		UCM		P-Value
	Number	Percentage	Number	Percentage	
Males	19	45.20	23	54.80	0.424
Mode of delivery, C/S	29	43.90	37	56.10	0.023
GW <30	15	50.00	15	50.00	0.925
Antenatal steroid administration	25	48.10	27	51.90	0.815
PPROM	2	28.60	5	71.40	0.281
Preeclampsia	3	50.00	3	50.00	0.916
IUGR	1	25.00	3	75.00	0.331

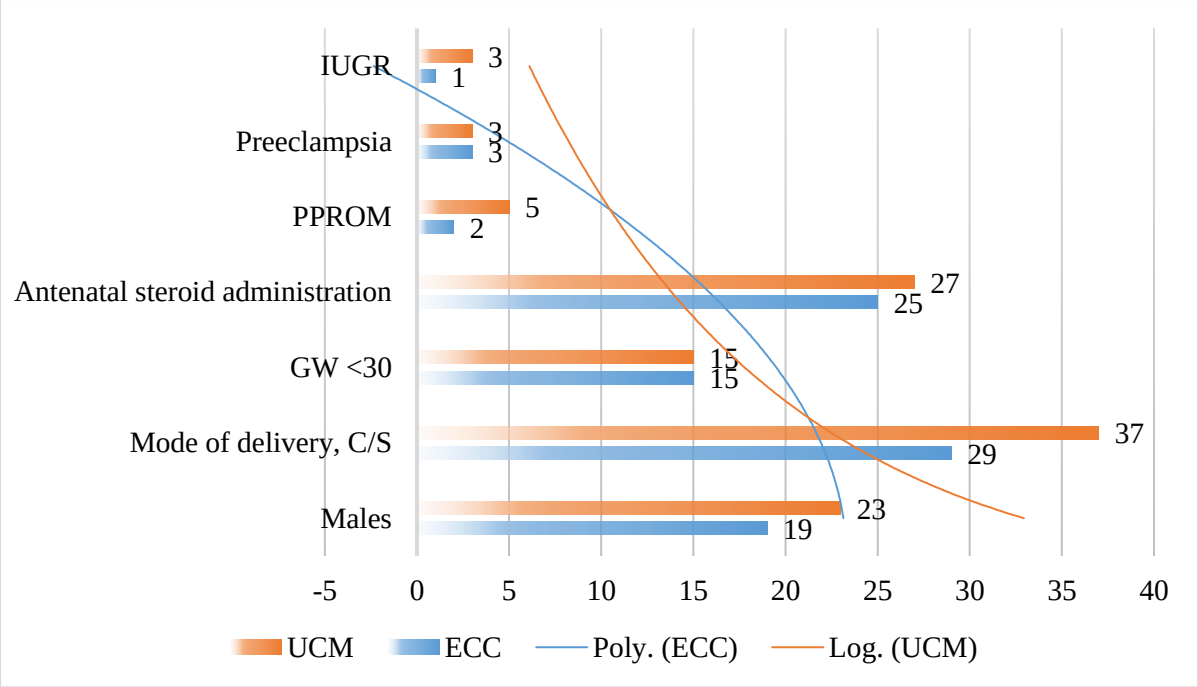


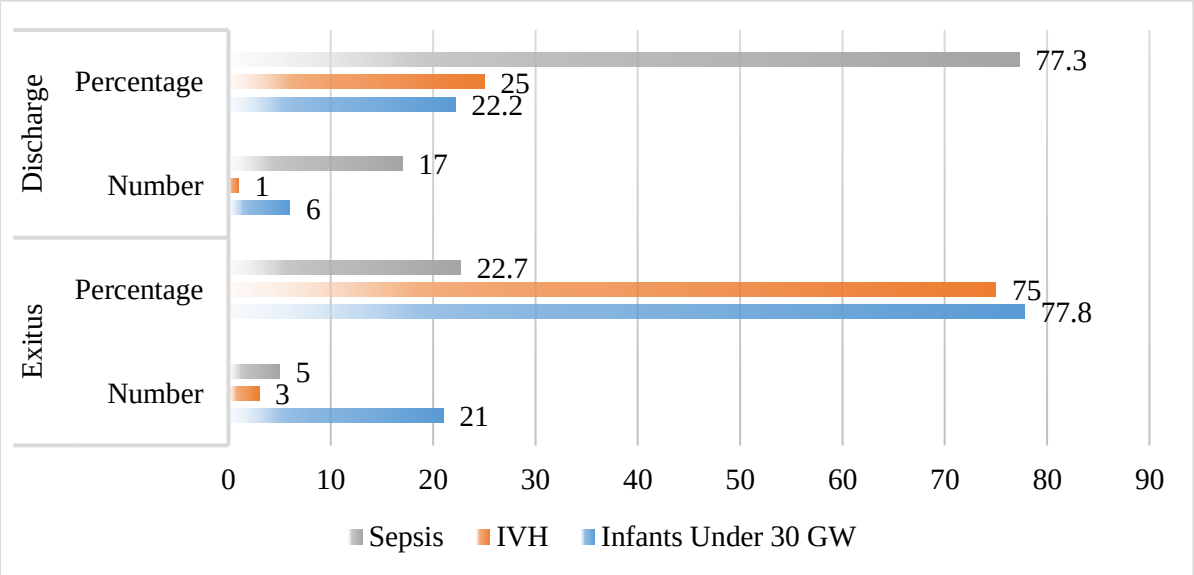
Table – II: Various Parameters

Variables	ECC		UCM		P-Value
	Mean/Median	±SD/Range	Mean/Median	±SD/Range	
TTD cm	1.62	0.287	1.54	0.202	0.201 (a)
TSA cm2	1.67	0.436	1.52	0.337	0.099 (a)
TI cm3	2.8	1.127	2.4	0.784	0.077 (a)
TIWR cm3/Kg	2.04	0.89	1.82	0.744	0.241 (a)
Leucocyte	10100	1200-47300	9200	4640-63700	0.820 (b)
ALC	5480	1880-30200	6660	2880-51900	0.213 (b)
ANC	2370	305-29800	1440	18-8200	0.017 (b)
Hemoglobin, gr/dl	16.94	2.2	17.55	2.23	0.234 (a)
Hematocrit	49.56	6.11	49.63	8.31	0.965 (a)
Platelet counts	210713	68592	225210	69982	0.368 (a)
Peak serum bilirubin, mg/dl	11.6	3.48	12.68	3.29	0.180 (a)
Birth weight, gr	1454	394	1408	387	0.607 (a)
Weight at discharge, gr	1860	820-2640	1885	620-2990	0.343 (b)
Duration of hospital stay, day	28	4,96	29.5	3,81	0.837 (b)
RDS	23	52.3	21	47.7	0.544 (c)
HSPDA	5	33.3	10	66.7	0.166 (c)
IVH	2	50	2	50	0.956 (c)
Sepsis	7	46.7	8	53.3	0.863 (c)
Discharge	35	54	29	46	0.027 (c)

Table – III: Discharge-group and Exitus Features

Features	Exitus		Discharge		P-Value
	Grams/No	Grams/%	Grams/No	Grams/%	
Birth Weight (gram)	1120	407	1480	376	0.014 (a)

Infants Under 30 GW	21	77.8	6	22.2	0.022 (b)
IVH	3	75	1	25	<0.001 (b)
Sepsis	5	22.7	17	77.3	0.041 (b)



DISCUSSION:

FTIs and PTIs with no requirement of resuscitation when born can have DCC (Delayed Cord Clamping) for 30+ seconds as recommended by the International Liaison Committee [15]. UCM is equally safe and effective as DCC [16, 17]. According to some studies, thymic function and TI has an association [18, 19]. TS have an association with infant mortality. Our study aims at evaluating interactions between TS and UCM and whether UCM effects perinatal mortality/morbidity. The results found no effects on parameters of thymus including TTD, TSA, TIWR, and TI among PTIs of gestation (<32 weeks) within 24-hours of life. We found ANC in UCM-Group significantly lower than ECC-Group like an earlier study [20]. According to some studies, the rate of neutrophil recovery is faster among bone-marrow transplantation than in cord-blood transplantation groups [21, 22]. In a study, Kiliçdag et al. found haemoglobin level significantly higher with lower haematocrit level on the first day but the differences on day 3rd and 7th were not significant among UCM and non-UCM-Group [20]. This may be due to the immediate resuscitation by neonatologists. Infants who are extremely immature raise concern for resuscitation as UCM may not be sufficient. The present study consists of 2 patients each in UCM-Group and ECC-Group having IVH. The same result of no significant relation between IVH and UCM was present in Takami et al.'s study [17]. The mortality rate has no relation with UCM as the number of new-borns was higher (n=6 with gestation <30 weeks) in UCM-Group. The present study finds mortality rates higher among infants who had sepsis, IVH, and hsPDA. Another study associate's infant's mortality with TS measured especially at eight-week age but there is no measurement of TS at birth [15]. In our study, we found TIWR higher among infants administered with RDS. Our study faced some limitations like insufficient standardization of UCM, maybe that is why the difference of haemoglobin level between groups was insignificant. Our findings suggest a procedural training for neonatologists and obstetricians. Our findings also suggest additional larger researches with increased sample size to clarify the effects of TS on mortality/morbidity among PTIs. The technique of UCM is standardised and Takemi et al. suggest (20 cm/s) of milking velocity [17]. Another study suggests milking velocity to be (20 cm/2s) [13]. Studies mentioned previously performed milking 2 to 3 times [13, 17]. UCM once after the cut of the cord is equally effective as milking multiple times among infants born at gestation (<29 weeks) [24].

CONCLUSION:

We did not find any association of UCM with TS within the first 24-hours among PTIs. The frequency of UCM is still unknown. Further studies are required to investigate the effective technique of milking.

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