Chapter

Severe Hypocalcemia after Total Parathyroidectomy Plus Autotransplantation for Secondary Hyperthyroidism-Risk Factors and a Clinical Algorithm

Fong-Fu Chou and Jin-Bor Chen

Abstract

Severe hypocalcemia is a serious complication occurring after parathyroidectomy for secondary hyperparathyroidism. Totally, 322 patients who were successfully treated with total parathyroidectomy and bilateral thymectomy plus autotransplantation were studied. Group A (247 patients) developed mild hypocalcemia. Group B (75 patients) who had post-operative serum Ca levels <6.5 mg/dL or needed >4 g of intravenous (i.v.) Ca gluconate to keep Ca levels ≥6.5 mg/dL developed severe hypocalcemia. Preoperatively, patient age was recorded, and serum Ca, P, alkaline phosphatase (Alk-ptase), and intact parathyroid hormone (iPTH) levels were checked. These serum levels were checked again 18 h post-operatively. The algorithm showed that i.v. Ca gluconate 8 g/150 dL (5% glucose)/day was administered for Ca levels <6.5 mg/dL, 4–6 g/75 dL/day for levels <7.6 mg/dL, and 2 g/15 dL/15 min for symptomatic hypocalcemia. Young age, low Ca, and high Alk-ptase levels and long operation time were independent risk factors for severe hypocalcemia. Serum Ca levels <7.6 mg/dL at 18 h post-operation were the optimal cutoff value for hypocalcemia that needed i.v. Ca gluconate. The post-operative hospitalization in Group B was 3–5 days shorter than that previously reported. The readmission rate (0.62%) due to hypocalcemia was rare.

Keywords: secondary hyperparathyroidism, total parathyroidectomy plus autotransplantation, severe hypocalcemia, intravenous calcium gluconate

1. Introduction

In patients with end-stage renal disease (ESRD), parathyroid hyperplasia, high circulation parathyroid hormone (PTH), and hyperphosphatemia characterize secondary hyperparathyroidism (SHPT).

SHPT is a serious manifestation of chronic kidney disease (CKD) with negative effects on patients' life quality and outcome.

In ESRD, medical treatment for secondary hyperparathyroidism has three main strategies: reduction of P uptake by dialysis, dietary restriction, and/or P-binders; calcimimetics; and vitamin D.

Due to toxicity, aluminum-based P-binders have been replaced by those containing Ca salts. At high doses, Ca-based P-binders may elevate the risk of vascular calcification. Ca-free P-binders with dietary P restriction appear to lower fibroblast growth factor-23 and improve cardiovascular and renal outcomes in patients with SHPT [1].

Despite the availability of several P-binders, the ideal P-binder that combines high efficacy, low pill burden, minimal side effects (including gastro-intestine), and low cost is still not available [2], and the effect on survival is unclear [3].

In EDRD patients, vitamin D may improve abnormal mineral homeostasis; however, a steady escalation of vitamin D analog dose is not feasible due to hypercalcemia, hyperphosphatemia, and/or parathyroid gland resistance, despite the concurrent use of calcimimetics [4].

Calcimimetics such as cinacalcet therapy are currently a class of agents that activate the Ca sensing receptor and potentiate the effect of extracellular Ca. Literature supports cinacalcet therapy to improve patients' outcomes, especially with regard to vascular calcifications and presumably the very lethal condition of calciphylaxis [5].

Additional clinical evidence suggests that cinacalcet in combination with low-dose vitamin D is more effective in lower PTH than calcitriol alone. However, cinacalcet is administered orally and has been associated with gastrointestinal intolerance along with hypocalcemia [6].

In addition, poor adherence has been observed among dialysis patients self-administering cinacalcet [5]. Cost effectiveness is another consideration; the addition of cinacalcet contracts an additional US$3000–4000 per year on the top of the costs of vitamin D and P-binders [7].

If calcimimetics side effects are intolerable, some researchers have reported that parathyroidectomy may be more cost-effective than cinacalcet in some patients with ESRD and suffering from uncontrolled SHPT [4].

2. Parathyroidectomy rates, indications, and methods

Parathyroidectomy was required in about 10% of patients after 10 years and 20% after 20 years in dialysis patients [8]. The parathyroidectomy rate was 8.8/1000 patient-years from 1991 to 2009 in the Swedish dialysis and transplant population [9]. A trend toward a dip in parathyroidectomy rate was found during the era of cinacalcet. This change in treatment strategy was accompanied with increased preoperative PTH levels reflecting delayed surgery and increased disease severity [10].

The overall rate of parathyroidectomy in the United States was approximately 5.4/1000 patients between 2002 and 2011. The rate decreased from 2003 (7.9/1000 patients), reached a nadir in 2005 (3.3/1000 patients), increased again through 2006 (5.4/1000 patients), and remained stable since that time. Rates of in-hospital mortality after parathyroidectomy decreased from 1.9% in 2003 to 0.8% in 2011 [11].

In-hospital mortality has seldom happened in Kaohsiung Chang Gung Memorial Hospital during 30 years in over 2000 patients undergoing parathyroidectomy plus autotransplantation for secondary hyperparathyroidism, owing to routine cardiac 2D-echography, thallium-201 myocardial imaging, and EKG examinations before surgery [12]. In recent 5 years, sestamibi parathyroid scintigraphy is also routinely performed preoperatively.

The indications for parathyroidectomy are symptoms of bone pain, skin itching, general weakness, insomnia, and soft tissue calcification with Ca levels ≥10.2 mg/dL, P levels ≥4.7 mg/dL, alkaline phosphatase (Alk-ptase) levels ≥94 IU/L, intact parathyroid hormone (iPTH) levels ≥800 pg./mL, and bone mineral density (T-score) ≤ −2.5

in dialysis patients. All oral medications including calcitriol, sevelamer, and cinacalcet have to be discontinued 1 month before surgery to avoid severe hypocalcemia in the post-operation period.

During surgery, if four or more glands and bilateral thymus are removed (total parathyroidectomy and bilateral thymectomy) (TPX & BT), l00 mg of parathyroid gland with diffuse hyperplasia is autotransplanted (AT) into the subcutaneous tissue of the forearm without harboring the arteriovenous fistula [13]. If less than four glands are found and removed, bilateral thymectomy is performed, but AT is omitted.

3. Definition of severe hypocalcemia post-parathyroidectomy and risk factors

Previously, the critical value of hypocalcemia (CVH) was defined as Ca levels ≤6.0 mg/dL within 48 h of total parathyroidectomy, indicating the possibility of life threatening complications [14] or as profound and prolong hypocalcemia (hungry bone syndrome) with corrected serum Ca levels of ≤8.4 mg/dL lasting for 4 or more days, that occurred anytime within 1 month following the parathyroidectomy [15]. Bone hungry syndrome occurred frequently around 25–27.4% after total parathyroidectomy for secondary hyperparathyroidism [4, 15] and CVH around 15.3% [14].

In a recent study, we included 322 patients who were successfully treated with TPX & BT plus AT. They were divided into two groups. Group A (mild hypocalcemia) patients had serum Ca levels ≥6.5 mg/dL at 18 h post-operation and needed ≤4 g i.v. Ca gluconate to keep Ca levels ≥6.5 mg/dL during the post-operative period (7 days). Group B (severe hypocalcemia) patients had serum Ca levels <6.5 mg/dL at 18 h post-operation or needed >4 g of i.v. Ca gluconate during the post-operative period to keep Ca levels ≥6.5 mg/dL. Surgery was considered successful when iPTH levels were lowered to <72 pg./mL within 1 week after surgery [16]. The rate of severe hypocalcemia was 23.3% in our study. It appeared that our study included a larger sample size than previous series did [14, 15, 17–20]; thus, our results were more dependable, but a few risk factors we identified were different from those reported previously.

Using the ROC curve analysis of Ca levels at 18 h post-operation for predicting hypocalcemia that needed i.v. Ca gluconate, the maximal Youden index was 0.415 and the optimal cutoff value was 7.6 mg/dL, with sensitivity of 0.72 (95% CI 0.590–0.839), specificity of 0.695 (95% CI 0.620–0.748), and area under the curve 0.749 ± 0.032 (mean ± SE) (95% CI 0.686–0.812) (**Figure 1**); patients who met this criterion should be treated with i.v. Ca gluconate. Previous reports suggested that Ca levels of 7.5–8.0 mg/dL at 18 h post-operation could predict severe hypocalcemia, and our results support this finding [18, 20].

Preoperatively, patients were younger in Group B [50 (40–46)] [median (interquartile range)] than in Group A [58 (52–64)] ($p < 0.001$); serum P, Alk-ptase, and iPTH levels were significantly higher, but serum Ca levels were significantly lower in Group B than those in Group A (**Table 1**). Same findings were reported previously [14, 15]. There were no significant differences between the two groups in terms of sex, symptoms, body weight, and duration of dialysis (**Table 1**). The amount of blood loss during surgery was not significantly different between the two groups. The operation time, total weight of removed parathyroid glands, duration of post-operative hospitalization (days), and total amount of i.v. Ca gluconate administered were significantly more, but calcium levels at 18 h post-operation were significantly lower in Group B than in Group A ($p = 0.014$, $p = 0.035$, $p < 0.001$, $p < 0.001$, and $p < 0.001$, respectively) (**Table 2**).

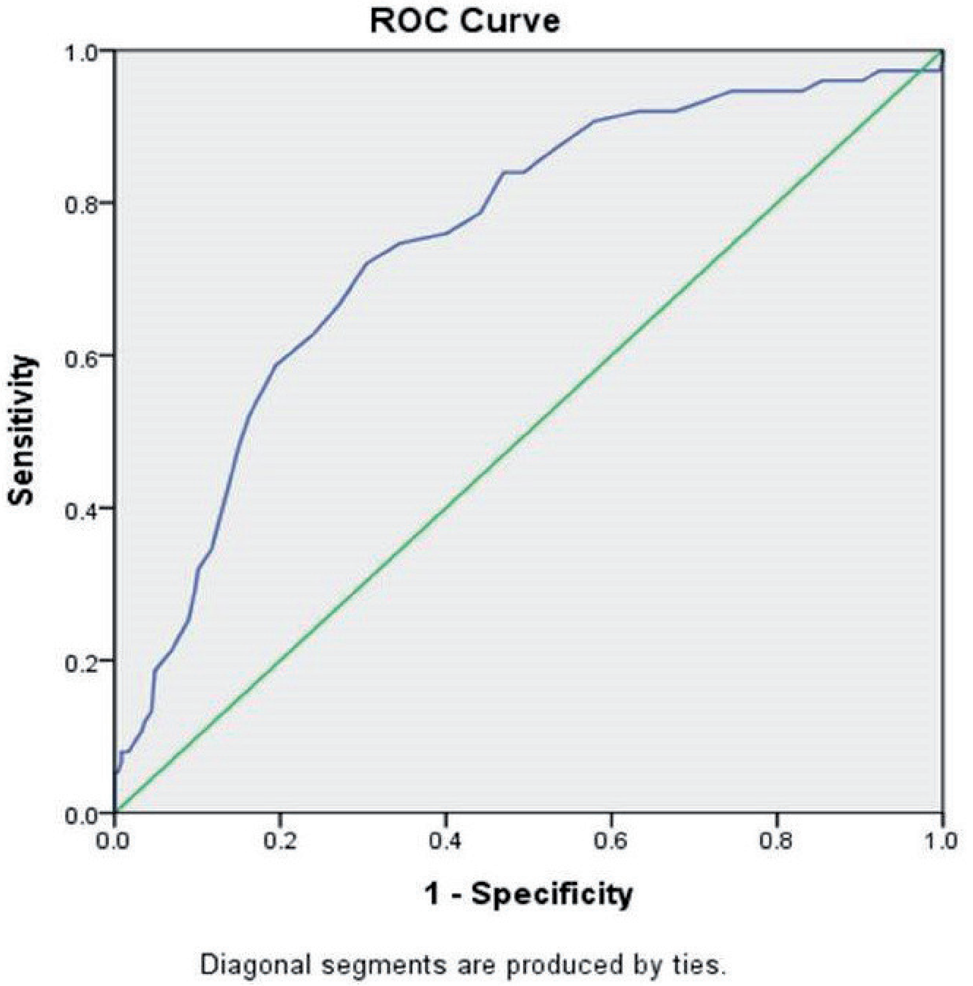

Figure 1.
Using receiver operating characteristics (ROC) curve, maximal Youden's index = 0.415, sensitivity = 0.72, 1-specificity = 0.305, area under curve = 0.749 ± 0.032 (SE), 95% confidence interval = 0.686–0.812, and optimal cutoff calcium value = 7.6 mg/dL (at 18 h post-operation) to predict severe hypocalcemia.

We believe that younger patients have better bone-formation abilities than older patients; thus, they are more likely to have severe hypocalcemia after parathyroidectomy [15, 21, 22].

In our study, severe hypocalcemia occurred in 75 patients (23.3%), which is lower than the rates (27.4–97%) reported previously, likely owing to the definition of severe hypocalcemia [15, 20–22].

We found that mean preoperative Ca levels were lower in Group B than in Group A but Alk-ptase levels in Group B were higher than in Group A (**Table 3**). The cause was not very clear, but this had also been reported previously [15, 20–22].

Before patient discharge, Ca levels in Group B were lower than in Group A, but Alk-ptase levels in Group B were higher than in Group A (**Table 3**). Although it was unclear whether serum Ca levels in patients with severe hypocalcemia remained significantly lower throughout the year after operation, as reported previously [15], we found that all patients in our study could maintain Ca levels >8.0 mg/dL after 3 months with the use of oral Ca carbonate <3 g/day and calcitriol <0.5 μg/day. We speculated that the autotransplanted parathyroid tissue might start to function 1–3 weeks later, as reported previously [23].

Preoperative P levels were higher in Group B than in Group A, which had rarely been reported previously [24].

High Alk-ptase levels are characteristic of bone diseases involving increased osteoblastic activity, bone formation, and resorption in secondary

[Normal ranges]	Group A (N=247) Mild hypocalcemia	Group B (N=75) Severe hypocalcemia	p
Age	58 (52–64)	50 (40–64)	<0.001
Sex M/F	96/151	37/38	0.111*
Skin itching (+/-)	161/86	54/21	0.328*
Bone pain (+/-)	176/71	53/22	1.0*
General weakness (+/-)	121/126	32/43	0.358*
Insomnia (+/-)	154/93	44/31	0.590*
Body weight (kg)	57.1 (49.9–64.9)	59.2 (52.5–69.9)	0.122
Duration of hemodialysis (years)	10 (6.8–13) (N=207)	8.0 (5.8–11.3) (N=58)	0.205
Duration of peritoneal dialysis (years)	6.0 (4.3–8.8) (N=40)	7.0 (5.0-9.5) (N=17)	0.629
Ca [7.9-9.9 mg/dL]	10.4 (10–10.9)	10.3 (9.5–10.7)	0.007
P [2.4-4.7 mg/dL]	5.6 (4.6–6.7)	6.4 (5.7–7.1)	<0.001
Alk-ptase [28-94 IU/L]	141 (99–228)	227 (169–420)	<0.001
iPTH [14-72 pg/mL]	1298 (1025–1750)	1740 (1295–2359)	<0.001

**Using X^2-test.*
Using Mann-Whitney U test.
All data = median (interquarter range) (IQR).
Alk-tase = alkaline phostaphatase.
iPTH = intact parathyroid hormone.

Table 1.
Age, sex, symptoms, body weight, duration of dialysis and preoperative serum calcium (Ca), phosphorus (P), Alkaline-phosphatase (Alk-ptase) and intact parathyroid hormone (iPTH) levels. Comparison between mild hypocalcemia (Group A) and severe (Group B) hypocalcemia groups.

	Group A (N=247) Mild hypocalcemia	Group B (N=75) Severe hypocalcemia	p
Blood loss (cc)	15 (10–20)	17.5 (10–21)	0.560
Operation time (min)	131 (117–156)	145 (122–166)	0.014
Total weight of removed parathyroid glands (g)	3.3 (2.3–4.8)	3.8 (2.8–5.4)	0.035
Days of postoperative hospitalization	5 (5–5) 5.0 ± 1.1	5 (5–8) 6.4 ± 2.5	<0.001 <0.001*
Total i.v. Ca gluconate (g)	0 (0–0)	12 (8–18)	<0.001
Ca levels 18 h after operation	8.2 (7.5–8.8)	7.2 (6.6–7.8)	<0.001

**Using Student't test.*
Using Mann-Whitney U test.
Data = median (interquarter range) (IQR).
Data = mean±SD (standard deviation).

Table 2.
Blood loss during surgery, operation time, total weight of removed parathyroid glands, days of postoperative hospitalization and total intravenous (i.v.) Ca gluconate and Ca levels at 18 h post-operation. Comparison between mild (Group A) and severe (Group B) hypocalcemia groups.

hyperparathyroidism. Preoperative Alk-ptase levels were higher in Group B than in Group A. We found that preoperative Alk-ptase levels were an independent risk factor for severe hypocalcemia, similar to previous reports [14, 15, 17–19, 24].

After TPX & BT plus AT, Alk-ptase levels increased progressively, reflecting increased bone formation, which peaked at 2 weeks [15] and decreased gradually

[Normal ranges]	Group A (N = 247) Mild hypocalcemia	Group B (N = 75) Severe hypocalcemia	p
Ca [7.9–9.9 mg/dL]	7.3 (6.8–7.9)	7.0 (6.6–7.7)	0.013
P [2.4–4.7 mg/dL]	4.0 (3.2–5.1)	4.1 (3.2–4.9)	0.958
Alk-ptase [28–94 IU/L]	192 (113–343)	349 (191–636)	<0.001
iPTH [14–72 ng/mL]	8.8 (2.9–16.4)	10.1 (2.8–20.6)	0.343

Using Mann-Whitney U test.
All data = median (interquarter range) (IQR).

Table 3.
Serum calcium (Ca), phosphate (P), alkaline phosphatase (Alk-ptase) and intact parathyroid hormone (iPTH) levels at the day of discharge. Comparison between mild (Group A) and severe (Group B) hypocalcemia groups.

Risk factors unit	Coefficient	p	Odds ratio	95% CI
Age 1year	−0.045	=0.001	0.956	0.931–0.982
Ca 1 mg/dL	−0.520	0.007	0.595	0.409–0.866
Alk-ptase 1 IU/L	0.003	<0.001	1.003	1.001–1.004
Operation time 1 min	0.010	0.016	1.010	1.002–1.018

Using binary logistic regression test.
Ca = calcium levels.
Alk-ptase = alkaline phosphatase.

Table 4.
Risk factors of severe hypocalcemia after total parathyroidectomy plus auto transplantation.

to normal levels at 3 months post-operation (**Table 4**). Before patients were discharged in our series, the mean Alk-ptase level was still higher in Group B than in Group A showing that oral Ca carbonate and calcitriol should be continually administered for 2 weeks to 3 months, according to serum Ca levels [15].

Preoperatively, high iPTH levels were a clear indicator of the severity of renal hyperparathyroidism and bone disease. Preoperatively, high iPTH levels increased both bone formation and bone resorption; after parathyroidectomy, bone resorption would decrease and bone formation would increase; thus, severe hypocalcemia could develop after surgery [14, 22, 24].

We found that the total weight of the removed parathyroid glands was more in Group B than in Group A, as was the operation time. The total weight of parathyroid glands and the operation time contributed to severe hypocalcemia, might be due to advance disease and extensive dissection during surgery, but were rarely reported before [20, 25, 26].

Multi-variant binary logistic regression test showed that young age, low preoperative Ca levels, high preoperative Alk-ptase levels, and long operation time were independent risk factors for severe hypocalcemia, with associated odds ratio of 0.956, 0.595, 1.003, and 1.010, respectively (p = 0.001, p = 0.007, p < 0.001, and p = 0.016, respectively) (**Table 4**).

In our study, Ca levels were negatively correlated with P levels (r = −0.255, p < 0.001), and Alk-ptase levels were positively correlated with iPTH levels (r = 0.449, p < 0.001); therefore, preoperative Ca and Alk-ptase levels were finally identified as independent risk factors for severe hypocalcemia combined with young age and long operation time.

4. Treatment of severe hypocalcemia with our algorithm

Cozzolino et al. [27, 28] proposed a dose corresponding to the rate of 1–2 mg/kg/h for i.v. Ca gluconate, which could be increased or decreased by 25–50% from the initial value. Loke et al. [17] developed a titration regimen in which a 10% Ca gluconate infusion was started at 4.5 mL/h when serum Ca levels were < 8 mg/dL and then increased to 6.5 mL/h and finally to 9.5 mL/h if Ca levels continually declined. The algorithms they proposed were too complicated for clinical applications, and therefore, we modified it into our clinical algorithm (**Figure 2**). We adopted the clinical algorithm developed by Cozzolino et al. [28], with some modifications.

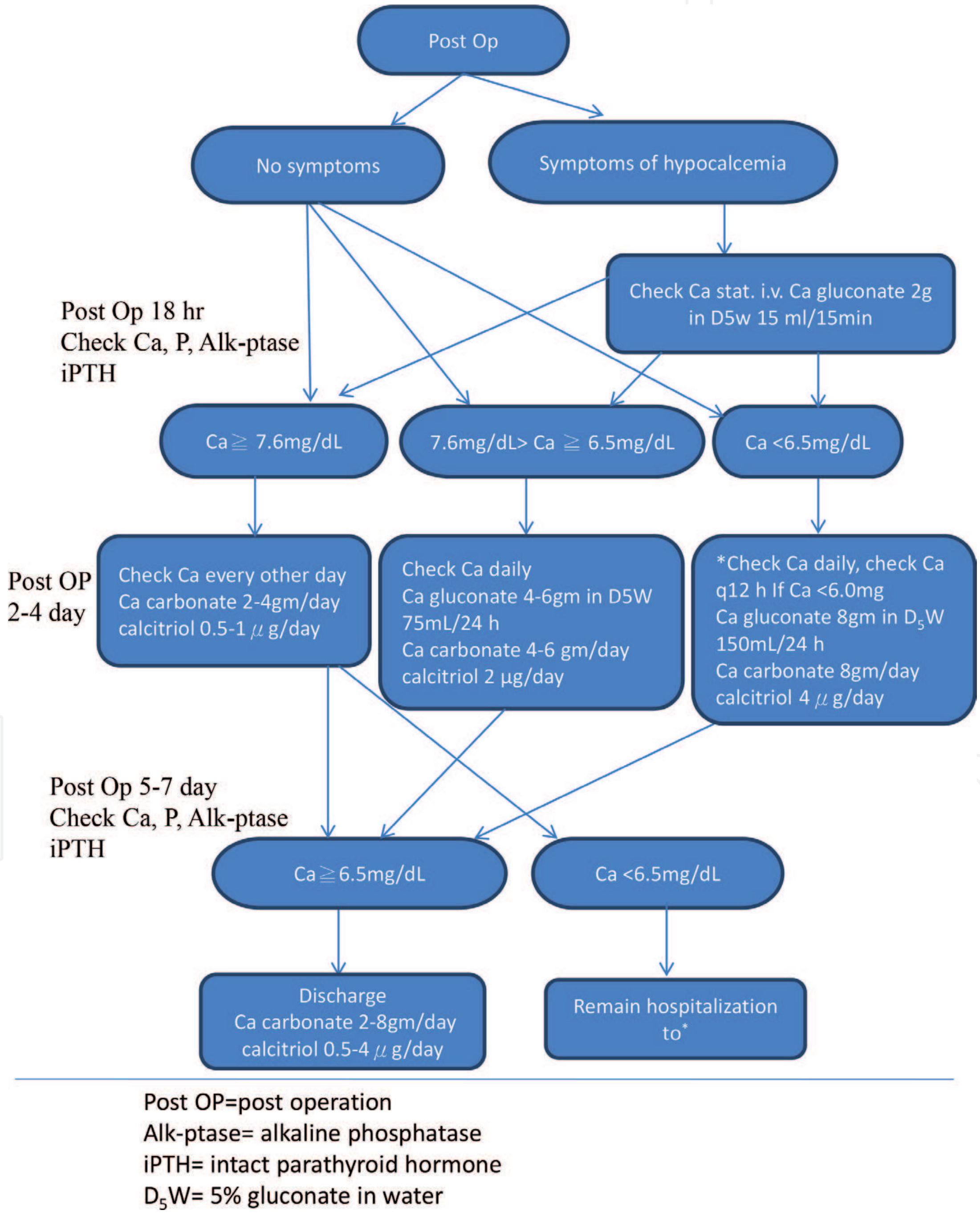

Figure 2.
The clinical algorithm for the treatment of hypocalcemia after total parathyroidectomy plus autotransplantation for secondary hyperparathyroidism.

At 18 h post-operation, Ca, P, and iPTH levels were checked to ensure that the operation had been successful and the levels of iPTH were < 72 pg/mL and P levels were above the normal lower limit (2.4 mg/dL).

If serum Ca levels were > 7.6 mg/dL at 18 h post-operation, oral Ca carbonate 2–4 g/day and calcitriol 0.5–1 μg/day were administered; Ca levels were checked on alternate days.

If serum Ca levels were ≤7.6 mg/dL and >6.5 mg/dL at 18 h post-operation, i.v. Ca gluconate (10%) 4–6 g in 75 mL of 5% glucose in water (D5W) or normal saline was administered for 24 h, concomitant with oral Ca carbonate 4–6 g/day and calcitriol 2 μg/day; Ca levels were checked daily.

If serum Ca levels were ≤6.5 mg/dL at 18 h post-operation, i.v. Ca gluconate 8 g in 150 mL D5W was administered for 24 h, concomitant with oral Ca carbonate 6–8 g/day and calcitriol 4 μg/day; Ca levels were checked daily except Ca levels <6.0 mg/dL. In that situation, Ca levels were checked every 12 h until they reached levels ≥6.0 mg/dL.

If patients had symptoms and signs of hypocalcemia, such as paresthesia of the mouth and extremities, muscle spasms, Chvostek's sign, Trousseau's sign, seizure, tetany, EKG abnormalities, arrhythmia, and hypotension, Ca levels were checked immediately and i.v. Ca gluconate 2 g in 15 mL D5W was administered in 15 min; Ca levels were then checked as usual and treated accordingly (**Figure 2**).

At 5–7 days post-operation, if patients' Ca levels were > 7.6 mg/dL, they were discharged with oral calcium carbonate 2–4 g/day and calcitriol 0.5–2 μg/day.

If Ca levels were stable and ≥ 6.5 mg/dL, they were discharged with oral Ca carbonate 6–8 g/day and calcitriol 4 μg/day. If Ca levels were < 6.5 mg/dL, they were kept in hospitalization and treated as per the clinical algorithm (**Figure 2**).

Following the clinical algorithm post-operatively, we administrate i.v. Ca gluconate 4–6 g in 75 mL D5W or normal saline in 24 h for patients with Ca levels <7.6 mg/dL, Ca gluconate 8 g/day in 150 mL D5W or normal saline in 24 h for patients with Ca levels <6.5 mg/dL, and i.v. Ca gluconate 2 g/15 mL D5W or normal saline in 15 min for patients with symptoms and signs of hypocalcemia. More concentrated solution for continuous infusion should be infused via central line [29]. Either 10% Ca gluconate (40 mg of elemental calcium per 10 mL) or 10% Ca chloride (270 mg of elemental calcium per 10 mL) can be used to prepare the infusion solution. Ca gluconate is preferred because it causes less tissue necrosis if extravasated [30]. The amount of i.v. Ca gluconate is adjusted by serum Ca levels and duration (days), neither by patients' body weight nor i.v. speed.

The K/DOQI guidelines and others suggest that serum Ca levels should be measured every 4–6 h post-operation [27, 31], but according to our experience and some other authors [28], this is not necessary except when Ca levels are <6.0 mg/dL. In such cases, we measured Ca levels every 12 h, until they were stable and reached ≥6.0 mg/dL.

5. Duration of hospital stay

In our study, the duration of post-operative hospital stay of Group A (5.0 ± 1.1 days) (mean ± SD) was significantly shorter than that of Group B (6.4 ± 2.5 days, $p < 0.001$). The duration of post-operative stay in our series was shorter than that reported previously: 7.8 ± 2.9 days (mild hypocalcemia) versus 9.3 ± 3.9 days (severe hypocalcemia) according to Yang et al. [14] and 10.2 ± 2.3 days (mild hypocalcemia) versus 15.6 ± 6.6 days (severe hypocalcemia) according to Ho et al. [15]. It was obvious that the duration of post-operative stay in our series was 3–5 days shorter than that from previous reports of severe hypocalcemia, suggesting that the clinical algorithm we adopted was acceptable.

Causes	Mild hypocalcemia (Post-Op days)	Severe hypocalcemia (Post-Op days)
Pancreatitis	1 (24)	
Bloody stool		1 (27)
Sepsis		1 (19)
Brain infarction	1 (30)	
Hypocalcemia [gastritis]		1 (3)
[Combined with heart failure]		1 (2)
Cellulitis [lower extremity]		1 (4)

No surgical mortality.
3 months after parathyroidectomy, no one needs calcium carbonate more than 2 g/daily or calcitriol more than 0.5 μg/day to keep calcium levels over 8.0 mg/dL.

Table 5.
Causes of readmission within one month post operation (Post-Op).

6. Readmission rate

A total of 2756 parathyroidectomy procedures were performed in patients with CKD, with unplanned readmission rate of 17.2 and 6.8% due to hypocalcemia/hungry bone syndrome. In one study, readmission occurred within 30 days after discharge, but readmission for severe hypocalcemia peaked within just 10 days and decreased thereafter [32].

Post-parathyroidectomy readmission rates for patients with CKD are five times higher than those for general population [32]. Using routing AT in our series, we found that seven patients (2.1%) underwent readmission due to various causes, and only two of them were due to hypocalcemia. One patient was readmitted 3 days after discharge due to gastritis, and the other at 2 days due to hypocalcemia and heart failure. However, no mortality was observed in our series (**Table 5**).

7. Conclusions

After successful TPX & BT plus AT for secondary hyperparathyroidism, severe hypocalcemia occurred in 23.3% of patients in our series. The risk factors for severe hypocalcemia were young age, low preoperative Ca levels, high preoperative Alk-ptase levels, and long operation time. Serum Ca levels <7.6 mg/dL at 18 h post-operation were the optimal cutoff value for hypocalcemia that needed i.v. Ca gluconate. When the suggested clinical algorithm was followed, the mean duration of post-operative hospital stay due to severe hypocalcemia was short (6.4 ± 2.5 days) and readmission rate (0.62%) due to hypocalcemia was quite low.

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