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Original Article

Change of ionized calcium level in the first 48 hours of age of preterm newborns administered with two different dosages of intravenous calcium gluconate

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Abstract

Background Physiologically, serum calcium level declines till nadir in a few hours after birth and continues for 24-48 hours. No study performed in order to know the alteration of ionized calcium level of newborn in the first 48 hours of age. The sick newborn must have parenteral calcium to avoid hypocalcemia but there is still no agreement about the dose.

Objective To determine the change of ionized calcium level in the first 48 hours of age of preterm newborns administered with peripheral drip intravenous 10% calcium gluconate of 2.6 mL/kg/day and 5 mL/kg/day.

Methods An open labeled randomized controlled clinical trial was performed between April and June 2009. After birth blood specimen of preterms was obtained for leukocyte, platelet, magnesium, phosphorous, and ionized calcium measurements. Subjects received either 2.6 mL/kg/day or 5 mL/kg/day of peripheral drip intravenous 10% calcium gluconate immediately after birth for 48 hours. Blood specimens was obtained again on 48 hours of age for ionized calcium. This study were analyzed using repeated measures analysis of varians.

Results Forty preterm newborns (20 subjects each group) were analyzed. There was no statistical difference between both doses (Factor-A) on 48 hours ionized calcium level (P=0.33) and ionized calcium level alteration based on time (Factor-B) (P=0.20). Interaction between both factors was significantly different (P=0.035).

Conclusion Ionized calcium level in 48 hours of age of preterm newborn administered with both doses of 10% calcium gluconate is not different but dose of 2.6 mL/kg/day yields physiologic alteration of ionized calcium level compared with 5 mL/kg/day. **[Paediatr Indones. 2010;50:96-100]**.

Keywords: *Preterm newborn, early onset hypocalcemia, 10% calcium gluconate*

Calcium is the most abundant mineral in the body. Of the body's total calcium, 99% are in bone, and serum levels constitute less than 1%. Although total serum calcium levels are often measured and reported, ionized calcium is the active and physiologically important component.[1-4]

Early onset hypocalcemia is most commonly observed problems among preterm newborns. The incidence of neonatal hypocalcemia varies in different studies. Hypocalcemia occurs in 30% of newborns with very low birth weight (<1500 g) and in as many as 89% of newborns whose gestational age at birth was less than 32 weeks. A high incidence is also reported in newborns born to mothers with diabetes mellitus and in newborns with birth asphyxia.[1-2]

Physiologically serum calcium level changes in a few hours after birth continuing for 24-48 hours and then stabilizes; the serum calcium level declines but still in normal range.[3-5] No study has been performed

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in order to know the alteration of ionized calcium level of newborn in the first 48 hours of age. The sick newborns must have parenteral calcium in order to avoid hypocalcemia but there is still no agreement about the dose. Hypocalcemia must be prevented in order to avoid impairment of cardiovascular and central nervous system.[1]

This study aimed to know the alteration of ionized calcium level in the first 48 hours of age of preterm newborn administered with peripheral drip intravenous 10% calcium gluconate 2.6 mL/kg/day and 5 mL/kg/day.

Methods

An open-label randomized controlled trial was performed on preterm newborns in Child Health Department Hasan Sadikin Hospital Bandung between April and June 2009. We included sick preterm newborns and appropriate for gestational age, and excluded preterm newborns of mothers with diabetes mellitus, mothers with phenytoin and/or phenobarbital therapy, preterm newborns with major congenital anomaly or early onset sepsis, hypocalcemia, hypomagnesemia, or hyperphosphatemia at baseline. Parents of eligible newborns had consented to enroll their newborns.

We obtained baseline data on sex, birth weight, gestational age based on new Ballard score, leukocyte, pletelet, magnesium, phosphorous, and ionized calcium. The newborns received either 2.6 mL/kg/day or 5 mL/kg/day of peripheral drip intravenous 10% calcium gluconate immediately after birth till 48 hours of age. Blood specimens were obtained again on 48 hours of age for ionized calcium.

Statistical analysis was performed using chi-square for nominal difference of groups, t-test or Mann-Whitney for comparing mean of groups, and repeated measures analysis of varians for analyzing both treatment influences (Factor-A), the alteration of chronological ionized calcium level (Factor-B), and the interaction of both factors. $P<0.05$ was considered statistically significant. Data were analyzed using an SPSS version 17.0 for Windows. This study was approved by the Health Study Ethics Committee of the Medical School Padjadjaran University/Hasan Sadikin Hospital Bandung.

Results

During the study period data were collected from 46 subjects who met the inclusion criteria, but six subjects could not finished this study because two of them died and four subjects were discharged against medical advice. The subject characteristics based on birth weight, working diagnosis, magnesium and phosphate level is depicted in **Table 1**.

Table 1. Subject's characteristics

Characteristics	2.6 mL/kg/day (n=20)	5 mL/kg/day (n=20)
Birth weight, mean (SD), gram	1,702.3 (400.4)	1,727.9 (386.7)
Working diagnosis, n (%)		
• ELBW	5	3
• HMD	9	7
Magnesium, mean (SD), mg/dL	2.2 (0.5)	1.9 (0.3)
Phosphate, mean (SD), mg/dL	6.0 (1.2)	5.3 (1.3)

Note: ELBW = extremely low birth weight, HMD = hyaline membrane disease

Table 2. Ionized calcium level at baseline and 48 hours of age both groups

		Factor-B Ionized calcium level based on time, mean (SD), mg/dL	
		B1	B2
Factor-A	A1	4.93 (0.38)	4.46 (0.37)
Treatment	A2	4.69 (0.41)	4.80 (0.95)

Note: Factor-A: P=0.33 Factor-B: P=0.20 Interaction factor-A and B: P=0.035

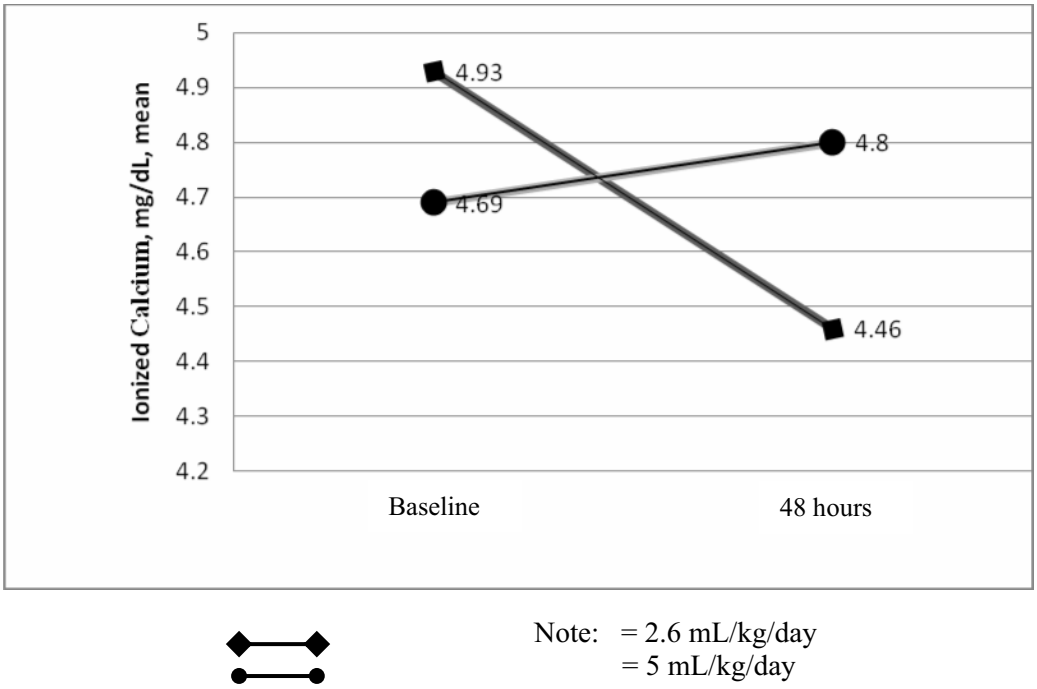

Figure 1. The means of ionized calcium level at baseline and 48 hours of age both groups

In this study there were two confounding factors, i.e. gestational age and diagnosis of severe asphyxia. The analysis of both confounding factors is depicted in **Table 2**.

Normal ionized calcium level of preterm newborns is 4-5.6 mg/dL.[3,6] The mean of ionized calcium level at baseline in group 2.6 mL/kg/day was 4.93 (SD 0.38) mg/dL, whereas at 48 hours of age was 4.46 (SD 0.37) mg/dL. In group 5 mL/kg/day, the mean of ionized calcium level at baseline was 4.69 (SD 0.41) mg/dL, whereas at 48 hours of age was 4.80 (SD 0.95) mg/dL. The difference of mean of both doses on ionized calcium level is depicted in **Figure 1**.

In group 2.6 mL/kg/day, the lowest level of ionized calcium on 48 hours was 4.01 mg/dL, whereas the highest one was 5.45 mg/dL. In group 5 mL/kg/day, the lowest level of ionized calcium was 3.59 mg/dL (three subjects), whereas the highest one was 7.67 mg/dL (three subjects).

Repeated measures analysis of variance was used to analyze the effect of administration of 10% calcium gluconate both doses on 48 hours ionized calcium level which is depicted in **Table 2**.

As shown in **Table 2**, there were no statistical differences between effects of administration with 10% calcium gluconate 2.6 mL/kg/day and 5 mL/kg/day doses (Factor-A) on 48 hours ionized calcium level (P=0.33). There were also no significant differences between the change of ionized calcium level based on time (Factor-B) (P=0.20). However, the change between both factors was significantly different (P=0.035).

Discussion

Out of 46 subjects who met the inclusion criteria, two died. It was not clear that the death of subjects was a "failure" due to the side effect of 10% calcium gluconate administration or the newborns suffered hypocalcemia or hypercalcemia associated with doses of 10% calcium gluconate administration. There is no known percentage of babies suffered from side effect of 10% calcium gluconate, hypocalcemia, or hypercalcemia. Because there were only two subjects died in this study, we assumed that the cause of death was associated with the underlying diseases,

i.e severe asphyxia and HMD. The fact is supported by Klaus and Fanaroff[5] that hypocalcemia without other diseases has good prognosis. Hypercalcemia is usually fatal when ionized calcium level reached more than 14 mg/dL.[7] Three subjects in group 5 mL/kg/day suffered from hypercalcemia on 48 hours of age but the level <14 mg/dL.

There were no significant differences between the effect of administration with 10% calcium gluconate 2.6 mL/kg/day and 5 mL/kg/day doses (Factor-A) on 48 hours ionized calcium level (P=0.33) and also with the alteration of ionized calcium level based on time (Factor-B) (P=0.20). Feed back mechanism by ionized calcium to parathyroid glands of preterm newborns starts on day 3-4 of life.[3] The doses of 10% calcium gluconate given before 3-4 days of age would not influence the action of parathyroid glands. According to the results, both doses of 10% calcium gluconate was sufficient for calcium requirement of body to maintain many important biologic functions such as calcium messenger system by which extracellular messengers regulate cell function, activation of cellular enzyme cascades, smooth muscle and myocardial contraction, nerve impulse conduction, and secretory activity of exocrine glands. Our findings agree with Klaus and Fanaroff[5] that 10% calcium gluconate administration of dose 2,6 mL/kg/day can prevent hypocalcemia of susceptible newborns. Our results also agree with Mainali[8] that 10% calcium gluconate administration of dose 5 mL/kg/day can prevent hypocalcemia of susceptible newborns.

Statistical analysis of interaction between treatment effect on 48 hours ionized calcium level and the alteration of serum ionized calcium level based on time showed significant difference (P=0.035). Physiologically serum calcium level alterations in a few hours after birth continue for 24-48 hours and then stabilize at normal range.[3-5] In sick preterm newborns the serum ionized calcium level must decline below nadir, therefore they will undergo hypocalcemia without preventive effort. In group 2.6 mL/kg/day, the pattern of ionized calcium level alteration was suitable with physiologic ionized calcium alteration (**Figure 1**). This result means that the dose was sufficient for body to maintain many important biologic functions and able to keep ionized calcium level in normal range (not hypocalcemia). This outcome agree with Klaus and Fanarof[5] that administration of 10% calcium gluconate dose 2.6 mL/kg/day is well tolerated by newborns.

By contrast, the alteration of ionized calcium level in group 5 mL/kg/day was not physiologic. The alteration formed increasing pattern of ionized calcium level but still in normal range. This pattern means that the dose was sufficient to maintain many important biologic functions but excessive.

In group 5 mL/kg/day, there were three subjects experience hypocalcemia and three subjects experience hypercalcemia on 48 hours of age. The factors caused hypocalcemia of three subjects were unclear. The hypocalcemic subjects were diagnosed as severe asphyxia (two subjects) and HMD (one subject). Severe asphyxia must be counted to be one of the etiology of the hypocalcemia although no significant difference in statistical analysis of both group. In this study, working diagnosis of severe asphyxia was according to APGAR score only, without laboratory assessment. Theoretically, respiratory distress due to severe asphyxia, HMD, etc will increase calcitonin level, disturb parathyroid hormone (PTH) function, disturb magnesium function to regulate and secrete PTH, and increase phosphate level due to increasing of catabolism process.[4,5,9] High concentration of serum calcitonin will rise urinary calcium excretion. Without adequate PTH secretion, this circumstance will decrease ionized calcium concentration. Another possibility was those subjects with hypocalcemia experienced hypomagnesemia or hyperphosphatemia on 48 hours of age, therefore hypocalcemia occurred. The limitations of our study associated this hypocalcemia circumstance were no measurement of calcitonin, magnesium, and phosphate level performed on 48 hours of age.

Three subjects experienced hypercalcemia in group 5 mL/kg/day were diagnosed as HMD (two subjects) and severe asphyxia (one subject). It seems that hypercalcemia was not associated with their underlying disease. One of important possibility was genetic factor that cause the circumstance. The same circumstance was showed in study by Sann *et al*[10] on 23 preterm newborns supplemented by 10% calcium gluconate mixed in milk then administration per oral. They found two subjects (8.7%) experienced hypercalcemia and the possible causes were not explained.

Those subjects experienced hypocalcemia and hypercalcemia on 48 hours of age were treated according to our protocol. Despite small percentage of hypocalcemia and hypercalcemia in our study, physicians must perform measurement of ionized calcium level on 48 hours of age.

In conclusion, ionized calcium levels in 48 hours of age of preterm newborns administered with both doses of 10% calcium gluconate is not different but dose of 2.6 mL/kg/day yields physiologic alteration of ionized calcium level compared with 5 mL/kg/day.

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