Comparison Effect of Loading Calcitriol and Titrating Calcitriol Treatment to Control Hypocalcemia after Parathyroidectomy in Chronic Kidney Disease: Randomized Control Trial, Open Labeled

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Background: *Postoperative parathyroidectomy hypocalcemia probably results from acute reversal of the parathyroid hormone induced contribution of bone to maintain serum calcium concentration.*
Objective: *Compare the effective treatment of calcitriol regimens (loaded and titrated) in control hypocalcemic hyperparathyroid (HPT) patients who were referred for parathyroidectomy.*
Material and Method: *A randomized control, open labeled study of 25 patients who underwent parathyroidectomy in Rajavithi Hospital from August 2009 to September 2010 was conducted. The authors randomized 25 patients with chronic kidney disease in two treatment arms of calcitriol (A: Titrated dose regimen, B: Loaded dose regimen), that met criteria. Biochemical factors available within 2 weeks before and after surgery were recorded and analyzed.*
Result: *No significant difference was observed in amount of calcium gluconate intravenous use, hypocalcemia and hospital admission durations between titrated and loaded regimen groups, i.e., p = 0.160, 0.645 and 0.460, respectively. Loaded regimen ameliorated the mean reduction of day 7 postoperative mean change of serum calcium level by 0.33±0.99 mg/dl and median change by 2.88 mg/dl (min, max = -0.80, 5.64) compared with titrate regimen mean change of serum calcium level by 2.68±2.16 mg/dl; median change 0.28 mg/dl (min, max = -0.84, 1.80) with significance, p = 0.036.*
Conclusion: *Loaded calcitriol regimen was superior to titrated calcitriol regimen compared with the control group the first 7 days postparathyroidectomy. Amount of calcium gluconate intravenous used, hypocalcemia and duration of hospital stay did not show any significance.*

Keywords: *Parathyroidectomy, Hyperparathyroidism, Hypocalcemia, Calcitriol*

J Med Assoc Thai 2014; 97 (Suppl. 11): S56-S61
Full text. e-Journal: *http://www.jmatonline.com*

Postoperative hypocalcemia in patients with renal hyperparathyroidism is a common problem after parathyroidectomy. Transient hypocalcemia was observed in 83% of the patients[1]. On the contrary, the presence of postoperative hypocalcemia is not a guarantee of surgical cure[2]. With renal hyperparathyroidism, Jofre et al[3] observed that 20% of their patients had hungry bone syndrome necessitating longer hospitalization, defined as calcium levels below 8.0 mg/dl for more than eight days. In addition to biochemical values, the presence or absence of hypocalcemic symptoms has also been taken into consideration in many studies. Comparisons are further complicated by the fact that a low serum calcium level does not always predict the development of symptoms or signs of hypocalcemia.

Oral calcium and active vitamin D supplements may be sufficient in some patients. On the other hand,

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intravenous calcium administration is often necessary if severe or symptomatic hypocalcemia develops. ''Need for intravenous calcium'' has been used as an indicator of the magnitude of hypocalcemia. Vitamin D usually takes two days to increase intestinal uptake of calcium. Preoperative vitamin D treatment is recommended, even in patients who have hypercalcemia. As aforementioned, intravenous calcium administration remains the most straightforward treatment to restore serum calcium levels rapidly. Cozzolino et al[4] proposed an algorithm to start calcium infusion when a steep fall in calcium levels is noted. However, it might be better to prevent hypocalcemia altogether.

Hungry bone syndrome, first described in 1948 by Albright and Reifenstein as cited in a previous study[5], is characterized by severe prolonged hypocalcemia after parathyroidectomy. The abrupt withdrawal of parathyroid hormone (PTH) results in a transient marked increase in bone remineralization and a rapid shift of calcium from the circulation to bone tissue[6,7]. After parathyroidectomy performed in dialysis patients with severe secondary hyperparathyroidism, acute functional changes are observable in bone cells. Several regimens are available to reduce hypocalcemic symptoms. Vitamin D therapy is often used, but it does not influence bone cell activity; instead, it improves hypocalcemia mainly through the known effect on intestinal calcium absorption[8]. In addition, combined oral and intravenous vitamin D and calcium supplements in the form of calcitriol (1,25-dihydroxycholecalciferol, (1, 25-$(OH)_2D_3$), active form of vitamin D) and calcium gluconate, respectively, have been shown to ameliorate hypocalcemia[9].

The aim of the present study was to compare the effective regimens of calcitriol administration to control hypocalcemia in chronic kidney disease patients undergoing successful parathyroidectomy from hyperparathyroidism.

Material and Method

Study design

From August 2009 to September 2010, 28 referred patients underwent parathyroidectomy for symptomatic hyperparathyroidism at our institute. Among them, three (10.7%) patients were excluded from the study because of primary hyperparathyroidism and no patient had persistent disease after surgery (postoperative intact parathyroid hormone (PTH) >300 pg/dl). The remaining 25 patients having chronic kidney disease stage 5, who underwent successful parathyroidectomy (PTX). This was a pilot study, sample were simple randomization.

Before surgery, serum levels of calcium, phosphorus, alkaline phosphatase (ALP), blood urea nitrogen (BUN) and creatinine were measured routinely using standard auto-analytical techniques. Intact PTH (1-84) was measured by the two-site immunoradiometric assay (ELSA-PTH; CIS Bio International, Gif-sur-Yvette, France) with a normal range from 10 to 65 pg/ml. All patients underwent dialysis the day before operation. Preoperative imaging of the parathyroid glands was not routinely used. Bilateral cervical exploration was performed in all patients to identify four parathyroid glands. Our goal was to control intact PTH to the target range of 150 to 300 pg/ml, as recommended by K/DOQI guidelines[10].

After surgery, immediate supplementation with oral calcium carbonate and oral vitamin D was initiated. Regimens of calcitriol treatment were defined in two regimens: subjects were assigned regimen A when admission number was odd and regimen B when admission number was even.

Group A: The titrated dose regimen group was defined by supplemented calcitriol titrated against serum calcium level (starting at 1 mcg/d, alfacidol (250 mcg) 2x2 daily) with constant dose of oral calcium carbonate (1 gm calcium carbonate 3x3 daily) but the amount of intravenous calcium gluconate was titrated against serum calcium when indicated (Table 1).

Group B: The loaded dose regimen group was defined by supplemented calcitriol loaded against serum calcium level (starting dose at 4 mcg/d, alfacidol (250 mcg) 4x4 daily) with constant dose of oral calcium carbonate tablet (1 gm calcium carbonate 3x3 daily) but the amount of intravenous calcium gluconate was titrated against serum calcium when indicated as shown in Table 1.

Analysis was performed with the SPSS version 17.0 (SPSS, Chicago, IL, USA). Data were presented as mean $\pm$ standard deviation (SD) or median (range) for continuous variables and number (%) for categorical variables. Differences in the frequencies of events between groups were analyzed using Chi-square test or Fisher's exact test. Student t-test or Mann-Whitney test were used to compare continuous variables between groups. A *p*-value less than 0.05 was considered significant. This study was approved by the ethics committee of Rajavithi Hospital.

Results

As shown in Fig. 1, 28 referred patients underwent parathyroidectomy for symptomatic

Table 1. Strategies to control hypocalcemia in postoperative parathyroidectomy

A: vitamin dose (titrating regimen)	Strategies
Step 1 vitamin 1-α 2x2	Increase dose to next step if corrected calcium ≤7.5 mg/dl, if corrected calcium <7 mg/dl*
Step 2 vitamin 1-α 3x2	Increase dose to next step if corrected calcium ≤7.5 mg/dl, if corrected calcium <7 mg/dl*
Step 3 vitamin 1-α 4x2	Increase dose to next step if corrected calcium ≤7.5 mg/dl, if corrected calcium <7 mg/dl*
Step 4 vitamin 1-α 4x3	Increase dose to next step if corrected calcium ≤7.5 mg/dl, if corrected calcium <7 mg/dl*
Step 5 vitamin 1-α 4x4	Increase dose to next step if corrected calcium ≤7.5 mg/dl, if corrected calcium <7 mg/dl *
B:Vitamin dose (Loading regimen)	**Strategies**
Step 1 vitamin 1-α 4x4 (2 days)	Continue dose if corrected calcium ≤7.5 mg/dl, if corrected calcium <7 mg/dl*
Step 2 vitamin 1-α 4x3 (2 days)	Continue dose if corrected calcium ≤7.5 mg/dl, if corrected calcium <7 mg/dl*
Step 3 vitamin 1-α 4x2 (2 days)	Continue dose if corrected calcium ≤7.5 mg/dl, if corrected calcium <7 mg/dl*
Step 4 vitamin 1-α 3x2 (2 days)	Continue dose if corrected calcium ≤7.5 mg/dl, if corrected calcium <7 mg/dl*
Step 5 vitamin 1-α 2x2 (2 days)	Continue dose if corrected calcium ≤7.5 mg/dl, if corrected calcium <7 mg/dl*

* Intravenous calcium treatment (calcium gluconate) was administered when the patient's serum level of corrected total calcium fell below 7.0 mg/dl or when the patient experienced severe hypocalcemic symptoms such as numbness, paresthesia, positive Chvostek's sign, carpopedal spasms or tetany.

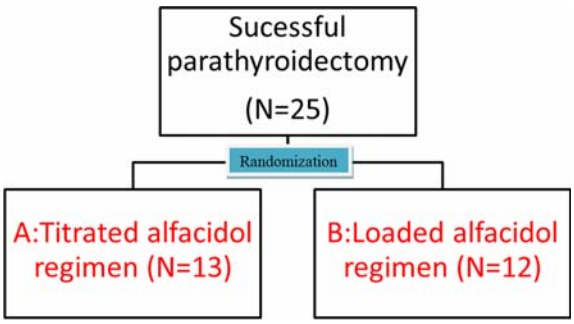

Fig. 1 Trial profile.

hyperparathyroidism at our institute and three patients with primary hyperparathyroidism were excluded. The 25 patients with chronic kidney disease stage 5, who underwent successful PTX, were reviewed in detail. After analyzing data, 13 patients were enrolled in the titrated regimen and 12 patients were enrolled in the loaded regimen group.

Basal clinical and biochemical data were different in titrated and loaded regimen groups such as age, BUN and creatinine level, i.e., $p = 0.043$, 0.029 and 0.015, respectively but other parameters were not different between both group as shown in Table 2. The loaded regimen group had more elderly patients than the titrated regimen group by ten years.

Even though the present study revealed no differences regarding calcium gluconate intravenous use, $p = 0.16$ (Table 3), we found that loaded calcitriol regimen could reduce the amount of calcium gluconate, 3.00 ampules (1 ampule; 10 ml). However, titrated calcitriol regimen totaled 7.58 ampules. The authors found that loaded calcitriol regimen could control postoperative calcium level to remain at normal range better than titrated calcitriol regimen as shown in Fig. 2. This study has shown that we can reduce postoperative hypocalcemia from the titrated regimen treatment group 84.6% to 33.3% by using loaded calcitriol regimen even without significance. Usinga loaded regimen shortened the length of stay (LOS) about 1.25 days after surgery better than a titrated regimen reducing healthcare costs after parathyroidectomy in hospital.

Discussion

Hyperparathyroidism has been associated with renal failure due to chronic parathyroid stimulation by hypocalcemia, which, in turn, results from hyperphosphatemia and low circulating 1, 25 (OH) 2D3. If prophylactic measures and medical treatment of hyperparathyroidism fail, parathyroidectomy should be

Table 2. General characteristic of patients with successful parathyroidectomy

Characteristic	Successful parathyroidectomy (n = 25)		*p*-value
	A: titrated (n = 13)	B: loaded (n = 12)	
Age (year)	39.17±12.17	49.42±11.20	0.043*
Sex (female)	6 (46.2%)	8 (66.7%)	0.302
Body weight (kg)	55.15±10.77	55.03±9.22	0.981
Duration of renal replacement (year)	6.42±2.94	8.25±3.84	0.204
Preoperative data			
Calcium (mg/dl)	10.98±1.13	11.058±1.07	0.882
Phosphate (mg/dl)	6.73±2.10	5.24±1.44	0.056
Calcium phosphate product (mg^2/dl^2)	74.55±26.19	58.66±18.49	0.102
Intact PTH (pg/dl)	1,353.63±536.81	1,846.93±796.19	0.089
Alkaline phosphatase (IU/L) (min, max)	171.5 (59, 813)	256 (55, 645)	0.929
BUN (mg/dl)	51.42±24.02	33.42±11.49	0.029*
Creatinine (mg/dl)	9.95±3.06	7.01±2.33	0.015*
25 (OH) vitamin D	28.7 (18.7, 32.3)	19.7 (6.1, 39.3)	0.299

Value are presented as mean±SD, median (min, max), number (percent). * Significance at $p<0.05$ by student t-test

Table 3. Outcome characteristics between calcitriol treatment group after successful parathyroidectomy

Characteristic	Successful parathyroidectomy (n = 25)		*p*-value
	A: titrated (n = 13)	B: loaded (n = 12)	
Amount of calcitriol (tab)	57.75±75.28	59.17±22.73	0.539
Calcium gluconate treatment (%)	8 (61.5)	4 (33.3)	0.158$^{\delta}$
Amount of calcium gluconate (iv)	7.58±8.96	3.00±6.18	0.160
Hypocalcemia (%)	11 (84.6)	4 (33.3)	0.645$^{\delta}$
Duration of hospitalization (day)	9.50±4.83	8.25±3.11	0.460
Mean change of calcium level in the first 7 days postsurgery	2.88 (-0.80, 5.64)	0.28 (-0.84, 1.80)	0.036*

Value are presented as mean ± SD, median (min, max), number (percent), * significance at $p<0.05$ by student t-test.[d] Test by Chi-square

performed to prevent the progression of bone disease. Hypocalcemic parathyroidectomy is a common problem after surgery. Transient hypocalcemia has been observed in 83% of the patients[1] similar to our finding regarding titrate regimen arms (84.6%). However, in the loaded regimen found transient hypocalcemia at only 33.3%. On the contrary, the presence of postoperative hypocalcemia is not a guarantee of surgical cure[2]. Hospital stay was prolonged among renal osteodystrophy patients due to hungry bone syndrome[3]. In addition to biochemical values, the presence or absence of hypocalcemic symptoms has also been considered in many studies. Medical treatment should not be prolonged at the expense of long repeated bouts of hypercalcemia or hyperphosphatemia with their irreversible consequences.

Previous studies[11-17] have used the calcium nadir level, changes of calcium levels, duration of hypocalcemia, or dosage of required calcium supplementation as estimates of the severity of hungry bone syndrome. Factors that have been found to be related to postoperative hypocalcemia include age, preoperative PTH, alkaline phosphatase levels, subperiosteal bone resorption and the histology of the bone biopsy[1-4,12-18]. However, the present study found no factors related to postoperative hypocalcemia in

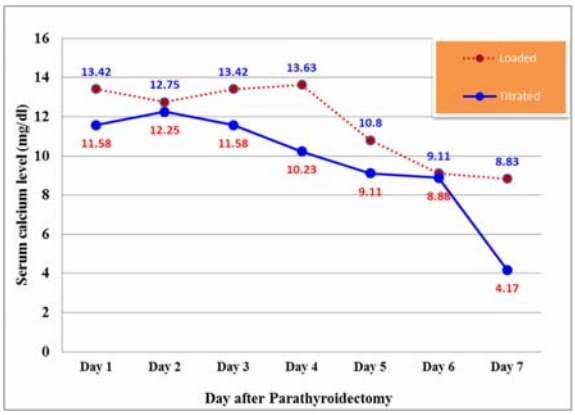

Fig. 2 Postoperative calcium level of parathyroidectomy from days 1 to 7.

renal hyperparathyroidism cases. This may have resulted from the cut off point for hypocalcimia below than 8.0 mg/dl, which was not an ideal parameter to predict serious emergency conditions in the intensive care unit.

Our retrospective study (unpublished) found that calcium-phosphorus products, age, regimen of treatment and phosphate level were related to need for intravenous calcium gluconate administration after parathyroidectomy. Calcium phosphorus product was the only independent factor to predict need for intravenous calcium supplement when that level was over than 53. However, the present study found no such correlation. This research was the first randomized design study to control hypocalcemia after parathyroidectomy among Thai patients with chronic kidney disease, but was limited by number of the patients resulting in less significant primary outcomes.

Conclusion

Based on our results starting a loaded calcitriol dose immediately after surgery in patients is an effective preventive strategy because this regimen can reduced the incidence of postoperative hypocalcemic parathyroidectomy from 84.6% to 33.3% and a loaded regimen can ameliorate the mean reduction of day 7 postoperative serum calcium level better than the titrating regimen. Further study requires enrolling more patients to investigate significant benefits from the loaded regimen. In addition, the research should employ a multicenter study that can produce guidelines for postoperative management of parathyroidectomy.

Potential conflicts of interest

None.

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เปรียบเทียบผลการรักษาภาวะแคลเซียมต่ำหลังการผ่าตัดต่อมพาราไทรอยด์ด้วยไวตามินดีแบบขนาดสูงกับไวตามินดีที่ค่อย ๆ เพิ่มขนาดในคนไข้ไตวายเรื้อรัง: การศึกษาแบบสุ่มและมีกลุ่มควบคุมโดยเปิดเผยข้อมูล

สถิตย์ นิรมิตรมหาปัญญา, ชัดสุภา ศิริรัชตะ, เบญจวรรณ นิรมิตรมหาปัญญา, ชัยชาญ ดีโรจนวงศ์, อุดม ไกรฤทธิชัย, พรเอก อภิพันธ์

ภูมิหลัง: *ภาวะแคลเซียมต่ำภายหลังการผ่าตัดต่อมพาราไทรอยด์เป็นผลมาจากการเปลี่ยนแปลงอย่างฉับพลันของพาราไทรอยด์ฮอร์โมนทำให้กระดูกเป็นอวัยวะที่ต้องคอยควบคุมสมดุลของแคลเซียมภายหลังการผ่าตัด*

วัตถุประสงค์: *เพื่อเปรียบเทียบการรักษาด้วยไวตามินดี (ใช้ยาขนาดสูงตั้งแต่เริ่มต้นและค่อย ๆ เพิ่มขนาดยา) ในการควบคุมภาวะแคลเซียมต่ำภายหลังการผ่าตัดต่อมพาราไทรอยด์*

วัสดุและวิธีการ: *การศึกษาแบบสุ่ม, แบบเปิดในผู้ป่วยที่มาผ่าตัดต่อมพาราไทรอยด์จำนวน 25 ราย ที่มาผ่าตัดที่โรงพยาบาลราชวิถีช่วง เดือนสิงหาคม พ.ศ. 2552 ถึง เดือนกันยายน พ.ศ. 2553 โดยทำการสุ่มผู้ป่วยเป็น 2 กลุ่มการรักษา กลุ่ม A ได้ไวตามินดีแบบค่อย ๆ เพิ่มขนาด, กลุ่ม B ได้ไวตามินดีขนาดสูงโดยผู้ป่วยไตวายทั้ง 25 ราย มีข้อบ่งชี้ในการผ่าตัดและเก็บข้อมูลทางชีวภาพในช่วง 2 สัปดาห์ ก่อนและหลังทำการผ่าตัดแล้วนำมาวิเคราะห์ทางสถิติ*

ผลการศึกษา: *จำนวนของการใช้แคลเซียมทางหลอดเลือดดำไม่แตกต่างกันในทั้ง 2 กลุ่ม รวมถึงภาวะแคลเซียมต่ำ และระยะเวลาการนอนในโรงพยาบาล โดยค่า p = 0.160, 0.645 และ 0.460 ตามลำดับ การให้ไวตามินดีขนาดสูงทำให้ควบคุมการเปลี่ยนแปลงระดับแคลเซียมภายหลังการผ่าตัดใน 7 วันหลังการผ่าตัดได้ดีกว่ากลุ่มที่ค่อย ๆ เพิ่มไวตามินดีอย่างมีนัยสำคัญสถิติ โดยค่ากลางของการเปลี่ยนแปลงของระดับแคลเซียมกลุ่มที่ให้ไวตามินดีขนาดสูงมีค่าเฉลี่ย (mean) ที่ 0.33±0.99 มก./เดซิลิตร และค่ามัธยฐาน (median) ที่ 0.28 มก./เดซิลิตร กับกลุ่มที่ค่อย ๆ เพิ่มไวตามินดีมีค่าเฉลี่ย (mean) ที่ 2.69±2.12 มก./เดซิลิตร และค่ามัธยฐาน (median) ที่ 2.88 มก./เดซิลิตร, p = 0.036)*

สรุป: *การใช้ไวตามินดีแบบขนาดสูงสามารถควบคุมระดับแคลเซียมใน 7 วัน หลังผ่าตัดได้ดีกว่าถึงแม้อัตราการใช้แคลเซียมในหลอดเลือดดำ, แคลเซียมต่ำและอัตราการนอนในโรงพยาบาลจะไม่แตกต่างกันทางสถิติ*