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Comparison of Calcium, Phosphate and Intact Parathyroid Hormone Levels Pre- and Post-Parathyroidectomy Among End Stage Renal Disease Patients in Kelantan: An Analysis of the Malaysian Dialysis and Transplant Registry Data

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Abstract: Introduction: Parathyroidectomy is the treatment of choice in patients with severe hyperparathyroidism associated with hypercalcemia and / or hyperphosphatemia that is refractory to medical therapy. After the surgery, serum calcium and intact parathyroid hormone levels are expected to reduce rapidly with necessary calcium replacement while serum phosphate levels gradually decrease for a few months post-operatively. The objective of this study is to compare the pre- and post-operative values of serum calcium, serum phosphate and intact parathyroid hormone levels in end stage renal disease (ESRD) patients who underwent parathyroidectomy.

Methods: A cross-sectional study was done using data obtained from Malaysian Dialysis and Transplant Registry involving 40 ESRD patients in Kelantan who were diagnosed with secondary or tertiary hyperparathyroidism and underwent parathyroidectomy from 1997 to 2012.

Results: The median (IQR) serum calcium level following parathyroidectomy was within acceptable range [2.3 (0.2) mmol/l vs 2.2 (0.5) mmol/l, p=0.01]. The mean (SD) serum phosphate level also displayed the same declining pattern but the figure remained on the higher side [2.2 (0.4) mmol/l vs 1.9 (0.4) mmol/l, 95% CI -0.5,-0.2, p<0.001]. There was a statistically significant median (IQR) intact parathyroid hormone level pre- and post-parathyroidectomy reduction in post-operative value [757.1 (586.4) pg/ml vs 99.3 (381.1) pg/ml, p<0.001].

Conclusion: Parathyroidectomy effectively reduced intact parathyroid hormone levels while maintaining serum calcium values within the normal range. Despite the surgery, patients continued to have high levels of serum phosphate.

Keywords: Parathyroidectomy, end stage renal disease, serum calcium, serum phosphate, intact parathyroid hormone.

Introduction

Secondary hyperparathyroidism (SHPT) is a common manifestationof long term effect in patients with chronic kidney disease (CKD)[1-4]. Levels of parathyroid hormone (PTH) increase as CKD progresses and lead to high prevalence of SHPT among end stage renal disease (ESRD) patients. Hypocalcemia, vitamin D deficiency and hyperphosphatemia are hallmarks of CKD and physiologically stimulate the PTH secretion. Patients with SHPT develop a broad range of symptoms and complications which are associated with high risk of morbidity and mortality. Its serious clinical consequences encompassa spectrum of renal osteodystrophy, calciphylaxia, alterations in cardiovascular structure and function, immune dysfunction as well as renal anemia[1-6].

Intact parathyroid hormone (iPTH) assay is widely used to estimate active PTH level, which is an important indicator for SHPT[1,4,7]. Based on the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI), the target range for biochemical markers in dialysis patients are 2.10–2.37 mmol/l for serum calcium, 1.13–1.78 mmol/l for serum phosphate and 150–300 pg/ml for iPTH[1].

The available therapeutic measures for the treatment of SHPT are mainly comprise of dietary phosphate restriction, administration of calcium supplement, phosphate binders and therapy with vitamin D sterols[1,4,9-11]. Over the years, the management of hyperparathyroidism has expanded to a variety of new vitamin D analogues, calcimimetics as well as aluminium-free, calcium-free phosphate binders[10,12]. For those who fail medical therapy, parathyroidectomy (PTX) is the treatment of choice which includes subtotal or total PTX, with or without implantation of parathyroid tissue[1,8,12,13].

A strong indication for PTX in CKD patients is severe hyperparathyroidism with persistent iPTH levels of more than 800 pg/ml associated with hypercalcaemia and/or hyperphosphataemia despite medical therapy[1,4]. Apart from that, patients who have hyperparathyroidism presented withcalciphylaxis, fractures, bone pain or pruritus are also candidates for PTX[4,8,13]. There also has been a trend to consider surgical intervention in SHPT with enlarged parathyroid glands of more than 500 mg or 1000 mg as they usually have nodular hyperplasia and are less likely to respond to medical treatment[9,13-15].

Experimental

Objectives:

The primary objective of this study is to compare pre- and post-operative levels ofserum calcium, serum phosphate and iPTH in ESRD patients who underwent PTX.

Methods And Materials:

This was a cross-sectional study done based on data obtained from Malaysian Dialysis and Transplant Registry involving 40 ESRD patients in Kelantan who were diagnosed with SHPT and underwent PTX from 1997 to 2012.Apart from patient demographics, data which were taken into account include pre- and post-operative levels of serum calcium, serum phosphate and iPTH.

Statistical Analysis:

Statistical analysis was performed using IBM Statistical Package for the Social Sciences (SPSS), version 20.0. Continuous variables were expressed as mean and standard deviation (SD)or median and interquartile range (IQR) while categorical variables were reported as frequency with percentage. Pre- and post-parathyroidectomy measurements were compared using paired t-test for normally distributed data and Wilcoxon-signed rank test for skewed data. All statistical tests with p-value <0.05 were considered significant.

Results

Between 1997 and 2012, a total of 40 ESRD patients in Kelantan underwent PTX due toSHPT resistant to medical therapy. The mean age of study participants was 50 $\pm$ 13.1 years old with 29(72.5%) were males and11 (27.5%)were females. The majority of the subjects were Malays (n=39, 97.5%) and the remaining 1 patient was Chinese.

An evaluation was done regarding the medications received by study subjects before undergoing PTX (Figure 1). It was found that 31 patients were on Calcium carbonate with Calcitriol, 7 subjects were prescribed with Calcium carbonate alone, 1 participant received Lanthanum carbonate plus Calcitriol and 1 patient was given Lanthanum carbonate alone (77.5%, 17.5%, 2.5% and 2.5% respectively). There were 32(80.0%) patients were prescribed with vitamin D supplement before the surgery. The results showed that patients who took vitamin D supplement had significant higher median(IQR) iPTH levels compared to those without [841.0 (637.3) vs 447.7 (313.5), p=0.02] (Table I). They also had lower mean (SD) serum calcium [2.3 (0.2) mmol/l vs 2.4 (0.2) mmol/l, p=0.344] and higher mean (SD) serum phosphate levels [2.2 (0.4) mmol/l vs 2.1 (0.6) mmol/l, p=0.489] but the differences were not significant (Table II).

PTX managed to decrease iPTH levels as there was a statistically significant median (IQR) iPTH reduction in post-operative value [757.1 (586.4) pg/ml vs 99.3 (381.1) pg/ml, $p<0.001$] (Table III). The differences between median (IQR) serum calcium and mean (SD) serum phosphate levels pre- and post-PTx were statistically significant but not clinically important. The median (IQR) serum calcium level following surgery was within acceptable range [2.3 (0.2) mmol/l vs 2.2 (0.5) mmol/l, $p=0.01$] (Table III). The mean (SD) serum phosphate level also displayed the same declining pattern but the figure remained on the higher side [2.2 (0.4) mmol/l vs 1.9 (0.4) mmol/l, 95% CI -0.5,-0.2, $p<0.001$] (Table IV).

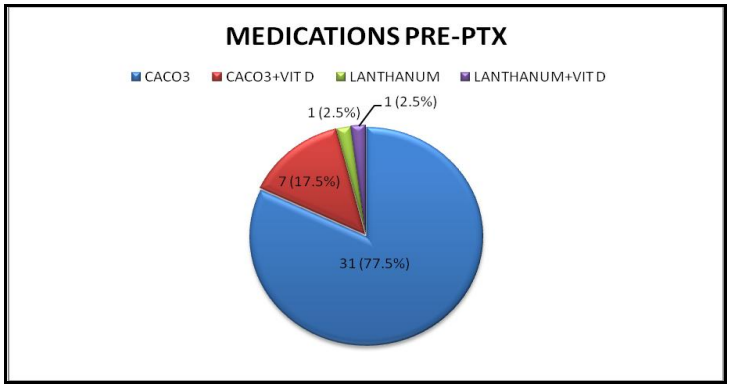

Figure 1: Medications prescribed for study subjects before PTX(n=40).

Table I: Comparison of median(IQR) iPTH levels pre-PTX based on medications prescribed (n=40).

Variables	Median (IQR)		Z stat[a]	*p*-value
	Patients on Vitamin D supplement (n=32)	Patients not on Vitamin D supplement (n=8)		
iPTH	841.0(637.3)	447.7(313.5)	-3.145	0.002

[a]Mann-Whitney U test

Table II: Comparison of mean(SD) serum calcium and serum phosphate levels pre-PTX based on medications prescribed (n=40).

Variable	Mean(SD)		Mean level difference (95% CI)	t-statistic (df)	*p*-value*
	Patients on Vitamin D supplement(n=32)	Patients not on Vitamin D supplement (n=8)			
Serum calcium	2.3(0.2)	2.4(0.2)	-0.1 (-0.2, 0.1)	-0.957 (38)	0.344
Serum phosphate	2.2(0.4)	2.1(0.6)	0.1 (-0.2, 0.5)	0.699 (38)	0.489

*Independent t-test; equal variances assumed

Table III: Comparison of median(IQR) serum calcium and iPTH levels pre- and post-PTX (n=40).

Variables	Median(IQR)		Z stat[a]	*p*-value
	Pre-level	Post-level		
Serum calcium	2.3(0.2)	2.2(0.5)	-3.238	0.001
iPTH	757.1(586.4)	99.3(381.1)	-4.906	< 0.001

[a]Wilcoxon Signed Rank test

Table IV: Comparison of serum phosphate levels pre- and post-PTX (n=40).

Variable	Mean (SD)		Mean level difference (95% CI)	t-statistic (df)	*p*-value*
	Pre-level	Post-level			
Serum phosphate	2.2 (0.4)	1.9 (0.4)	-0.3 (-0.5, -0.2)	-4.203(39)	< 0.001

*Paired t-test; normality assumption is assumed

Discussion

PTX has become a topic of interest among investigators over the years. Previous studies have reportedthat higher PTX rates were associated with younger age and female gender[17-19]. It is surprising, however, that subjects who underwent PTX in our setting were mostly male with the mean age of 50 ± 13.1 years old.

Conventional therapies for SHPT include phosphate binders, calcium and vitamin D supplements[1,4,10,11]. Calcium salts are used as phosphate-binding drugs with the most common being calcium carbonate[4,11,19-23]. Documentations pertaining to the use of calcitriol as one of vitamin D supplements have been around ever since 1980s[24-27]. This could be the reason why most of our subjects were prescribed with calcium carbonate and calcitriol before the surgery. However, this treatment is restricted by several factors especially the presence of extreme hypercalcaemia and hyperphosphataemia. This is due to the fact that calcium salts and vitamin D carry the risk of aggravating both conditions[4,11,28-31].

We found that patients who took vitamin D had significant higher iPTH levels compared to those without. However, the differences of serum calcium and phosphate levels between both groups were not significant. The results appeared to contradict other works done in the past such as by de Francisco and Carrera who noted that vitamin D supplements effectively suppress the production of iPTH but may lead to biomarkers imbalances[5]. Locatelli and his team had highlighted in their consensus that administration of vitamin D was useful in normalizing iPTH levels, given that the serum phosphate is within normal limits[23]. It is already known that calcitriol reduces iPTH by directly inhibiting its gene transcription. Calcitriol also induce the absorption of calcium by the intestines which elevates serum calcium in patients[32-34]. Therefore, we believed that the condition was a consequence of prescribing calcitriol at the later stage of the disease in which patients had already developed severe secondary hyperparathyroidism. However, it was impossible to determine the timing and duration of calcitriol given in our study due to the nature of registry analysis.

However, not all patients can be successfully treated with medical therapy and eventually require surgical intervention. PTX is considered as the last resort when all else fails[1,8,12,13]. In literature, it is clearly portrayed that patients experience benefits from PTX[13,32,35]. The operative procedure is proven to relieve symptoms and correct the biochemical parameters among patients with uncontrolled SHPT[8,13,32,35].

Following surgery, Tominaga et al. noted that iPTH levels plummeted while serum calcium and serum phosphate normalized among patients undergoing PTX in Japan[8,13].A comparative study was conducted in United States by Konstantinidis et al. between PTX and continued medical treatment (MTX) groups revealed that PTX patients had an overall improvement of their condition[32]. Similar findings were also reportedby Kestenbaum and colleagues who summarized that PTXresulted in a dramatic drop of iPTHlevel which subsequently reduced patient's clinical symptoms and mortality[17]. It was noted that our study population also displayed a significant reduction of iPTH level among patients after PTX.

However, our findings for serum calcium and serum phosphate were inconsistent with those reports. Even though our patients who underwent PTX showed a declining pattern in all biochemical parameters, the pre- and post-operative levels for serum calcium were within acceptable range. The best possible explanation was that patients were prescribed with calcium supplement before and after the intervention and that the dose was adjusted based on regular calcium level monitoring. Post-operative patients are always monitored closely as it is expectedserum calcium will decrease rapidly. After surgery, some patients are put on parenteral calcium gluconate infusion immediately besides oral calcium supplement[1].

Our study also showed that even though there was a reduction of serum phosphate after operation, the figure remained on the higher side. We assumed that the dietary restriction of high phosphate products in these patients was not well-managed. Dietary phosphate restriction has an important role in controlling the development of hyperparathyroidism[36-38] and inhibiting parathyroid cells proliferation as well as slowing down the progression of renal failure and soft tissue calcification[39]. However, it is difficult to achieve as phosphorus is so omnipresent in multitudes of foods[4,40,41].

As a conclusion, it was observed in this study that physician decision to start patients with vitamin D supplement was probably depended on intact parathyroid hormone levels, regardless of serum calcium and serum phosphate values. Calcium carbonate was widely used as phosphate binder while only a minority of the subjects was prescribed with Lanthanum carbonate. In case of parathyroidectomy, it effectively reduced iPTH levels while maintaining serum calcium values within the normal range. Despite the surgery, patients continued

to have high levels of serum phosphate. The major drawback of this work was that it was a retrospective analysis with a small sample size in a single-center setting. Therefore, any conclusions maybe limited in their implications as we were unable to retrieve detailed information on the patients' medications and diet.

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