Parathyroid Hormone as a Marker for Predicting the Severity of Hypocalcaemia Following Parathyroidectomy

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Abstract The purpose of this study is to determine preoperative predictors of the severity of the hypocalcaemia following parathyroidectomy. The case records of 70 patients who underwent parathyroidectomy for primary hyperparathyroidism from 2000 to 2013 was retrospectively studied. Their symptoms at presentation, biochemical parameters serum calcium, parathyroid hormone, alkaline phosphatase and parathyroid size on ultrasound were compared with their serial post-operative serum calcium levels at 24, 48, 72 and 96 h. For the purpose of analysis, patients were divided into three groups. Group 1—asymptomatic, biochemically normal (serum calcium always ≥ 8.5 mgs%); Group 2—asymptomatic, biochemically below normal (at least one reading < 8.5 , but none < 8.0); Group 3—symptomatic (any one reading < 8.0). No correlation was found between the severity of the presenting symptoms, pre-operative serum calcium levels or the parathyroid size with the post-operative calcium levels in the three groups. Though preoperative serum alkaline phosphatase levels were higher in Group 3, it was not statistically significant ($p = 0.069$). However, preoperative serum parathyroid hormone levels significantly correlated with

postoperative serum calcium levels in all three groups ($p = 0.006$). Pre-operative serum parathyroid hormone levels may serve as a marker for severe post-operative hypocalcaemia and thus identify patients requiring closer monitoring and longer hospitalization following parathyroidectomy.

Keywords Parathyroid · Hypocalcaemia · Parathyroid hormone · Parathyroidectomy · Primary hyperparathyroidism

Introduction

Primary hyperparathyroidism (PHP) is a generalized disorder of calcium metabolism due to an increased level of parathyroid hormone resulting in abnormally high levels of serum calcium and surgery remains the most effective treatment for hyperparathyroidism. Hypocalcaemia is a common sequel after surgery for primary hyperparathyroidism. In most cases it is transient and self-limiting. Occasionally the hypocalcaemia can be severe and sustained and such patients require close monitoring and prolonged hospitalization. The consequences of significant post operative hypocalcaemia (POH) can be potentially serious and it is clinically useful if we have some means of reliably predicting its occurrence so that appropriate preventive protocols can be devised. The purpose of this study was to identify patients at risk for significant hypocalcaemia after parathyroid surgery.

Materials and Methods

The case records of 70 patients who underwent parathyroidectomy for primary hyperparathyroidism from 2000 to 2013 in our institution were retrospectively studied.

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Their symptoms at presentation, preoperative biochemical parameters of serum calcium, parathyroid hormone (PTH), and alkaline phosphatase (ALP) and parathyroid size on ultrasound were compared with their serial post-operative serum calcium levels at 24, 48, 72 and 96 h.

Calcium and alkaline phosphatase were done on Dimension RxL Max (Siemens) using o-cresolphthalein complexone (OCPC) and enzymatic method respectively.

PTH was analyzed using chemiluminescence method on Immulite 1000 (Siemens).

The symptoms at the time of presentation were divided into none (asymptomatic patients diagnosed incidentally during routine evaluation), mild (weakness, generalized body pains), moderate (chronic pains, pain in joints, dysuria) and severe (bilateral/recurrent renal calculi, osteoporosis, multiple fractures, brown tumors of bone, duodenal ulcer, psychosis).

For the purpose of analysis, patients were divided into three groups post surgery.

- Group 1 Patients who were asymptomatic post-operatively and had biochemically normal post operative serum calcium always ≥ 8.5 mgs (n = 36).
- Group 2 Patients who were asymptomatic post-operatively but had at least one biochemical reading of post operative serum calcium levels < 8.5 , but none < 8.0 (n = 20).
- Group 3 Patients who were clinically symptomatic post-operatively (tingling, cramps, positive chvostek's/trousseau's sign) and/or had any one reading of post operative serum calcium level < 8.0 (n = 12).

Two patients whose biochemical parameters were from other laboratories were excluded from the study to avoid possible inter-instrumental variation.

The symptoms at presentation and the pre-operative parameters (serum calcium, ALP, PTH, size of parathyroid on USG) of these three groups (Groups 1, 2 and 3) were compared for statistical significance using Moode's median test and 1 proportion test.

Results

Table 1 gives the break-up of patients in the three groups based on their symptoms at presentation.

Of the 68 patients, pre operative serum calcium values was available for 65 patients and in almost all patients by 96 h the post operative serum calcium had stabilized and showing improvement towards normal levels. There was no correlation between pre-operative serum calcium levels and post-operative calcium levels in the three groups.

Table 1 Patients in the three groups based on their symptoms at presentation

Symptoms at presentation	Group 1 (n = 36)	Group 2 (n = 20)	Group 3 (n = 12)
None	3	1	1
Mild	11	7	2
Moderate	14	2	4
Severe	8	10	5

Table 2 shows mean and median of the preoperative calcium, ALP, PTH and tumor size in all the three groups.

Fifty eight patients had pre-op PTH levels available for analysis. The difference in the medians of preoperative PTH levels (278.0, 840.0 and 1519.0 pg/mL in Groups 1, 2 and 3 respectively) was statistically significant ($p = 0.006$).

Fifty six patients had pre-operative ALP levels available in the records with median values of 126.0 IU/L in Group 1, 192.0 IU/L in Group 2 and 358.0 IU/L in Group 3. Although serum ALP levels appeared higher in Group 3, it was not statistically significant ($p = 0.069$).

Coming to the size of the parathyroid on ultrasound examination, 66 out of the 68 patients had this recorded in their case files with size ranging from 10 to 62 mm. Once again the differences in the three groups were not of statistical significance.

Figure 1 depicts the box plot graph comparing medians of the four preoperative parameters with post operative hypocalcaemia.

Table 2 1 proportion test was applied to check if patients need to be attended to post-operatively with calcium supplementation when calcium values are between 8.0 and 8.4 mg/dL (as in Group 2) in spite of being asymptomatic, confirmed the hypothesis ($p = 0.215$)

Pre-op values	Group 1	Group 2	Group 3
Calcium (mg/dL)			
n	34	20	11
Mean $\pm$ SD	12.40 $\pm$ 2.40	12.65 $\pm$ 2.00	12.06 $\pm$ 2.23
Median	11.65	12.00	11.80
ALP (IU/L)			
n	29	17	10
Mean $\pm$ SD	264.3 $\pm$ 371.2	568.0 $\pm$ 782.0	981.0 $\pm$ 1258.0
Median	126.0	192.0	358.0
PTH (pg/mL)			
n	30	18	10
Mean $\pm$ SD	437.7 $\pm$ 403.2	1233.0 $\pm$ 1389.0	1660.0 $\pm$ 1295.0
Median	278.0	840.0	1519.0
Tumor size (cm)			
n	36	18	12
Mean $\pm$ SD	2.32 $\pm$ 1.12	3.14 $\pm$ 1.66	2.73 $\pm$ 1.08
Median	2.00	3.00	2.60

Fig. 1 Box plot showing correlation of medians of serum calcium (a), ALP (b), parathyroid size (c) and PTH (d)

Incidentally, even the two patients who were excluded from the study due to inter-instrumental variation also showed correlation with the findings in the study.

Discussion

Postoperative hypocalcaemia after surgery for primary hyperparathyroidism has an incidence ranging from 0 to 30 % [1]. Transient hypocalcaemia is much more common, complicating 12 % of parathyroidectomies for PHP [2]. Acutely, hypocalcaemia results in neuromuscular irritability which can present as numbness, paresthesia, muscular twitching and cramps. In serious cases, stridor, bronchospasm, cardiac arrhythmias, angina, cardiac failure, syncope, and seizures may occur [2]. It is thought that postoperative hypocalcaemia is related to the acute fall in PTH after surgery which causes a reduction in serum calcium and a corresponding increase in serum phosphate. In some cases where prolonged hyperparathyroidism induces a state

of high bone turnover, the fall in PTH may result in unopposed bone deposition of calcium and phosphate, causing Hungry Bone Syndrome [3] with alarmingly low levels of both serum calcium and phosphates.

Some centers prefer to give postoperative calcium supplementation to all patients following parathyroidectomy. These centers typically deal with early cases and have few or no postoperative symptomatic hypocalcaemia patients and prefer to do parathyroidectomy as day care procedures [4]. A study done by Thomas et al. analyzed whether parathyroid surgery can be done safely as an outpatient procedure. In one series from the United Kingdom, of 50 patients operated in a day-surgery setting, all were discharged with oral calcium of 800 mg twice daily and alfacalcidol 1 µg daily. No patient developed symptomatic hypocalcaemia during the first 2 weeks after surgery, and after replacement was stopped; all patients had normal serum calcium levels at a mean follow-up of 26 weeks [5]. In another study done by Steen et al. a preoperative calcium of <11 mg/dL was associated with an increased risk

of early postoperative hypocalcaemia but not with late hypocalcaemia. Of the patients in their study with postoperative hypocalcaemia, all had normal serum calcium levels by the time of their postoperative office visit several weeks later. This would imply that the majority of patients can be operated on safely in an outpatient setting and that long-term supplementation of calcium should not be necessary, as any postoperative hypocalcaemia after surgery for primary hyperparathyroidism is largely transient [6]. While this practice works well in advanced countries due to early presentation of these patients—most of whom are either asymptomatic or identified during routine evaluation, the scenario is vastly different in our patients and other centers in developing countries. Many patients present with advanced symptoms and large adenomas and develop more severe and protracted hypocalcaemia requiring close monitoring and longer hospitalization. In order to identify such patients, surgeons have tried to define factors that could predict the severity of postoperative hypocalcaemia and identify those patients who may need further monitoring or supplementation. Knowledge of these factors may also benefit surgeons who practice day care parathyroidectomy to identify occasional patients who may need to be informed about the possibility of developing symptomatic hypocalcaemia on discharge and may require to report to the emergency department.

No study has reported a correlation of presenting symptoms with the degree of post operative hypocalcaemia. However it is well known that persistent hypocalcaemia may occur in patients with bone symptoms since recalcification in bone starts after parathyroidectomy and these patients should be treated by oral or intravenous administration of calcium after the operation. Our study also showed that there was no correlation between presenting symptoms and post operative hypocalcaemia and that some of the patients who reported with no symptoms and underwent surgery for incidentally detected hyperparathyroidism also developed post operative hypocalcaemia.

Pre-operative serum PTH levels may correlate to the weight of excised single parathyroid adenomas [7]. Correlation between serum PTH and adenoma weight has been studied by several authors [7–14], as well as serum calcium and adenoma weight [7]. However, results from different studies have been variable. Randhawa et al. [12] observed no relationship between serum calcium and PTH levels and adenoma weight or volume while other studies [7, 13, 14] demonstrated significant correlations between preoperative serum calcium and PTH and adenoma weight. No consensus has been reached, however, on whether parathyroid weight alone can predict postoperative hypocalcaemia. In our study we looked only at the preoperative size of the adenoma on ultrasound and not adenoma weight and found

no correlation between the size and post-operative calcium levels, despite the wide range of adenoma sizes from 1 to 6.2 cm.

Consistent with several studies, our study also showed that there is no correlation between preoperative serum calcium and post operative calcium levels. A study by Westerdahl et al. showed that preoperative normal calcium was an independent predictor of late (>8 weeks later) postoperative hypocalcaemia [7]. Early hypocalcaemia, defined as within 4 days from surgery, was seen in 26 % of patients undergoing surgery for a single parathyroid adenoma [7]. A bilateral neck exploration, a history of cardiovascular disease and hyperparathyroidism due to renal pathology [15] were independent risk factors for the development of early symptomatic hypocalcaemia in this study. The calcium levels in most of these patients normalized in 8 weeks. Loke et al. [16] in a retrospective study on 29 patients showed a strong relationship between ALP and trough serum calcium, and those patients with a pre-operative ALP <340 U/L are unlikely to have symptomatic POH (100 % sensitivity, 95 % specificity). Our study did indicate that serum ALP levels were generally higher in those with severe POH, but did not show statistical significance.

A prospective study done by Kald et al. on 156 patients predicted severe postoperative hypocalcaemia with a sensitivity of 100 % and specificity of 66 % [8]. With an increase in the cut off serum PTH concentration from 25 to 35 pmol/L specificity was maintained at 100 % with an increased sensitivity of 74 %. Of great importance is a negative predictive value of 100 % meaning that if a patient did not have any of the predictive factors present there was no risk of becoming severely hypocalcaemic. Patients with risk factors for severe postoperative hypocalcaemia were divided into two groups. A “higher risk group” defined by a preoperative PTH levels >35 pmol/L (five times the upper reference value) and a “lower risk group” with PTH < 35 pmol/L. The majority of the patients suffering severe postoperative hypocalcaemia belonged to the former group. The relatively high risk for severe postoperative hypocalcaemia among these patients (41 %) suggests that they should undergo in-hospital surveillance until the serum calcium level has stabilized to an acceptable level with or without calcium and/or vitamin D supplementation. The significance of increased levels of PTH have previously been shown in patients with postoperative hungry bone syndrome, whilst serum concentration of calcium measured preoperatively seems to underestimate the presence of advanced disease in patients in whom the bones are affected [1, 10].

Our study similar to Kald et al. [9] showed statistically significant correlation between pre-operative serum PTH and fall in post operative calcium causing POH. Going by

the mean PTH values in the three groups, one could surmise that patients whose pre operative serum PTH levels was, in general, below 500 pg/mL would be asymptomatic post-operatively with calcium levels well within normal range and could be discharged immediately, provided they did not suffer severe bone symptoms pre-operatively. Those with levels above 500 pg/mL but below 1000 pg/mL would require monitoring and oral calcium supplementation and those with levels above 1000 pg/mL may require longer hospitalization and possibly intravenous calcium supplementation.

Successful parathyroid surgery in this new paradigm relies on recent technological advances including focused ultrasound, technetium sestamibi scans, and the use of intraoperative parathyroid hormone level estimation [17]. The combination of these technologies has proven better than using any one of them alone. However, it cannot be concluded that while preoperative localization procedures combined with intraoperative PTH measurements can increase the rate of successful surgery it may not reduce the risk for postoperative hypocalcaemia in patients with significant risk-factors for severe postoperative hypocalcaemia.

Conclusion

In conclusion, the severity of the postoperative hypocalcaemia after parathyroid surgery is not dependent on age, sex, duration of symptoms, preoperative serum calcium levels and tumor size, but is dependent on the degree of bone decalcification and elevation of the serum alkaline phosphatase levels and most significantly elevated PTH levels.

Compliance with Ethical Standards

Conflict of interest None.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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