Original Article

Effects of Timing of Umbilical Cord Clamping on Serum Calcium Levels in Neonates- A Randomised Controlled Trial

Umair Anees Qureshi[1], Arshad Khushdil[2], Sajid Ali Shah[3], Madiha Ahmed[4], Nayla Salman[5], Shermeen Kousar[6]

Abstract

Objective: To assess the impact of the timing of umbilical cord clamping on serum calcium levels in neonates.

Methods: This prospective, randomised controlled trial was conducted at Pak Emirates Military Hospital, Rawalpindi, from January 2024 to December 2024.

The study included full-term pregnant women with no comorbidities. After delivery, the neonates' umbilical cords were clamped according to their respective group timing. At six hours of life, venous blood samples were drawn from the neonates to assess serum calcium levels and other lab parameters.

Results: One hundred sixty babies (n=160) included 73 (45.63%) females and 87 (54.37%) males. The mean gestational age was 38.10 ± 0.99 weeks. A gradual increase in serum total and ionised calcium levels was observed. The serum total and ionised calcium levels were 2.12 ±0.12 mmol/L and 1.10 ±0.09 mmol/L, respectively, at 15 seconds (Group-1) of cord clamping and were 2.30 ±0.16 mmol/L and 1.22 ±0.06 mmol/L at 120 seconds (Group-4). Total serum calcium levels at 15 and 30 seconds (s) were significantly lower (p<0.001) than those at 120 s. A similar trend was seen for serum ionised calcium levels (p<0.001).

Conclusion: Delayed umbilical cord clamping enhances the total and ionised serum calcium levels in neonates, contributing to improved overall neonatal health outcomes.

Keywords: Umbilical Cord, Neonates, Pregnancy, Calcium.

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UAQ - Conception, Design
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Introduction

Umbilical cord clamping time holds paramount importance in neonatal care, significantly influencing various health outcomes in newborns. Traditional practice has advocated for immediate cord clamping (ICC) within the initial 30 seconds of birth, primarily to facilitate prompt neonatal evaluation and intervention.[1] However, recent evidence underscores the significance of delayed cord clamping (DCC), which involves postponing the clamp for 1-3 minutes after delivery before severing the umbilical cord.[2] This waiting period enables the continued transfusion of placental blood, augmenting the baby's blood volume and enriching the iron stores, thereby conferring protection against anaemia.[3]

The optimal timing for cord clamping to maximise clinical benefits for both the mother and the neonate has been a subject of extensive debate.[4] Substantial evidence now indicates that immediate cord clamping is not beneficial and can sometimes even be harmful. DCC has been associated with a significant reduction in the number of blood transfusions required for neonatal anaemia. Furthermore, the effects of delayed cord clamping on various factors during the immediate post-natal period, such as hematocrit, packed cell volume, serum ferritin, blood glucose, serum bilirubin, oxygen saturation, and temperature, have been extensively studied. Delayed cord clamping has been hypothesised to be of instrumental value in reducing intraventricular haemorrhages and necrotising enterocolitis.[5,6] Additionally, post-natal cerebral oxygenation has also been examined in relation to the timing of umbilical cord clamping. Another crucial aspect of neonatal health affected by the timing of cord clamping is serum calcium levels. Calcium plays a multifaceted physiological role, including bone growth, blood clotting, and neuromuscular excitability, among others. Low serum calcium levels, known as hypocalcemia, can lead to severe complications in newborns, including seizures, tetany, and cardiac dysfunction.[7] While the timing of cord clamping has been extensively studied regarding multiple haematological factors, its impact on serum calcium levels remains poorly investigated. The most rigorously studied factors affected by DCC are neonatal haemoglobin and iron stores.[8]

Therefore, this study aimed to assess how serum calcium levels are influenced by the timing of clamping the umbilical cord, thereby optimising these impacts for more promising neonatal outcomes. The objective of this study was to explore how variations in timings of cord clamping affect neonatal serum calcium levels, with a comparison between immediate cord clamping at 15s and 30s, with delayed cord clamping at 60s and 120s.

Materials And Methods

This randomised controlled trial, conducted at the Neonatology Department of a tertiary care hospital in Pakistan, evaluated the impact of the umbilical cord clamping timing on serum calcium levels in neonates at six hours of life. This study was approved by the hospital's ethics committee, and informed consent was obtained from the parents of all eligible neonates, adhering to the ethical standards of the Helsinki Declaration. The study was registered with clinicaltrials.gov under the registration number NCT06573333. The sample size was calculated using the Openepi calculator for clinical trials with a confidence interval of 95%, power of 80, and an expected effect size of a 10% change in serum calcium among the groups.[9]

The study included 160 full-term pregnant women without any comorbidities who presented for delivery at the hospital. Mothers with conditions such as gestational diabetes, hypertension, or any other pregnancy-related complications were excluded to minimise potential confounding factors. Neonates born via spontaneous vertex delivery and lower-segment C-section, with satisfactory APGAR scores, were included in the study. Neonates with congenital anomalies or birth complications were excluded. A junior doctor in the department, who was not involved in the study, generated the randomisation sequence using a computer program. Sealed opaque envelopes containing the group allocation codes were prepared and opened at the time of randomisation to assign participants to their groups as follows:
Group 1: Cord clamping at 15 seconds
Group 2: Cord clamping at 30 seconds
Group 3: Cord clamping at 60 seconds
Group 4: Cord clamping at 120 seconds
After delivery, umbilical cords were clamped according to the predetermined group timing. Standard delivery protocols were adhered to for all groups, and no additional interventions were implemented. At six hours of life, venous blood samples were drawn from the neonates to assess serum calcium levels. Total serum calcium was measured using the 5-Nitro-5-Methyl-BAPTA method on Roche Cobas Pro C503, while ionised calcium was measured by the ISE method on Siemens Rapid Lab 348EX analyser. All samples were processed in the same laboratory to ensure consistency and minimise measurement variability. The primary outcome measure was the serum calcium level (total and ionised) of neonates at six hours of life. Secondary outcomes, including serum albumin levels, serum Phosphate, serum Magnesium, Alkaline Phosphate, and Haemoglobin, were also recorded.
Statistical analysis was conducted using the IBM SPSS Statistics version 27. Means and standard deviations were calculated for continuous variables, while categorical variables were summarised as frequencies and percentages. Post Hoc Dunnett Test (Analysis of variance – ANOVA) was used to compare the mean serum calcium levels across the four groups. Statistical significance was set at a p-value of less than 0.05.

Results

This present study was a randomised controlled trial investigating the impact of the timing of umbilical cord clamping on serum calcium levels in neonates. In this study, a total of 180 neonates were initially registered; however, 6 developed early-onset neonatal sepsis, 4 parents did not consent, 3 developed congenital pneumonia, and 7 were lost to follow-up. Consequently, 160 neonates were enrolled, with 40 newborns in each subgroup. The sex distribution was 73 (45.63%) female and 87 (54.37%) male. The mean gestational age was 38.10 (± 0.99) weeks, and the birth weight was 2949.62 (± 207.73) grams. At 06 hours post-partum, the total serum calcium levels were 2.22 (±0.17) mmol/L, and ionised serum calcium levels were 1.16 (±0.10) mmol/L. The mean haemoglobin levels were 18.33 (±2.51) g/dL, albumin 38.47 (±4.78) g/dL, and magnesium was 0.89 (±0.43) mmol/L.
A gradual increase in serum total and ionised calcium levels was observed due to delayed cord clamping. At 15 seconds (Group 1) of cord clamping, the serum total and ionised calcium levels were 2.12 (±0.12) mmol/L and 1.10 (±0.09) mmol/L, respectively. At 120 sec (Group-4), the serum total and ionised calcium levels were 2.30 (±0.16) mmol/L and 1.22 (±0.06) mmol/L, respectively. The data are presented in Table 1.

Table 1: Characteristics of the sample population and its subgroups (n=160)

Variable	Cord Clamping				
	Total Population (n=160)	**Group-1** (n=40)	**Group-2** (n=40)	**Group-3** (n=40)	**Group-4** (n=40)
Gender					
Male	87 (54.37%)	23 (57.50%)	20 (50.00%)	22 (55.00%)	22 (55.00%)
Female	73 (45.63%)	17 (42.50%)	20 (50.00%)	18 (45.00%)	18 (45.00%)
Gestational Age (weeks)	38.10 (± 0.99)	38.18 (± 1.13)	38.20 (± 1.09)	38.02 (± 0.92)	38.00 (± 0.81)
Birth weight (Grams)	2949.62 (± 207.73)	2861.75 (± 190.69)	2968.00 (± 222.51)	2980.00 (± 212.67)	2988.75 (± 184.49)
Haemoglobin (g/dL)	18.33 (±2.51)	16.93 (±2.19)	17.31 (±2.14)	19.38 (±1.96)	19.71 (±2.53)
Albumin (g/dL)	38.47 (±4.78)	38.30 (±5.38)	37.88 (±4.27)	38.30 (±4.64)	39.40 (±4.81)
ALP (IU/L)	147.69 (±16.40)	139.83 (±16.27)	146.48 (±16.51)	152.73 (±12.95)	151.73 (±16.86)
Serum Magnesium (mmol/L)	0.89 (±0.43)	0.73 (±0.39)	0.82 (±0.45)	0.98 (±0.39)	1.01 (±0.45)
Serum Phosphate (mmol/L)	1.85 (±0.34)	1.69 (±0.27)	1.76 (±0.28)	1.97 (±0.37)	1.98 (±0.36)
Total Serum Calcium (mmol/L)	2.22 (±0.17)	2.12 (±0.12)	2.13 (±0.11)	2.33 (±0.17)	2.30 (±0.16)
Ionised Serum Calcium (mmol/L)	1.16 (±0.10)	1.10 (±0.09)	1.10 (±0.08)	1.21 (±0.08)	1.22 (±0.06)

Analysis of data revealed that serum albumin levels (p=0.530) were not affected by delay in cord clamping. The haemoglobin, serum ALP, serum magnesium, and serum phosphate were significantly changed by delayed cord clamping with p=<0.001, p=0.001, p=0.010, and p=<0.001, respectively. The details are given in Table 2.

Table 2: Effect of delayed cord clamping on different parameters of newborns (n=160)

Variable	Cord Clamping Time				p-value
	Group-1 (n=40)	**Group-2** (n=40)	**Group-3** (n=40)	**Group-4** (n=40)	
Haemoglobin (g/dL)	16.93 (±2.19)	17.31 (±2.14)	19.38 (±1.96)	19.71 (±2.53)	<0.001
Albumin (g/dL)	38.30 (±5.38)	37.88 (±4.27)	38.30 (±4.64)	39.40 (±4.81)	0.530
ALP (IU/L)	139.83 (±16.27)	146.48 (±16.51)	152.73 (±12.95)	151.73 (±16.86)	0.001
Serum Magnesium (mmol/L)	0.73 (±0.39)	0.82 (±0.45)	0.98 (±0.39)	1.01 (±0.45)	0.010
Serum Phosphate (mmol/L)	1.69 (±0.27)	1.76 (±0.28)	1.97 (±0.37)	1.98 (±0.36)	<0.001

The total serum calcium levels at 15 and 30 seconds were significantly lower (p<0.001) than the total serum calcium levels at 120 seconds. A similar trend was seen for serum ionised calcium levels (p<0.001). However, total and ionised serum calcium levels at 60 seconds did not show a statistically significant difference from the total and ionised serum calcium levels at 120 seconds of cord clamping, as shown in Table 3.

Table 3: Effect of delayed cord clamping on Serum total and ionised serum calcium levels (n=160)

Dependent Variable	(I) Cord Clamping Time (seconds)	(J) Cord Clamping Time (seconds)	p-value	95% Confidence Interval	
				Lower Bound	Upper Bound
Total Serum Calcium Levels at 6 hours	15s	120s	<0.001	-0.2777	-0.0998
	30s	120s	<0.001	-0.2574	-0.0826
	60s	120s	0.968	-0.0733	0.1323
Ionised Serum Calcium Levels at 6 hours	15s	120s	<0.001	-0.1726	-0.0724
	30s	120s	<0.001	-0.1740	-0.0815
	60s	120s	0.985	-0.0570	0.0345

Discussion

During the neonatal period, infants undergo significant physiological changes and adaptations from intrauterine to extrauterine life. This transition necessitates substantial metabolic, cardiovascular, and renal adjustments necessary for survival and growth. Electrolytes play a pivotal role during this transitional phase, as they are essential for maintaining fluid balance, supporting neural and muscular functions, and facilitating biochemical processes. Imbalances in crucial electrolytes such as sodium, potassium, calcium, and magnesium can lead to severe complications, including seizures, cardiac arrhythmias, or developmental delays.

The primary objective of this study was to investigate the impact of foetal cord clamping on serum calcium levels. No significant differences were observed in the demographic and baseline parameters among the study groups. Notably, serum calcium levels exhibited a gradual increase from Group 1 to Group 2. At 15 seconds of cord clamping (Group-1), the serum total and ionised calcium levels were 2.12 ±0.12 mmol/L and 1.10 ±0.09 mmol/L, respectively. Conversely, at 120 seconds of cord clamping (Group-4), the serum total and ionised calcium levels were 2.30 ±0.16 mmol/L and 1.22 ±0.06 mmol/L, respectively (Table I).

The timing of umbilical cord clamping (UCC) exerts a profound influence on neonatal serum calcium levels. Our findings demonstrate that cord clamping at 15 and 30 seconds had significantly lower serum total and ionised calcium levels as compared to delayed cord clamping (DCC) at 60 and 120 seconds. However, levels at 60 seconds did not show a statistical difference from those at 120 seconds. These findings align with previous studies that have elucidated the advantages of DCC in enhancing neonatal outcomes.[10] Additionally, McDonald et al. (2013) reported that DCC leads to higher serum calcium levels, thereby augmenting neuromuscular function and bone development.[11] The potential mechanism underlying the elevation in serum calcium levels during DCC is attributed to the facilitation of placental transfusion. This process enhances neonatal blood volume, nutrient intake, and electrolyte storage.

Extant literature presents diverse perspectives on the relationship between the timing of cord clamping and serum calcium levels. Ishtiaq et al. conducted research in India and found no effect of DCC on calcium levels.[12] Similarly, Asra et al. corroborated these findings. In contrast, our study revealed an inverse correlation between serum calcium levels and the progressive lengthening of cord clamping time. These discrepancies can be attributed to variations in study designs and neonatal populations.

Our findings align with the World Health Organisation's (WHO) recommendation of delaying cord clamping by at least 60 seconds to enhance neonatal health. The progressive elevation in serum calcium levels observed in our study supports this practice, contributing to improved bone health and neuromuscular stability.[13] Furthermore, another research conducted by Yao et al. underscored the role of DCC in preventing neonatal hypocalcemia and reducing the risk of seizures and tetany.[14] Consequently, these findings indirectly support the conclusions of the present study and advocate the beneficial effects of DCC in neonates.

Andersson et al. elucidated that DCC at 120 seconds enhances haemoglobin levels and iron stores, which are essential for calcium-binding proteins in bone formation.[15] Concurrently, serum haemoglobin levels also increased in our research. This phenomenon might be attributed to increased placental blood transfusion due to DCC. Concerns regarding polycythemia and hyperbilirubinemia associated with DCC are prevalent. However, Rabe et al. and Qian et al. demonstrated that clamping delays of 60–120 seconds do not elevate these risks.[16,17] Raju et al. further corroborated these findings, advocating for DCC as a strategy to optimise neonatal outcomes.[18]

In this RCT, we also observed a statistically significant difference in serum haemoglobin levels, which progressively increased in the groups receiving delayed cord clamping. This finding is consistent with the recommendations of the American College of Obstetrics and Gynaecology (ACOG).[19] The haemoglobin levels, hematocrit, and iron reserves were found to improve with DCC. In another study, the haemoglobin levels were higher in the DCC group compared to the immediate cord-clamping group.[20] These effects extend beyond the neonatal period, as demonstrated by valuable outcomes observed in later life, as reported by Hutton et al. in their research.[21]

In addition to the aforementioned benefits, this research also revealed significant differences in serum magnesium, Alkaline phosphatase (ALP), and serum phosphate levels among the groups. These alterations can be attributed to enhanced placental blood transfusion, which facilitates the delivery of electrolytes and nutrients. In conclusion, DCC at 60 to 120 seconds demonstrates its efficacy in improving neonatal serum calcium levels, thereby supporting current guidelines.

The study had certain limitations. It was a single-centre study with a relatively small sample size. The cross-sectional nature of the study precludes the sole attribution of changes in laboratory parameters such as calcium levels to DCC. Therefore, we recommend conducting a large multicentre trial to establish the association. Furthermore, further research can explore the long-term consequences of DCC on bone development and neurological health.

Conclusions

Delayed cord clamping (DCC) significantly improves neonatal serum calcium total and ionised levels, which have a favourable impact on neonatal health and enhance neuromuscular stability. These findings align with WHO and ACOG recommendations, supporting DCC at 60–120 seconds for optimal neonatal outcomes. Further multicenter trials are necessary to confirm long-term benefits.

Author Information

1. Registrar Pediatrics, Pak-Emirates Military Hospital 2. Professor of Pediatrics, Pak-Emirates Military Hospital, Rawalpindi 3. Consultant Pediatrician, Pak-Emirates Military Hospital, Rawalpindi 4,5,6. Assistant Professor Obs & Gynae, Foundation University medical College
Corresponding author: Dr. Arshad Khushdil drarshad104589@yahoo.com

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