Cutoff Point of Intraoperative Parathyroid Hormone in Predicting Successful Parathyroidectomy in Renal Hyperparathyroidism

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Background: *It is unclear when intraoperative intact parathyroid hormone (IOPTH) measurement should be performed, and there is also some uncertainty about the best cutoff point to use in predicting the success of parathyroidectomy in renal hyperparathyroidism.*

Objective: *To determine the cutoff values for IOPTH, both for parathyroid levels and for postoperative timing after parathyroidectomy in order to compare successful parathyroidectomy with persistent hyperparathyroidism in renal hyperparathyroidism.*

Material and Method: *This was a retrospective study of 85 patients who underwent total parathyroidectomy with autotransplantation in the Head and Neck Surgery Department in Rajavithi Hospital between October 1st 2014 and September 30th 2016. IOPTH levels were measured preoperatively at IOPTH 0 minutes, and at 10-minute intervals after successful parathyroidectomy for a duration of 1 hour (IOPTH at 10, 20, 30, 40, 50 and 60 minutes) with iPTH level on day 3 (72 hours after surgery) below 65 pg/ml taken as a predictor of successful treatment of renal hyperparathyroidism.*

Results: *Fifty-eight patients (68.2%) had successful treatment according to the above criteria. The ROC values of the decrement of IOPTH levels at 10, 20, 30 and 40 minutes were 0.644, 0.767, 0.799, and 0.809 respectively. In all patients that were successfully treated, the decrement of IOPTH was more than 80%, while all patients whose treatment was unsuccessful had an IOPTH decrement of less than 70%. An IOPTH level decrement of between 70 and 80% 20 minutes postoperatively had a sensitivity of 82.1 to 96.4%, while a decrement of IOPTH level of more than 90% after 20 minutes yielded 100% specificity for successful treatment of renal hyperparathyroidism.*

Conclusion: *The cutoff point for IOPTH time at 20 minutes with at least a 80% decrement yields a sensitivity of 82.1% for predicting successful surgery, while more than 90% decrement in IOPTH levels has 100% specificity for predicting successful treatment.*

Keywords: *Intraoperative, Intact parathyroid hormone, Hyperparathyroidism and chronic renal failure*

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Secondary hyperparathyroidism (HPT) most commonly occurs secondary to chronic renal failure (CRF) and is frequently referred to as renal HPT. Estimates report that as many as 90% of patients with CRF develop this disease by the time hemodialysis is initiated[1,2], and tertiary HPT is most prevalent in the setting of renal transplant where patients with secondary HPT continue to have elevated PTH levels after receiving a renal allograft. CRF is observed in up to 30% of kidney transplant recipients and was first described in the early 1960's. The diagnosis and workup of patients with secondary and tertiary HPT combines both clinical and laboratory investigations. In secondary HPT, laboratory tests may reveal hypocalcemia or normocalcemia and hyperphosphate-mia with elevated intact PTH levels and decreased vitamin D levels. In contrast, patients with tertiary HPT will have normal or elevated serum calcium concentrations in combination with moderately elevated intact PTH levels[1].

Management of patients with secondary HPT is predominantly medical, while treatment of patients with tertiary HPT is surgical. Although novel methods for medically treating patients with secondary HPT have been introduced, surgical intervention is still necessary at times. About 1 to 2% of patients with secondary HPT require parathyroidectomy each year[3].

The best surgical approach for renal hyperparathyroidism is still debated, and controversy

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remains regarding treatment election and how post-surgical recurrence and the risk of definitive hypoparathyroidism are to be avoided. Total parathyroidectomy with parathyroid gland autotransplantation is the preferred technique for the management of these patients[4-7]. The surgical procedure involves bilateral neck exploration, seeking total removal of abnormal parathyroid tissue. Persistence and/or recurrence can indicate inadequate resection of hyperfunctioning tissue. Reoperation has been reported to be necessary for recurrent renal hyperparathyroidism in about 15% of cases, mostly due to the presence of supernumerary glands, inadequate initial parathyroidectomy or the continued hyperplasia of remnant tissue[8].

Since its introduction, IOPTH monitoring has been performed in people with primary hyperparathyroidism in several medical centers, and has become a well-recognized predictor of surgical success in these patients[9-12]. By resorting to IOPTH measurements, the surgeon can confirm total removal of the abnormal parathyroid glands and avoid overlooking remaining or supernumerary hyper-functional glands. However, the role of IOPTH monitoring in the surgical treatment of renal hyperparathyroidism is less well-established[13]. There is no standard definition of IOPTH decay in renal hyperparathyroidism surgical treatment, since impaired renal function and delayed renal clearance of PTH can interfere with IOPTH monitoring; furthermore, few large series using IOPTH monitoring in renal patients have been published[13].

In 2005, Haustein SV et al reported that a decrease in intraoperative PTH levels of more than 50% 10 minutes after parathyroidectomy indicated adequate resection[14]. In the same year, the Journal of Langenbeck's Archives of Surgery reported that a PTH level at 15 minutes post-operatively with a value of less than 150 pg/ml predicts operative success in patients with renal failure in 98.7% of cases. In contrast, if the relative PTH level after 15 minutes is higher than 30%, high postoperative PTH values are predicted, with a successful treatment probability of 86.7%[15]. According to a study by Woo Young Kim et al in 2012, a decline of more than 85% intraoperative PTH at 40 minutes enables prediction of success[16]. In 2013, Ohe MN et al found that an 80% decrease in IOPTH at 20 minutes, compared to IOPTH at 0 minutes, predicted a cure in all patients throughout the follow-up of 26.5 months whereas a drop of less than 70% pointed to missed or hyperfunctioning supernumerary gland, and that it is predictive of surgical failure in 66.6% of cases[17]. In 2016, Vulpio et al reported that the absolute and percentage of IOPTH decay at 30 minutes after parathyroid gland excision had high sensitivity (100%), specificity (92%), negative predictive value (100%) and accuracy (93%) in predicting the persistence of renal hyperparathyroidism[18].

Several studies have studied the cutoff point of intraoperative parathyroid hormone in predicting successful treatment in renal hyperparathyroidism, but the results vary and there is no consensus as to which cutoff point is the best.

The aim of the present study was to evaluate the usefulness of IOPTH monitoring in dialysis or kidney transplanted patients with secondary or tertiary hyperparathyroidism. Our aim was to define an IOPTH cutoff value in order to avoid missed and/or supernumerary parathyroid glands and improve the success rates of treatment.

Material and Method

This was a retrospective study of patients who underwent operations at the Head and Neck Surgery Department in Rajavithi Hospital between October 1st, 2014 and September 30th, 2016. This research was approved by Ethics committee of our institution (approval No. 165/2556).

Eighty-five renal patients underwent total parathyroidectomy with auto transplantation from October 2014 to September 2016, in Bangkok, Thailand. Patients were referred to our institution for surgery because of persistent hypercalcemia which was not responding to medical interventions, and/or persistent hyperphosphatemia despite the continued use of dietary phosphorus restrictions and phosphate binding agents, with symptoms such as intractable pruritus, severe bone pain, fractures or high risk of fracture, skeletal deformities, extra-skeletal calcification, development of calciphylaxis and radiographic evidence of renal osteodystrophy.

Serum calcium, phosphorus, alkaline phosphatase, creatinine, 25 hydroxy vitamin D levels and intact parathyroid hormone (iPTH) were measured before parathyroidectomy in all patients. Intact PTH (1 to 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.

Total parathyroidectomy with auto transplantation was performed in 85 patients. Surgical cure was defined as iPTH levels on day 3 of lower than 65 pg/ml.

Intraoperative PTH (IOPTH) was performed in an attempt to confirm total removal of the parathyroid glands every 10 minutes for 1 hour starting after removal of all parathyroid glands. The time required to carry out the assay was 20 minutes.

Results

A total of 85 patients with renal hyperparathyroidism fulfilling surgical indications underwent parathyroidectomy with auto transplantation in the Head and Neck Surgery Department in Rajavithi Hospital between October 1st 2014 and September 30th 2016. Fifty-eight patients had successful operations (iPTH level day 3 of less than 65 pg/ml), while the other 27 patients' hormone levels failed to fall below 65 pg/ml.

The demographic characteristics of all patients, presented in Table 1, were well balanced between groups with no significant difference with the exception of iPTH at day 3.

Intraoperative parathyroid hormone levels (IOPTH) were collected after 10, 20, 30, 40, 50 and 60 minutes, starting after all parathyroid glands were removed. Intraoperative intact parathyroid hormone levels at each different time point are shown as the ROC in Fig. 1, showing that the greatest area under the curve was at 60 minutes where the AUC was 0.821 (95% CI 0.728 to 0.913). The point 10 minutes post-operation yielded the lowest AUC of 0.644 (95% CI 0.535 to 0.793) while the AUC at 20 minutes, 30 minutes, 40 minutes and 50 minutes were 0.766 (95% CI 0.656 to 0.88), 0.799 (95% CI 0.696 to 0.902), 0.809 (95% CI 0.707 to 0.910) and 0.799 (95% CI is 0.707 to 0.910) respectively.

The mean drop of IOPTH levels of the successful and unsuccessful groups were analyzed and are shown in Fig. 2. All the patients in the successful group had decreases in iPTH levels from 10 to 60 minutes of least 80% from the baseline, while the patients in the unsuccessful group had drops in IOPTH levels of less than 70% from the baseline of iPTH.

Fig. 2 demonstrates that all the patients that had successful operations had a more than 80% decrement of IOPTH levels from baseline at all times except at 10 minutes, when it was 79.5%. In the group that underwent unsuccessful surgery, there was a less than 70% decrement in IOPTH levels from baseline at each time except at 60 minutes, when it was 70.2%. From these results, we calculated the sensitivity, specificity, PPV, and NPV for different percentage decrement of IOPTH levels, and the results are shown in Table 2. The values of more than 70% and more than 80% decrement of IOPTH at 20 minutes were the best and showed sensitivity of 82.1% to 96.4% and specificity of 29.6% to 55%. The decrement of more than 90% of IOPTH level showed very low sensitivity but had specificity of 100% at 20 minutes. From these findings, the cutoff timing for intraoperative parathyroid hormone monitoring is at 20 minutes for the best sensitivity. Decrements of more than 70% to more than 80% gave the best sensitivity but a decrement of over 90% in intraoperative parathyroid hormone monitoring would yield 100% specificity that the patient's surgery was successful.

The sensitivity, specificity, positive predictive values (PPV), and negative predictive values (NPV) were calculated at 70%, 80% and 90% decrement of intraoperative parathyroid hormone levels from baseline at each time point after parathyroidectomy (at 10, 20, 30, 40, 50 and 60 minutes), and the results

Table 1. General demographic characteristics of patients who underwent total parathyroidectomy with autotransplantation

	Successful (n = 58)	Failure (n = 27)	*p*-value
Age (yrs)	47.16±12.72	45.19±12.48	0.785
Sex (female)	30 (51.7)	15 (55.6)	0.742
BMI (kg/m^2)	23.44±4.12	22.59±4.81	0.253
iPTH pre-op (pg/ml)	1,977.00±806.00	2,195.00±1,062.00	0.301
Calcium (mg/dl)	10.35±0.91	10.41±0.83	0.805
Phosphorus (mg/dl)	5.80±1.66	6.16±2.36	0.057
GFR (mL/min/1.73 m^2)	7.24±3.75	7.67±5.79	0.163
25 OHD (ng/ml)	25.82±12.37	29.10±14.70	0.300
iPTH day3 (pg/ml)	18.22±11.57	498.59±541.35	<0.001*

Values are presented as number (percent), mean ± SD. * Significant at $p<0.05$

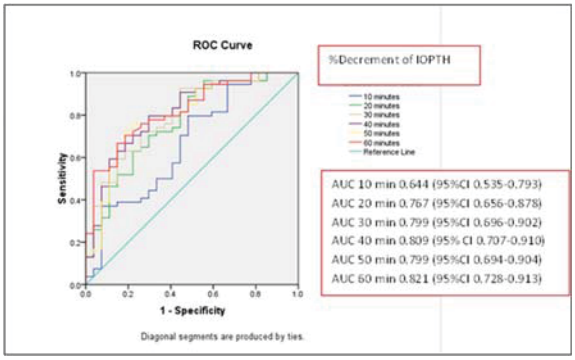

Fig. 1 ROC of percent decrement of intraoperative parathyroid hormone with the area under the curve (AUC).

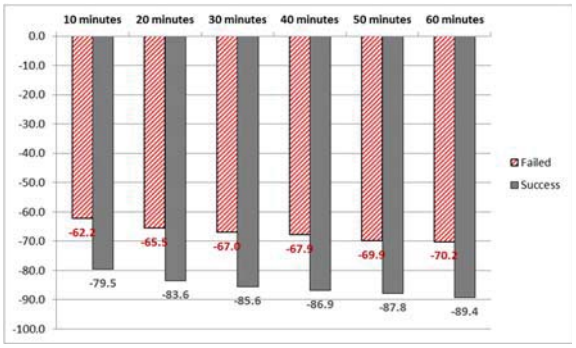

Fig. 2 Mean decrement of intraoperative parathyroid hormone from baseline at 10, 20, 30, 40, 50 and 60 minutes after parathyroidectomy.

Table 2. Sensitivity, specificity, NPV and PPV of different percentage decrements in intraoperative parathyroid hormone from baseline at each time point after parathyroidectomy

IOPTH Decrement >70%					
Time after PTX (min)	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	Accuracy
10	89.3 (88.3 to 90.3)	33.3 (29.9 to 36.7)	73.5	60.0	79.5
20	96.4 (95.8 to 97.0)	29.6 (26.3 to 32.9)	74.0	80.0	74.7
30	96.4 (95.8 to 97.0)	29.6 (26.3 to 32.9)	74.0	80.0	75.0
40	96.4 (95.8 to 97.0)	25.9 (22.8 to 29.0)	73.0	77.8	74.4
50	96.4 (95.8 to 97.0)	22.2 (19.2 to 25.2)	71.6	75.0	72.0
60	98.2 (97.8 to 98.6)	22.2 (19.2 to 25.2)	72.0	85.7	73.2
IOPTH Decrement >80%					
Time after PTX (min)	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	Accuracy
10	66.0 (64.4 to 67.6)	55.0 (51.4 to 58.6)	75.5	44.1	62.7
20	82.1 (80.9 to 83.3)	55.0 (51.4 to 58.6)	79.3	60.0	73.5
30	92.9 (92.1 to 93.7)	40.7 (37.2 to 44.2)	76.5	73.3	75.9
40	92.9 (92.1 to 93.7)	40.7 (37.2 to 44.2)	76.5	73.3	75.9
50	94.5 (93.8 to 95.2)	40.7 (37.2 to 44.2)	76.5	78.6	75.6
60	96.4 (95.8 to 97.0)	33.3 (37.2 to 44.2)	74.6	81.8	75.6
IOPTH Decrement >90%					
Time after PTX (min)	Sensitivity (95% CI)	Specificity (95% CI)	PPV	NPV	Accuracy
10	7.1 (6.3 to 7.9)	96.3 (95.0 to 97.6)	80.0	33.3	36.1
20	12.5 (11.4 to 13.6)	100.0 (100.0 to 100.0)	100.0	35.5	41.0
30	21.4 (20.1 to 22.7)	96.3 (95.0 to 97.6)	92.3	65.0	45.8
40	34.0 (32.4 to 35.6)	92.6 (90.7 to 94.5)	90.5	40.3	53.0
50	47.3 (45.7 to 48.9)	88.9 (86.7 to 91.1)	90.0	45.3	61.0
60	54.5 (52.9 to 56.1)	88.9 (86.7 to 91.1)	90.1	49.0	65.9

Values are presented as n (%)

are shown in Table 2.

Discussion

From the ROC of the mean intraoperative parathyroid hormone decrement at 10, 20, 30, 40, 50 and 60 minutes, indicated that the best AUC is at 60 minutes; however, from a practical point of view, it is very difficult for surgeons to wait for the results of intraoperative decline of parathyroid hormone level until 60 minutes after parathyroidectomy. At 20, 30 and 40 minutes, the area under the curve of ROC values were 0.767, 0.799, 0.809 respectively while their 95% CI overlapped each other; based on the principle that the faster is the better, we proposed the 20 and 30 minutes points.

This research is the first report at Rajavithi Hospital to have given information regarding cutoff points for both decrements in IOPTH levels and timing of IOPTH measurement in predicting successful treatment. The number of patients included in the research was sufficient for analysis, and its results are also consistent with those of the study by Ohe MV et al[17], which reported that an 80% decrement in IOPTH levels at 20 minutes predicts cure in 80.2% of patients, while a decrement of less than 70% at 20 minutes predicts failure in 66.6% of cases.

The limitations of this study were: firstly, that it was a retrospective study; secondly, that it was conducted in a single centre; and thirdly, that information regarding calcium and IOPTH levels at follow-up time were not reported to confirm cure. Further research is needed in the form of multicenter, prospective studies.

Conclusion

From our results, we propose that the cutoff point of intraoperative parathyroid hormone level decrement of more than 70% to 80% at 20 minutes after parathyroidectomy gives 82.1% to 96.4% sensitivity, but a decrement of greater than 90% in IOPTH at 20 minutes can yield 100% specificity in predicting that the patient has had successful treatment of renal hyperparathyroidism.

What this study adds?

The present study help Surgeons who underwent total parathyroidectomy with auto transplantation in renal hyperparathyroidism to improve success rate for surgery.

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Potential conflicts of interest

None.

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