ORIGINAL ARTICLE

Improvement of Anemia After Parathyroidectomy in Chinese Patients With Renal Failure Undergoing Long-term Dialysis

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Hypothesis: Most patients undergoing long-term dialysis are anemic because of underproduction of erythropoietin and its inhibition by high parathyroid hormone levels due to secondary hyperparathyroidism. Renal anemia can be improved by parathyroidectomy.

Design: Retrospective cohort study.

Setting: Regional hospital.

Patients: Twenty-three Chinese patients without a previous functioning renal transplant underwent parathyroidectomy for severe secondary hyperparathyroidism in a 3-year period.

Intervention: Total parathyroidectomy with or without parathyroid autograft at the forearm.

Main Outcome Measures: The preoperative and 6-month postoperative hematological and biochemical variables were compared for any differences by means of a paired *t* test.

Results: The mean±SD follow-up duration was 17.7±8.1 (range, 6-34) months. Three patients (13%) developed persistent or recurrent hyperparathyroidism and 2 patients (9%) were biochemically hypoparathyroid. The other 18 patients (78%) were euparathyroid. Surgical morbidity was minimal; only 1 patient had complications, consisting of a postoperative fever of unknown origin that resolved with conservative treatment. The mean±SD hemoglobin level (8.6±2.1 vs 9.4±2.1 g/dL) but not the mean platelet level was significantly ($P=.04$) increased 6 months postoperatively. Likewise, the following other mean±SD biochemical values improved after surgery: parathyroid hormone (2235±500 vs 151±312 pg/mL; $P<.001$), alkaline phosphatase (645±349 vs 123±82 U/L; $P<.001$), calcium (10.8±4.0 vs 9.3±1.0 mg/dL; $P<.001$), phosphate (1.93±0.73 vs 1.50±0.51 mmol/L; $P=.02$), and albumin (3.5±0.5 vs 3.8±0.6 g/dL; $P=.006$).

Conclusions: Parathyroidectomy is highly effective to control secondary hyperparathyroidism with an exceedingly low complication rate. The hemoglobin level was significantly elevated 6 months postoperatively. The long-term effect warrants future trials.

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PARATHYROIDECTOMY IS AN EFfective treatment for hyperparathyroidism secondary to chronic renal failure (CRF) that does not respond to maximal medical suppression.[1-3] Renal osteodystrophy, soft-tissue calcification, severe pruritus, and muscle weakness are widely accepted indications for parathyroidectomy.

Anemia is frequently encountered in CRF and is probably related to the diminished production of erythropoietin and bone marrow fibrosis secondary to renal hyperparathyroidism.[4,5] A high parathyroid hormone (PTH) level was shown to inhibit the response of erythropoietin therapy.[6] However, parathyroidectomy for the amelioration of anemia in CRF has shown conflicting results. Barbour[5] and McGonigle et al[7] discovered that the hemoglobin level increased in only half the patients undergoing parathyroidectomy. Their series were small, each consisting of about 10 patients. More recently, Rashed et al[8] failed to show any significant change in hemoglobin level after surgery in their series of 26 patients. This diversity of results may be related to the heterogeneity of the patient cohorts, concomitant use of recombinant human erythropoietin, or different timing of measurements. To our knowledge, a similar study on Chinese patients has not been reported. Furthermore, this aspect of parathyroidectomy on patients with CRF (hereinafter referred to as *CRF patients*) has been seldom discussed in surgical journals. This study intends to elucidate the intermediate-term effect of parathyroidectomy on the hemo-

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Table 1. Hematological and Biochemical Variables Before and After Parathyroidectomy

Variables	Mean ± SD (Range) Level Preoperative	Postoperative	*P* Value
Hemoglobin, g/dL	8.6 ± 2.1 (4.3-13.7)	9.4 ± 2.1 (6.1-14.1)	.04
Platelet count $\times 10^3/\mu L$	261 ± 86 (108-411)	271 ± 100 (104-475)	.46
Parathyroid hormone, pg/mL	2235 ± 500 (1169-3744)	151 ± 312 (1-1377)	<.001
Alkaline phosphatase, U/L	645 ± 349 (200-1535)	123 ± 82 (47-324)	<.001
Calcium, mg/dL	10.8 ± 4.0 (9.0-12.3)	9.3 ± 1.0 (6.6-11.1)	<.001
Phosphate, mmol/L	1.93 ± 0.73 (0.63-4.19)	1.50 ± 0.51 (0.51-2.37)	.02
Albumin, g/dL	3.5 ± 0.5 (2.6-4.7)	3.8 ± 0.6 (2.0-4.6)	.006

SI conversion factors: To convert alkaline phosphatase to microkatals per liter, multiply by 0.0167; calcium to millimoles per liter, multiply by 0.25; and parathyroid hormone to nanograms per liter, multiply by 0.1053.

globin level in relatively homogeneous Chinese CRF patients with severe hyperparathyroidism who underwent management in a single center.

METHODS

SUBJECTS

Our renal center serves 464 CRF patients, with 404 receiving peritoneal dialysis and 60 receiving hemodialysis. Recombinant human erythropoietin therapy is administered at 2000 U/wk subcutaneously for patients with symptomatic anemia and an hemoglobin level lower than 8 g/dL. From January 1, 2002, through December 31, 2004, a total of 27 patients underwent parathyroidectomy for secondary hyperparathyroidism. Four patients were excluded because they had received a functioning renal transplant before parathyroidectomy. Hence the remaining 23 patients underwent evaluation for outcome. None of them had iron deficiency anemia or external blood loss. Total parathyroidectomy with a parathyroid autograft to the forearm was the preferred operation in our hospital. If fewer than 4 parathyroid glands were identified, the parathyroid autograft would not be performed.

All the blood samples were obtained before dialysis to eliminate the dilution effect on the results. We implemented close monitoring of serum calcium levels coupled with intravenous calcium supplementation, if necessary, in the early postoperative period. During the study period, the recombinant human erythropoietin dosage remained unchanged. After discharge, hematological variables were checked at least every 3 months.

The biochemical variables were measured by an automated multichannel analyzer (Roche Modula DP System; Roche Diagnostics, Indianapolis, Indiana) and intact 1-84 PTH by an automated analyzer (Immulite; Diagnostic Products Corporation, Los Angeles, California) with a reference range of 15 to 65 pg/mL. Because the optimal bone histomorphometry could be achieved at 2 to 3 times the upper limit of a normal PTH level in patients undergoing long-term dialysis,[9] postoperative hyperparathyroidism was defined as a PTH level of more than 3 times the reference range. Hematological variables were assayed using a hematology analyzer (LH 750; Beckman Coulter, Inc, Fullerton, California). The data are expressed as mean ± SD and were analyzed with the paired *t* test. Differences were considered statistically significant if $P<.05$.

SI UNIT CONVERSION FACTORS

To convert alkaline phosphatase levels to microkatals per liter, multiply by 0.0167; calcium levels to millimoles per liter, multiply by 0.25; and PTH levels to nanograms per liter, multiply by 0.1053.

RESULTS

Twenty-three CRF patients (7 men and 26 women) who had undergone parathyroidectomy fulfilled the inclusion criteria. Their ages ranged from 25 to 66 years, with a mean age of 50.0 ± 11.6 years. Causes of CRF included hypertensive nephropathy (n=10), polycystic kidney disease (n=3), IgA nephropathy (n=2), systemic lupus erythematosus (n=2), urate nephropathy (n=2), glomerulonephritis (n=1), and renal stone (n=1). The cause was unknown in 2 patients. Modes of dialysis were hemodialysis in 7 patients and peritoneal dialysis in 16. Mean duration of dialysis before surgery was 73.0 ± 54.1 (range, 22-254) months. Indications for parathyroidectomy included renal osteodystrophy with or without bone pain (n=18), followed by pruritus (n=4), muscle weakness (n=3), bone fracture (n=2), and ectopic calcification (n=2). Some patients had more than 1 indication. Of the 23 patients, 16 were taking recombinant human erythropoietin. The mean postoperative follow-up duration was 17.7 ± 8.1 (range, 6-34) months.

Twenty patients underwent total parathyroidectomy with an autograft, whereas 3 other patients received parathyroidectomy without the autograft because only 3 parathyroid glands were identified. Results of a PTH assay on postoperative day 1 confirmed complete parathyroid removal in these 3 cases because their PTH levels were no higher than 39 pg/mL. The mean operative time was 191.0 ± 59.7 (range, 90-295) minutes. There was no mortality. Likewise, the incidence of surgical complications was negligible; 1 patient developed a fever of unknown origin but recovered with conservative treatment. There was no vocal cord palsy or postoperative airway problem. Three patients (13%) developed postoperative hyperparathyroidism (recurrent due to graft hyperplasia in 1 patient and persistent in 2). Two additional patients (9%) were hypoparathyroid and the other 18 (78%) were euparathyroid.

The preoperative and 6-month postoperative biochemical and hematological values are summarized in **Table 1**. The mean ± SD hemoglobin level rose significantly from 8.6 ± 2.1 to 9.4 ± 2.1 g/dL after parathyroid-

Table 2. Hematological and Biochemical Variables Before and After Parathyroidectomy in Patients With or Without Recombinant Human Erythropoietin Administration

Variables[a]	Mean ± SD (Range) Level		*P* Value
	Preoperative	Postoperative	
Hemoglobin, g/dL			
Without	9.2 ± 2.4 (6.1-13.7)	9.4 ± 2.4 (7.1-14.1)	.75
With	8.3 ± 2.0 (4.3-10.9)	9.3 ± 2.0 (6.1-12.9)	.03
Parathyroid hormone, pg/mL			
Without	2235 ± 594 (2027-3744)	113 ± 159 (1-363)	<.001
With	2122 ± 434 (1169-2527)	167 ± 363 (2-1377)	<.001
Alkaline phosphatase, U/L			
Without	394 ± 194 (290-1535)	129 ± 77 (57-270)	.007
With	599 ± 330 (200-1065)	121 ± 87 (47-324)	<.001
Calcium, mg/dL			
Without	11.1 ± 1.0 (9.2-12.2)	9.4 ± 0.4 (9.0-9.9)	.02
With	10.7 ± 1.04 (9.0-12.3)	9.2 ± 1.2 (6.6-11.1)	.01
Phosphate, mmol/L			
Without	1.63 ± 0.46 (1.25-2.52)	1.53 ± 0.67 (0.75-2.37)	.65
With	2.04 ± 0.79 (0.63-4.19)	1.46 ± 0.48 (0.51-2.18)	.03
Albumin, g/dL			
Without	3.4 ± 0.2 (3.2-3.8)	3.7 ± 0.6 (2.6-4.4)	.20
With	35.3 ± 6.4 (26.0-47.0)	38.6 ± 6.1 (20.0-46.0)	.02

SI conversion factors: To convert alkaline phosphatase to microkatals per liter, multiply by 0.0167; calcium to millimoles per liter, multiply by 0.25; and parathyroid hormone to nanograms per liter, multiply by 0.1053.

[a]Indicates with and without recombinant human erythropoietin.

ectomy (*P*=.04). To ensure stable preoperative and postoperative hemoglobin values, the mean hemoglobin levels from 2 to 3 different measurements were also compared. The difference was even more significant: mean±SD preoperative vs 6-month postoperative hemoglobin levels were 8.6±2.0 vs 9.3±1.7 g/dL (*P*=.03). Conversely, the platelet count remained unchanged at $261 \pm 86 \times 10^3$/μL vs $271 \pm 100 \times 10^3$/μL (*P*=.46). The mean±SD PTH, alkaline phosphatase, calcium, and phosphate levels were significantly lower, at 2235±500 vs 151±312 pg/mL (*P*<.001), 645±349 vs 123±82 U/L (*P*<.001), 10.8±4.0 vs 9.3±1.0 mg/dL (*P*<.001), and 1.93±0.73 vs 1.50±0.51 mmol/L (*P*=.02), respectively. Likewise, the albumin level was significantly elevated after surgery (3.5±0.5 vs 3.8±0.6 g/dL; *P*=.006). When subgroups underwent evaluation, similar significant changes persisted in the subgroup receiving recombinant human erythropoietin. In contrast, the changes in hemoglobin, albumin, and phosphate levels became insignificant, whereas the differences in PTH, calcium, and alkaline phosphatase levels remained significant in the subgroup without recombinant human erythropoietin (**Table 2**).

COMMENT

From our experience and that of others,[1,2] parathyroidectomy is efficacious in controlling secondary hyperparathyroidism. The patients' PTH, alkaline phosphatase, calcium, and phosphate levels improved remarkably after surgery. Moreover, the complication rate in this series was minimal, with only 1 case of postoperative fever of unknown origin that resolved after conservative treatment. There was no mortality or recurrent laryngeal nerve injury. Hence, parathyroidectomy is the treatment of choice for patients undergoing long-term dialysis who have severe hyperparathyroidism that does not respond to medical therapy. Widely accepted indications for parathyroidectomy encompass renal osteodystrophy, ectopic calcification, pruritus, and muscle weakness.[8,10-12]

Most CRF patients are anemic. The mechanisms consist of reduced genesis of erythropoietin by the kidneys, diminished red blood cell precursors due to bone marrow fibrosis,[4,5] and resistance to erythropoietin as a result of hyperparathyroidism.[13] Exogenous erythropoietin in a recombinant human form can partially reverse renal anemia. Rao et al[6] showed that the dose of recombinant human erythropoietin is influenced by the level of PTH; a higher dose is required to maintain a satisfactory hematocrit level in patients with excessively elevated PTH levels. In addition, Ureña et al[14] and Washio et al[15] demonstrated incremental changes in serum erythropoietin levels in the early postoperative period (6 hours to 2 weeks) after parathyroidectomy. More recently, Yasunaga et al[16] further corroborated that the elevated erythropoietin level is sustainable 1 year after surgery. The effect of hyperparathyroidism on renal anemia is therefore substantial, and parathyroidectomy is a good model to testify to the relationship; anemia should be corrected or improved after surgery. However, this expected result cannot be validated consistently.[5,7,8] In keeping with the finding by Zingraff et al,[4] platelet count after parathyroidectomy in this series remains unchanged, which indicates that the benefit of correction of hyperparathyroidism does not extend to thrombocytopoiesis.

In a multicenter trial, Coen et al[17] described the long-term benefit of enhanced erythropoiesis after parathyroidectomy in patients undergoing long-term dialysis. In our series, the patients were relatively homogeneous and underwent management in a single center. This eliminates the inherent drawbacks of a multicenter trial, eg, a heterogeneous patient cohort or protean treatment protocols. No patient in our series experienced blood loss or iron deficiency anemia. Similarly, none of them was undergoing anticoagulant therapy that would affect the hemoglobin value. There was no major alteration of the cholecalciferol (vitamin D) supplementation during the 6 months following surgery, which is important to avoid the hungry bone syndrome and prevent recurrent hyperplasia of the autotransplanted parathyroid. Moreover, all of the blood samples were obtained before dialysis to minimize the dilution effect on the measured laboratory variables. The data at postoperative month 6 were collected and compared in this study because all of the patients were followed up at least 6 months postoperatively. Increment of hemoglobin level after the operation, if it happens, has been shown to plateau by 6 months postoperatively.[5,13] On the other hand, the results of the earlier postoperative period were not evaluated because the effect of parathyroidectomy on erythropoiesis takes at least 3 months to occur.[14,16,17]

The beneficial effect of parathyroidectomy on erythropoiesis has been shown to take place regardless of the administration of recombinant human erythropoietin.[13,16] However, our study cannot demonstrate a significant erythropoietic effect on the subgroup that did not receive recombinant human erythropoietin. This is probably owing to the small sample size, with only 7 patients not receiving the therapy. Nevertheless, the mean hemoglobin level in this subgroup did rise 0.2 g/dL. If more patients who do not receive recombinant human erythropoietin therapy are enrolled, we speculate that a significant difference can be discovered. The less plausible explanation for the lack of improvement in hemoglobin levels is that the action of PTH on renal anemia is restricted to the inhibition of erythropoietin without affecting its production; parathyroidectomy can demonstrate improvement only in those patients receiving an exogenous erythropoietin supplement. This latter postulation is unlikely because elevated erythropoietin levels after parathyroidectomy have been demonstrated to be sustainable 1 year postoperatively.[16] Unfortunately, erythropoietin levels are not normally measured in our hospital. Likewise, bone marrow erythroid progenitors or red blood cell survival examination is not routinely performed on our patients to discriminate between enhanced red blood cell production and survival secondary to parathyroidectomy.

In our institution, administration of recombinant human erythropoietin is considered for symptomatic patients with hemoglobin levels lower than 8 g/dL. There was no change in the recombinant human erythropoietin dosage throughout the 6-month study period because this was a retrospective study. As of this writing, we have not systematically evaluated the perioperative hemoglobin level. Furthermore, the clinical significance of the increment of hemoglobin level from 8.6 to 9.4 g/dL as result of parathyroidectomy is modest, although the difference is statistically significant. Longer follow-up is necessary. Conclusions regarding whether parathyroidectomy is more beneficial to patients with more severe secondary hyperparathyroidism cannot be drawn from this series because most of the cases referred from our renal physician (Y.-W.H.)for surgery resulted from severe hyperparathyroidism. This is reflected by the markedly elevated preoperative PTH level of 2235 pg/mL (Table 1).

It will be interesting to follow the trend of hemoglobin level in the cases with postoperative hyperparathyroidism (2 persistent and 1 recurrent). The first persistent case had improvement of the hemoglobin level from 13.7 to 14.1 g/dL because the PTH level dropped from 3744 to 266 pg/mL. The second case of persistent hyperparathyroidism had hemoglobin levels unchanged from 10.0 to 9.9 g/dL because the PTH level only slightly decreased from 1990 to 1377 pg/mL. For the case with recurrent hyperparathyroidism, the hemoglobin level also improved from 4.3 to 6.9 g/dL because the postoperative PTH level was substantially reduced by the surgical procedure (471 pg/mL 6 months postoperatively vs >2480 pg/mL preoperatively). This observation supports the beneficial effect of parathyroidectomy on hemoglobin level by lowering the PTH level.

The elevation of albumin levels after parathyroidectomy for secondary hyperparathyroidism has been reported previously.[16] The mechanism is not well understood but possibly is related to improved well-being, better mobility, and increased appetite.[16] Although the increased albumin level in this series was significant in the group receiving recombinant human erythropoietin (from 3.5 to 3.9 g/dL) but not the other group (from 3.4 to 3.7 g/dL) (Table 2), both groups saw albumin levels increase by approximately 0.3 g/dL. The small sample size in the latter group can explain the statistical discrepancy.

In conclusion, parathyroidectomy is highly effective in controlling renal hyperparathyroidism with minimal morbidity. In addition, renal anemia improves significantly after the operation. More trials are needed to corroborate the long-term effect. If proved, renal anemia might be considered as a new indication for parathyroidectomy in patients undergoing long-term dialysis.

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