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Randomized controlled trial of prophylactic intravenous calcium therapy for post–exchange blood transfusion hypocalcaemia in the newborn: A preliminary report

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Abstract *Background:* Exchange Blood Transfusion (EBT) is a form of massive blood transfusion mostly used to treat severe hyperbilirubinaemia and anaemia in the newborn period. Hypocalcaemia is a known complication of EBT hence the practice of prophylactic administration of intravenous calcium.
Objective: To compare the prevalence of post-EBT hypocalcaemia among babies who received prophylactic intravenous calcium and babies who received a placebo.
Materials and Methods: A randomized placebo-controlled trial among hospitalized babies who required EBT for hyperbilirubinaemia in a Nigerian tertiary facility was done. Following strict methods of randomization, some babies received prophylactic calcium (calcium group) while the others received sterile water (placebo group) during EBT. Serum calcium was measured pre-EBT and at six and 24 hours post-EBT.
Results: All the 16 and 13 babies recruited into the calcium and placebo groups had double volume EBT. Babies in both arms of the study were comparable in terms of age, body weight and EGA. The mean serum calcium levels pre-EBT and at six hours and 24 hours post-EBT were 8.1 ± 1.6mg/dl, 8.2 ± 1.1mg/dl and 8.4 ± 1.1mg/dl respectively for the calcium group and 8.6 ± 2.6mg/dl, 9.0 ± 1.6mg/dl and 9.1 ± 1.7mg/dl for the placebo group.
The prevalence of hypocalcaemia at six hours post-EBT was 37.5% and 15.4% in the calcium and placebo groups respectively.
Conclusion: The study did not demonstrate a clear role of prophylactic intravenous calcium therapy during EBT in the prevention of hypocalcaemia. It may be safer to screen for hypocalcaemia and treat it appropriately.

Keywords: Calcium, Exchange Blood Transfusion, Hyperbilirubinaemia, Hypocalcaemia, Prophylaxis.

Introduction

Exchange blood transfusion (EBT) is a form of massive whole blood transfusion mostly used to rapidly remove toxins (such as bilirubin, sensitized red cells, bacterial toxins, and poisons) or replace red cells in dire emergencies. Traditionally, double-volume EBT (use of 160ml/kg whole blood) is used in the management of severe hyperbilirubinaemia while the single volume transfusion is used to treat severe neonatal anaemia, especially in the first week of life.[1] EBT-related morbidities include hypothermia, hypoglycaemia, metabolic acidosis, hypocalcaemia, hyperkalaemia, thrombocytopaenia, cardiac arrhythmias, apnea, septicaemia, omphalitis, necrotizing enterocolitis, and intestinal perforation. [2]

Hypocalcaemia occurs following extensive chelation of calcium by the anti-coagulants contained in the donor's blood. [3] This is more commonly associated with massive transfusions like EBT, unlike top-up transfusion which requires relatively smaller quantities of anti-coagulant preserved donor blood. Although local data on the prevalence of post-EBT hypocalcaemia are sparse, reports of hypocalcaemia complicating EBT have been made from different parts of the world. [4-6] In a US study, 38% of the babies who had EBT had hypocalcaemia and 45% of these hypocalcaemic babies required calcium therapy. [7] Similar reports have been made from Iran. [8]
Significant morbidities like jitteriness, lethargy, apnea or seizures may be associated with hypocalcaemia. Therefore, intravenous 10% Calcium gluconate is routinely administered during EBT to prevent hypocalcaemia at the rate of 1ml (100mg) for every 100ml of exchanged blood. [9] However, this practice appears controversial as it is no longer recommended in most parts of the technically-advanced parts of the world, on the premise that

only diagnosed hypocalcaemia should be treated. [1, 10]
From the perspective of the complex interaction between calcium and anti-coagulants in donor blood, infants undergoing EBT may develop extremely low serum total and ionized calcium. [11, 12] On the other hand, such infants may also have dangerous fluctuations in serum calcium levels with the risk of cardiac toxicity. [11, 13] Therefore, whilst calcium therapy is required for the former situation, it is contraindicated in the latter situation. Though uncommon, deaths occurring during EBT are not unknown and may be ascribed to hypercalcaemia and cardiac arrhythmias. Therefore, with the high rate of EBT in most newborn units in the developing world, Nigeria inclusive, [14, 15] as well as the continual use of prophylactic intravenous calcium therapy, it is imperative to search for statistical evidence in support of, or against the use of prophylactic calcium therapy during EBT for newborn infants. This is required to update existing local guidelines on EBT.
This study was designed to compare the prevalence of post-EBT hypocalcaemia among babies who received prophylactic intravenous calcium therapy and those who received a placebo.

Materials and Methods

This was a randomized placebo-controlled trial conducted at the Neonatal Ward of the Olabisi Onabanjo University Teaching Hospital, Sagamu between January 2018 and December 2019. There are 28 cot spaces in the ward and the average annual admission rate is 450.
The study population comprised hospitalized newborn babies aged from birth to 28 days who required double-volume EBT. These babies were divided into two as follows:

Babies in Group A received prophylactic intravenous calcium therapy while babies in Group B received sterile water as a placebo. When babies required multiple sessions of EBT, only the first session of EBT was captured in the study. Babies who required other forms of transfusion apart from exchange transfusion were excluded.

Randomization

Sequence generation: The sequence of randomization was done using computer-generated blocks.
Allocation concealment: Allocation was concealed in serially numbered sealed opaque envelopes. The allocation was only known when the envelope was unsealed at the point of EBT.
Blinding: The researchers were not blinded to the intervention used but the laboratory scientists assaying serum calcium were blinded to the intervention.
Babies in Group A (Calcium group) received slow intravenous calcium (1ml of 10% Calcium gluconate after transfusion with every 100ml of whole blood) while the babies in Group B (Placebo group) received slow intravenous sterile water (1ml after transfusion with every 100ml of whole blood). According to standard practice, the heart rates of the babies were recorded every 10 minutes throughout EBT. There was no crossing-over between the two arms of the study.

Data collection

The data recorded for each baby included the age at the point of EBT, sex, estimated gestational age (EGA), body weight, and serum bilirubin values. For babies in both arms of the study (Groups A and B), two millilitres (2ml) of venous blood were obtained immediately before EBT, six hours after EBT and 24 hours after EBT for the estimation of total serum calcium. These blood samples were preserved in Lithium heparin bottles and processed in the laboratory within an hour of collection. Babies who received calcium were monitored for unwanted effects like vomiting, bradycardia, phlebitis and skin necrosis at the site of injection, hypotension, and cardiac arrhythmias.
For this study, hypocalcaemia was defined as total serum calcium less than 7mg/dl and 8mg/dl in preterm and term babies respectively. Hypercalcaemia was defined as total serum calcium greater than 13mg/dl. [3]

Ethical Considerations

Written informed consent was obtained from any of the parents/guardians present at the moment of recruitment while ethical clearance was obtained from the Health Ethics Research Committee of the Olabisi Onabanjo University Teaching Hospital, Sagamu (Certificate number: OOUTH/HREC/120/2017).

Data Management

This was done with SPSS version 21.0 statistical software. The data for the babies in the two arms of the study were analysed using simple descriptive and inferential statistics. The One-way ANOVA test, Student's t-test, Pearson Chi-Squared test, and Yate corrected Chi-Squared test were applied as necessary. Statistical significance was established with p values less than 0.05.

Results

A total of 16 and 13 babies were recruited into the calcium group and the placebo group respectively. Table I shows that there were more males than females (68.8% vs 31.2%) in the calcium group whereas there were more females than males (69.2% vs 30.8%) in the placebo group with a statistical difference ($p = 0.039$).
Aside from sex, the characteristics of the babies in the two groups were statistically comparable as shown in Table 1. The mean age of the babies in the calcium group was 118.5 ± 51.6 hours compared to 121.5 ± 69.4 hours for the placebo group ($t = -0.132$, p 0.896). The mean EGA of the babies in the calcium and placebo groups were similarly comparable (36.8 ± 3.1 weeks vs 35.8 ± 4.3 weeks; $t = 0.688$, $p = 0.497$). Similarly, the mean bodyweight of the babies in the calcium group and

placebo groups were comparable (2.4 ± 1.0 kg vs 2.1 ± 0.9 kg; t = 0.647, p = 0.527). The proportions of babies in the two groups who were fed on breast milk at the time of the study were also comparable (62.5% vs 84.6%; p = 0.365) as shown in Table 1.

Severe hyperbilirubinaemia was the indication for the procedure in all the babies studied hence, double volume exchange blood transfusion was performed in all the subjects. The mean volumes of blood transfused in the calcium and placebo groups were also comparable (352.8 ± 131.8 mls Vs 349.2 ± 144.8mls; t = 0.07, p = 0.945). For the calcium group, the mean volume of 10% Calcium gluconate administered during the procedure was 3.6 ± 1.3mls compared to 3.5 ± 1.3mls of placebo in the comparative group (t = 0.299, p = 0.767).

Table 1: Clinical characteristics and distribution of babies according to serum calcium levels in the calcium and placebo groups

Parameters		Calcium Group N = 16 (%)		Placebo Group N = 13 (%)		Statistics
Sex	Female	5	31.2	9	69.2	$\chi^2 = 4.245$
	Male	11	68.8	4	30.8	P = 0.039
Age (Hours)	<72	2	12.5	2	15.4	$\chi^2 = 0.05$*
	≥72	14	87.5	11	84.6	P = 0.823
Weight	<2.5	8	50.0	9	69.2	$\chi^2 = 0.444$*
	≥2.5	8	50.0	4	30.8	P = 0.505
EGA (weeks)	Preterm	5	31.2	6	46.2	$\chi^2 = 0.677$
	Term	11	68.8	7	53.8	P = 0.411
Feeding	Breast milk	10	62.5	11	84.6	$\chi^2 = 0.817$*
	NPO	6	37.5	2	15.4	P = 0.365
6th-Hour Calcium	Normal	10	62.5	11	84.6	$\chi^2 = 0.823$*
	Low	6	32.5	2	15.4	P = 0.364
24th-Hour Calcium	Normal	14	87.5	11	84.6	$\chi^2 = 0.100$*
	Low	2	12.5	2	15.4	P = 0.750

*Yates correction appled

Serum calcium levels

The mean serum levels of calcium Pre-EBT and at six hours and 24 hours post EBT were 8.1 ± 1.6mg/dl, 8.2 ± 1.1mg/dl and 8.4 ± 1.1mg/dl respectively for the calcium group and 8.6 ± 2.6mg/dl, 9.0 ± 1.6mg/dl and 9.1 ± 1.7mg/dl respectively for the placebo group. The pre-EBT mean serum calcium levels was lower in the calcium group compared to the placebo group but without statistical significance (8.2 ± 1.6mg/dl vs 8.6 ± 2.6mg/dl; t = -0.570, p = 0.574).

Although the mean serum calcium level for the placebo group was higher than the mean serum calcium level for the calcium group at six hours post-EBT, the difference was not statistically significant (9.0 ± 1.6mg/dl vs 8.2 ± 1.1mg/dl; t =-1.564, p = 0.129). Similarly, the 24-Hour mean serum calcium level was higher in the placebo group compared to the calcium group without significance (9.1 ± 1.7mg/dl vs 8.4 ± 1.7mg/dl; t = -1.167, p = 0.253).

Comparison of the pre-EBT, six-hour and 24-Hour mean serum calcium levels in the calcium group showed no significant difference (F = 0.248, p = 0.780). Similarly, the comparison of the pre-EBT, six-hour and 24-Hour mean serum calcium levels in the placebo group showed no statistical difference (F = 0.189, p = 0.828).
As shown in Table 1, the proportion of babies in the calcium group with sixth-hour hypocalcaemia was higher than the proportion of babies in the placebo group with sixth-hour hypocalcaemia but without statistical significance (37.5% vs 15.4%; p = 0.364). On the contrary, the proportion of babies with 24th-Hour hypocalcaemia was lower in the calcium group compared to the placebo group but without statistical significance (12.5% vs 15.4%; p = 0.750).

Also, the proportion of babies with hypocalcaemia at the sixth-hour and 24th-Hour decreased from 37.5% to 12.5% in the calcium group but without significance (Yate corrected $\chi^2 = 1.500$; p = 0.220) whereas the proportion of babies with hypocalcaemia in the placebo group remained the same (15.4% vs 15.4%) at the sixth-hour and 24th-Hour.

Discussion

All the babies in the present study had double-volume exchange transfusion and the babies in the two arms of the study were comparable in terms of age, body weight and EGA. The babies in the two arms of the study also received comparable volumes of blood. Therefore, it can be assumed that there is no clinical ground for bias in the interpretation of the findings.

It is noteworthy that the three mean values of total serum calcium for babies in both arms of the study remained within the normal range, irrespective of calcium or placebo administration unlike what an earlier study reported. [16] This may be in keeping with an earlier suggestion that the changes in serum calcium levels during EBT are negligible. [12] Although the mean serum calcium levels consistently increased over 24 hours in both arms of the study, the sixth-hour and 24th-hour serum calcium levels were consistently higher in the placebo group compared to the calcium group but without statistical significance. This is contrary to the expectation that the babies who received calcium therapy should have higher levels of serum calcium compared to babies who received a placebo as earlier reported. [16] It is also discordant with an earlier report that when prophylactic calcium is routinely administered during EBT, serum calcium is only elevated mid-procedure and thereafter, declines to pre-EBT level at the end of the procedure. [17] This may further support the hypothesis of transient hypercalcaemia mid-procedure as well as spontaneous

normalization of serum calcium levels after the procedure. Unfortunately, the present study did not measure serum calcium mid-procedure and immediately post-EBT, hence comparison with the present study may be difficult.

However, it is unclear why the mean serum calcium consistently increased even in the placebo group. It is attractive to speculate that in the absence of supplemental calcium administration, the chelation of calcium by the transfused donor blood stimulated parathormone action in the placebo group, thus raising serum calcium levels. [3] Hormonal studies are strongly desired to unravel these unexplained observations.

In the same vein, the prevalence of hypocalcaemia at the sixth-hour post-EBT was higher in the calcium group compared to the placebo group (32.5% vs 15.4%). It is difficult to explain the observed pattern of hypocalcaemia among calcium-treated babies except by the plausible stimulation of calcitonin secretion by exogenous calcium thus precipitating lower serum calcium levels at the sixth-hour post-EBT. On the other hand, the calcium group had a lower proportion of babies with hypocalcaemia at the 24th-hour compared to the placebo group (12.5% vs 15.4%). This observation may suggest that the effect of prophylactically administered calcium was possibly delayed till the 24th-hour post-EBT or the effect was augmented by the usual spontaneous normalization of serum calcium level at the 24th-hour post-EBT. [11] Interestingly, the proportion of babies with hypocalcaemia in the placebo group remained the same at both the 6th-hour and the 24th -hour. With the plausible spontaneous correction of serum calcium levels at about 24 hours post EBT, [11] a lower proportion of babies in the placebo would have been expected to have hypocalcaemia at 24 hours. It is unclear why there was no commensurate decline in the proportion of babies with hypocalcaemia at 24 hours in the placebo group. However, the small size of the population studied may make explanation of the observation difficult.

In addition, hypercalcaemia was not recorded in both arms of the study. This is most relevant in the calcium group where calcium administration was previously suspected to be associated with transient hypercalcaemia. [13] Perhaps, hypercalcaemia could have occurred following calcium administration during EBT, but this was missed as serum calcium was not measured in the midst of EBT in the present study and neither was electrocardiographic monitoring done during the procedure. Therefore, it is plausible that transient occurrences of hypercalcaemia could have been missed but the absence of hypercalcaemia at the earliest post-EBT measurement of serum calcium at the sixth-hour post-EBT probably suggests that, even if hypercalcaemia occurred earlier in the calcium group, it was transient.

Although the mean serum calcium in each arm of the study progressively increased through the sixth-hour assay to the 24th-hour assay, the trend lacked statistical significance, probably because of the small size of the population studied. Nevertheless, the observed trend is difficult to explain in the context of the present study.
The present study is a preliminary report on an on-going study, hence the small size of the population. Therefore, the small population used in the present study is acknowledged as a limitation. Nevertheless, the present study will be replicated on a larger scale with modifications such as the measurement of ionized serum calcium alongside total serum calcium as well as the use of subgroup analysis to address the possible role of modifiers such as feeding, type of anti-coagulant in donor blood, and serum levels of calcitonin and parathormone. It is also attractive to measure serum calcium mid-procedure during EBT and immediately post-EBT.

Conclusion

In conclusion, this study has not demonstrated a clear role of prophylactic calcium therapy during EBT in the prevention of EBT-related hypocalcaemia as some babies who received calcium therapy during EBT developed hypocalcaemia after the procedure. The reduction in the proportion of babies with hypocalcaemia between sixth-hour and the 24th-hour post-EBT may be in keeping with the suggested spontaneous normalization of serum calcium after EBT. Perhaps, the occurrence of clinical signs of hypocalcaemia may be an additional screening tool at the sixth-hour and 24th-hour before instituting treatment for hypocalcaemia. It may be safer to detect hypocalcaemia and treat it appropriately rather than treat prophylactically.

Authors' Contributions
OTA and AVA conceived and designed the study. OOO and OOB participated in the design of the study. OTA and AVA analysed and interpreted the data. All the authors participated in literature reviews, drafting the manuscript and approval of the final version of the manuscript.
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Erratum: Authors' names correction

This corrects the article "Management of acute kidney injury with encephalopathy in a 5-year-old male using improvised peritoneal dialysis in University of Uyo Teaching Hospital, Uyo, Nigeria". A Case Report " in Niger J Paediatr 2019; 46(2): 68-72

Ikpeme E was listed as the author.

The correct Authors list should be: Ikpeme EE, Dixon-Umo OT, Kan KM, Hogan EJ

And the article should be cited as. Ikpeme EE, Dixon-Umo OT, Kan KM, Hogan EJ. "Management of acute kidney injury with encephalopathy in a 5-year-old male using improvised peritoneal dialysis in University of Uyo Teaching Hospital, Uyo, Nigeria". A Case Report " In Niger J Paediatr 2019; 46(2): 68-72