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Original Article

Prophylactic efficacy of 400 *vs.* 200 mg/kg /day calcium gluconate to prevent neonatal hypocalcemia

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Abstract

Background Serum calcium is at its lowest level within 24-48 hours after birth, rendering the neonate vulnerable to hypocalcemia. In our center, despite prophylactic administration of 200 mg/kg/day calcium gluconate, the prevalence of neonatal hypocalcemia remains high.

Objective To determine the prophylactic efficacy of 400 *vs.* 200 mg/kg/day calcium gluconate in preventing neonatal hypocalcemia.

Methods A randomized clinical trial with a pre- and post-test experimental design was done on neonates who fasted or received only minimal enteral feeding. Subjects were randomized to receive either 400 mg/kg/day (intervention group) or 200 mg/kg/day (control group) of intravenous calcium gluconate. We compared serum ionized calcium levels on the first day of admission before calcium gluconate administration and on the third day of hospitalization between the intervention and control groups.

Results The median ionized calcium levels in the intervention *vs.* control group before calcium gluconate administration was 1.16 (range 0.4-2.4) mmol/L *vs.* 1.15 (range 0.6-4.5) mmol/L, respectively (P=0.561). After three days of calcium gluconate administration, the median ionized calcium level was 1.19 (range 0.7-1.45) mmol/L *vs.* 1.19 (range 0.68-4.6) mmol/L in the intervention vs. control group, respectively (P=0.828). The difference in pre- *vs.* post-administration ionized calcium levels was significant within the intervention group (P=0.032), but not within the control group (P=0.128).

Conclusion Prophylactic intravenous calcium gluconate at 400 mg/kg/day was not more effective in preventing neonatal hypocalcemia than 200 mg/kg/day. **[Paediatr Indones. 2023;63:346-52; DOI: https://doi.org/10.14238/pi63.4.2023.346-52**].

Keywords: *neonates; calcium gluconate; neonates*

Calcium is the most abundant mineral in the human body, accounting for 2% of total body weight. It plays important roles in nerve transmission, muscle contraction, blood coagulation, cell membrane permeability, and bone formation. Moreover, calcium regulates the function of hormones and growth factors.[1] Calcium balance is regulated by the parathyroid hormone. Calcium levels are maintained at adequate levels by three primary organ systems: the gastrointestinal system, the bones, and the kidneys. Calcium absorption is regulated by the gastrointestinal system and is influenced by calcium intake, age, and vitamin D. Bones regulate calcium level in the plasma and extracellular fluid through calcium exchange. The kidneys excrete the excess calcium absorbed by the intestines.[2] The parathyroid glands regulate calcium homeostasis by secreting parathyroid hormone (PTH) and raising calcium levels in the bloodstream.[1]

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During the third trimester of pregnancy, calcium is actively transported from the mother to the fetus via the umbilical cord. Serum calcium levels in newborns are regulated by PTH secretion, calcium intake, renal calcium secretion, calcium content in bones, and vitamin D levels.[3] Calcium levels in healthy newborns are at the lowest range within 24 to 48 hours after birth. Hypocalcemia in neonates is usually asymptomatic. However, some symptoms, such as lethargy, nausea, stomach distension, muscle weakness, trouble drinking, and irritability, may occur in newborns with hypocalcemia.[4]

According to patient medical records from the Neonatology Division of Haji Adam Malik Hospital between January and December 2018, 45.3% of neonates admitted had hypocalcemia and 3% were hypercalcemic despite having received prophylactic 200 mg/kg/day calcium gluconate added to their intravenous fluids. A study in India reported that giving 4 mL/kg/day of 10% calcium gluconate intravenously or orally for 72 hours can prevent hypocalcemia in high-risk infants.5 This study aimed to compare the efficacy of 400 *vs.* 200 mg/kg/day calcium gluconate as prophylaxis for neonatal hypocalcemia.

Methods

This randomized clinical trial with pre- and post-test experimental design was performed to compare calcium levels in neonates receiving 400 *vs.* 200 mg/kg/day prophylactic calcium gluconate to prevent hypocalcemia. The study was conducted at the Neonatology Division, Haji Adam Maik Hospital, Medan, Indonesia from February to December 2020. Subjects were neonates with at least a 3-day hospital stay who were fasted or received minimal enteral feeding. Exclusion criteria were neonates with rickets or other diseases that disturb calcium homeostasis, neonates whose mothers suffered from hyperparathyroidism, and those whose parents or guardians refused to give consent.

Subjects were recruited consecutively, then randomly assigned to an intervention group receiving 400 mg/kg/day of intravenous calcium gluconate or a control group receiving 200 mg/kg/day of intravenous calcium gluconate. The investigators evaluating the outcome were kept blinded from the dose of calcium gluconate received by each subject, as were the subjects' parents. Randomization was done using a randomization table. The minimum required sample size was 70 subjects, consisting of 35 subjects in each group.

Peripheral blood specimens were drawn before calcium gluconate administration on the first day of admission and on the third day of hospitalization. The ionized calcium level was considered hypocalcemic if it was <1.11 mmol/L, normocalcemic if it was between 1.11 mmol/L and 1.31 mmol/L, and hypercalcemic if it was >1.31 mmol/L.

Data analysis was done using *SPSS version 26.0 software* (*IBM*, Armonk, New York). Descriptive data was expressed as frequency and percentage for categorical data and as mean and standard deviations (SD) or median and range for continuous data. The independent variable was calcium gluconate dose (400 or 200 mg/kg/day), and the dependent variable was serum ionized calcium level in mmol/L. Bivariate analysis to compare ionized calcium levels between the two groups was done using the Mann-Whitney test. Comparison of ionized calcium levels within each group before and after calcium gluconate administration was done using the Wilcoxon signed ranks test. We compared calcium status (hypocalcemic, normocalcemic, or hypercalcemic) between the two groups and before vs. after calcium gluconate administration within each group using the Kruskal Wallis and Chi-square tests. A P value of <0.05 was considered statistically significant.

We sought informed consent from the neonates' parents before enrolling them in the study. The study protocol was approved by the Research Ethics Committee of the Faculty of Medicine, Universitas Sumatera Utara/Haji Adam Malik Hospital, Medan.

Results

Over half of the subjects were male (38/70; 54.3%). Median age was one day in the intervention group and two days in the control group. The most common indication for admission was asphyxia. **Table 1** shows the characteristics of the subjects. Hypocalcemia was noted in 45.7% of subjects in the intervention group and 31.4% in the control group.

Table 2 shows the ionized calcium levels of

the two groups before and after calcium gluconate administration. Since the data were abnormally distributed, we used medians and non-parametric hypothesis testing methods. The median ionized calcium level in the intervention vs. control group before calcium gluconate administration was 1.16 (range 0.4-2.4) mmol/L *vs.* 1.15 (range 0.6-4.5) mmol/L , respectively (P=0.561; Mann-Whitney test). On the third day of hospitalization, median ionized calcium level was 1.19 (range 0.7-1.45) mmol/L *vs.* 1.19 (range 0.68-4.6) mmol/L in the intervention and control group, respectively (P=0.828; Mann-Whitney test). The difference in median ionized calcium levels before *vs.* after calcium gluconate administration was significant within the intervention group (P=0.032), but not within the control group (P=0.128), analyzed using the Wilcoxon signed ranks test.

Table 3 shows the calcium status in both groups on the first day of admission before calcium gluconate administration, compared to that on the third day of hospitalization. In the intervention group, hypocalcemia was noted in 16/35 subjects before and in 8/35 subjects after administration of calcium gluconate. After administration, the number of normocalcemic subjects in the intervention group increased from 15/35 to 21/35 and there was a modest increase in the number of hypercalcemic subjects, from 4/35 to 6/35. Meanwhile, the control group showed a reduction in the number of hypocalcemic neonates, from 11/35 to 8/35, on the third day of hospitalization. However, the number of normocalcemic neonates in the control group remained the same, with an increase in the proportion of hypercalcemia, from 4/35 to 7/35. The chi-square and Kruskal-Wallis tests revealed no significant differences in calcium status between the intervention and the control groups.

Table 3. Calcium status in the intervention vs. control groups, before vs. after prophylactic calcium gluconate administration

Table 1. Subjects' characteristics

Characteristics	Intervention group (n=35)	Control group (n=35)
Gender, n		
Male	20	18
Female	15	17
Median age, days	1	2
Birth weight, n		
Low	15	18
Normal	17	16
Macrosomia	3	1
Gestational age, n		
Premature	17	17
Full term	18	18
Feeding, n		
Minimal enteral feeding	31	33
Fasted	4	2
Blood culture, n		
Bacterial growth	2	10
No bacterial growth	33	25
Diagnosis, n		
Asphysia	16	15
CHD	2	4
Post-op	3	3
Seizure	5	6
Jaundice	5	3
Other	4	4
Calcium level status,		
Hypocalcemia	16	11
Normocalcemia	15	20
Hypercalcemia	4	4

Table 2. Ionized calcium levels before and after prophylactic calcium gluconate administration

Ionized calcium level	Intervention group (n=35)	Control group (n=35)	P value (intervention *vs.* control)*
Before interventions, mmol/L			
Mean (SD)	1.28 (1.08)	1.58 (1.89)	0.561
Median (range)	1.16 (0.4-2.4)	1.15 (0.6-4.6)	
After interventions, mmol/L			
Mean (SD)	1.18 (0.16)	1.35 (0.65)	0.828
Median (range)	1.19 (0.7-1.45)	1.19 (0.68-4.6)	
P value (before *vs.* after)#	0.032	0.128	

*Mann-Whitney; #Wilcoxon signed ranks test

Table 3. Calcium status in the intervention vs. control groups, before vs. after prophylactic calcium gluconate administration

Calcium status	Intervention group (n=35)	Control group (n=35)	P value*
Pre-intervention (1st day hospital admission), n			
Hypocalcemia	16	11	0.446[a]
Normocalcemia	15	15	
Hypercalcemia	4	4	
Post-intervention (3rd day hospital admission), n			
Hypocalcemia	8	8	0.951[b]
Normocalcemia	21	20	
Hypercalcemia	6	7	

[a]Kruskal Wallis; [b]Chi-square

With regard to adverse effects, extravasation of calcium gluconate-containing intravenous fluid into the tissue occurred in one subject in the intervention group, but no tissue necrosis occurred. Two subjects who received 400 mg/kg/day calcium gluconate became hypercalcemic, which manifested as bradycardia.

Discussion

Serum calcium levels in newborns are linked to various factors, such as PTH secretion, dietary calcium intake, renal calcium reabsorption, calcium reserves in bone, and vitamin D status. Calcium levels decrease quickly in the first few hours after birth, reaching the lowest levels within 24 to 48 hours. This decrease is mainly due to the cessation of active calcium transport through the placenta. We found hypocalcemia in 27/70 (38.5%) neonates. This rate is slightly lower than that reported in our center in 2018. Our study was conducted between February and December of 2020, whereas the 2018 report covered neonates who were admitted to the hospital from January to December of 2018. Another study in Surakarta, Central Java, reported a higher incidence of hypocalcemia in low birth weight neonates, at 46.2%.[6]

Calcium gluconate is comprised of calcium salts derived from gluconic acid;. A 10 mL ampoule of 10% calcium gluconate contains 93 mg elemental calcium. It is more commonly used than calcium chloride because it has fewer adverse effects as well as a smaller risk of tissue necrosis from extravasation.[7] Extravasation of intravenous fluid containing calcium gluconate into the tissue, without resulting tissue necrosis, occurred in one subject in the intervention group. We found a lower rate of side effects than that reported by a study in India, which observed side effects in 35% of subjects from administration of 4 mL/kg/day of calcium gluconate.[5] In another study, among 60 subjects with extravasated calcium gluconate, the median volume of extravasated fluid was 4.9 mL, resulting in lesions such as erythema (49%), edema and necrosis (48%), and yellowish-red papules (33%).[8] Calcium-induced capillary vasoconstriction and intracellular fluid retention can cause tissue necrosis, resulting in deep tissue injury and late-onset calcification.[9]

The systemic toxicity symptoms of calcium gluconate are identical to those of hypercalcemia. Hypercalcemia often manifests as non-specific symptoms, such as fatigue, muscle weakness, anorexia, and polydipsia. It may cause electrocardiographic changes in the form of short QT intervals, prolonged PR intervals, broad QRS, T-wave abnormalities, and various degrees of heart block.[10] In this our study, two subjects who received 400 mg/kg BW/day calcium gluconate became hypercalcemic, which manifested as bradycardia.

There was no significant difference in post-administration serum ionized calcium levels between subjects who received 400 and 200 mg/kg/day calcium gluconate (P=0.828). However, the group that received the higher dose had a significantly higher median serum ionized calcium level after treatment than before (P=0.032). No significant before- *vs.* after difference was observed in the control group (P=0.128). The study in India reported significant differences in calcium levels and onset of hypocalcemia symptoms within 72 hours of administration of 4 mL/kg/day calcium gluconate. There was, however, no significant difference in calcium levels at 120 hours of administration.[5] Another study concluded that calcium supplementation increased ionized and total serum calcium levels from day 3 to day 7 of supplementation.[11]

In healthy term infant, ionized and total calcium levels decline after the placenta has disconnected and eventually reach their physiological nadir. Phosphate levels, on the other hand, increase. The rate and amount of calcium depletion are inversely proportional to gestational age. In the first few days of life, hypoparathyroidism occurs, organs are unresponsive to PTH, vitamin D metabolism is impaired, and at the same time, hyperphosphatemia, hypomagnesemia, and hypercalcitoninemia occur. After 48 hours, PTH secretion increases, resulting in increased intestinal calcium and phosphate absorption, renal calcium reabsorption, and renal phosphate excretion, causing calcium levels to rise and serum phosphate to decline. Throughout the first four weeks after birth, calcium reabsorption in the kidneys and intestinal absorption will mature.[12]

We had similar proportions of full-term and premature infants between groups. Premature babies, especially those born at less than 32 weeks' gestation, are at a higher risk of hypocalcemia at birth because of the shorter time of receiving calcium through the placenta. However, a previous study reported that gestational age was not associated with hypocalcemia.[13] Contrastingly, a Bosnian study reported that prematurity and low birth weight were risk factors for early onset hypocalcemia.[14]

Almost half of our subjects had low birth weight: 42.9% in the intervention group and 51.4% in the control group. Tsang et al. reported that low birth weight in premature infants was a risk factor for hypocalcemia in newborns. The number of glomeruli is reduced in newborns with low birth weight, resulting in an increase in postnatal renal flow and a decrease in glomerular filtration rate (GFR). Furthermore, digestive tract development of low birth weight infants is impeded, resulting in suboptimal calcium absorption from nutrient intake.[12]

Macrosomia (high birth weight) was noted in 3 (8.6%) neonates in the intervention group and 1 (2.9%) neonate in the control group . There were more hypercalcemia cases in the intervention group (45.7%) than in the control group (31.4%). Babies with macrosomia also have the tendency to suffer from hypocalcemia. However, the mechanism remains unknown to date. A pervious study reported a 7.9% incidence of hypocalcemia in macrosomia infants and a 9% incidence in the general population.[15]

In both groups, asphyxia was the most common indication for hospital admission. Almost half of the diagnoses at admission in both groups (45.7% in the intervention group and 42.9% in the control group) was asphyxia. A study reported a significant association between the severity of asphyxia and hypocalcemia in the newborn, with a prevalence ratio (PR) of 4.9 (95%CI 1.2 to 20.3; P=0.027) for hypocalcemia in severe asphyxia and a PR of 4.51 (95%CI 1.3 to 14.6; P=0.009) for hypocalcemia in moderate asphyxia.16 Asphyxia in infants can cause delayed eating, increased calcitonin hormone production, increased endogenous phosphate intake, and decreased PTH secretion, all of which contribute to hypocalcemia.[16,17] During asphyxia, there is an imbalance in the acid-base balance of the blood, which affects the ionized calcium level. Alkalosis raises albumin-bound calcium levels while lowering ionized calcium levels, resulting in hypocalcemia symptoms. In metabolic acidosis, on the other hand,

calcium-albumin binding is diminished and the level of ionized calcium increases.[18]

In our study, despite the administration of prophylactic calcium, mean ionized calcium levels dropped on the third-day measurement. This may have occurred due of the use of phototherapy in neonates with jaundice. The mechanism of phototherapy-induced hypocalcemia is through the inhibition of the pineal gland from transcranial illumination. As a result, melatonin release decreases, which further inhibits the effects of cortisol on calcium in bone. Cortisol causes hypocalcemia by increasing calcium absorption in the bones.[19] Jaundice occurred in 5/35 infants in the intervention group and 3/35 infants in the control group (Table 1).

Seizures in newborns may occur due to nerve damage, hypoxia, ischemia, or transient metabolic disturbances, such as hypoglycemia or hypocalcemia.20 Seizures may also be caused by intracranial bleeding, infections, or consequences of hereditary metabolic disorders, such as hypomagnesemia, hyponatremia, and hypernatremia.[6] There were slightly fewer seizure manifestations in the intervention group (5/35) than in the control group (6/35). Neonatal seizures caused by transient hypocalcemia are amenable to calcium level correction, with minimal long-term implications.

Our study is the first to compare the prophylactic effect of 400 *vs.* 200 mg/kg /day calcium gluconate in newborns. The dose of 200 mg/kg/day prophylactic calcium gluconate is commonly used in our neonatal intensive care unit (NICU). The strength of our study is the randomized clinical trial design, which was employed to reduce the effect of confounding factors. However, other factors, such as maternal calcium levels during childbirth, which is one of the factors affecting infant calcium levels, as well as other factors that might induce hypocalcemia in neonates, such as magnesium and vitamin D levels, were not analyzed.

In conclusion, a prophylactic calcium gluconate dose of 400 mg/kg/day is not more effective in preventing neonatal hypocalcemia than the current standard dose of 200 mg/kg/day. However, there was a significant difference in median ionized calcium levels before and after calcium gluconate administration in the group receiving the higher dose.

Conflict of interest

None declared.

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