# Role of parathyroidectomy on anemia control and erythropoiesis-stimulating agent need in secondary hyperparathyroidism of chronic kidney disease.

## A retrospective study in 30 hemodialysis patients

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**Role of parathyroidectomy on anemia control and erythropoiesis-simulating agent need in secondary hyperparathyroidism of chronic kidney disease.A retrospective study on 30 hemodialysis patients**

BACKGROUND: *Parathyroidectomy (Ptx) ameliorates anemia (A) and reduces postoperative erythropoiesis-stimulating agent (ESA) requirement. The authors retrospectively evaluated the effects of successful Ptx on chronic A and ESA need in 30 2HPT patients.*
METHODS: *From 2004 to 2009,30 anemic hemodialysis (HD) patients, affected by severe 2HPT, underwent Ptx -15 total parathyroidectomy (TP) and 15 TP + subcutaneous autoimplantation (TPai). Patients were evaluated for iPTH, hemoglobin (Hb) levels, erythrocyte count, hematocrit and erythropoietin dosing before and at 6, and 12 months after surgery.*
RESULTS: *In every case, Ptx achieved a dramatic reduction of iPTH levels. In 26/30 cases(86.6%) an improvement of Hb levels was observed,and 27/30 (90%) patients did not need postoperative ESA treatment,irrespective of the type of surgical procedure carried out (TP or TPai).*
CONCLUSIONS: *Successful Ptx for 2HPT of CKD determined a considerable improvement of A,reducing exogenous ESA need.In 2HPT of HD patients A is a secondary indication to surgical treatment,but we propose that this condition should be taken into more careful account, given the high costs of ESA therapy.*

KEY WORDS: Anemia, Chronic kidney disease, Erythropoietin, Parathyroidectomy, Secondary hyperparathyroidism

## Introduction

Depending on hemodialysis vintage and other factors, anemia (A), at times resistant to erythropoiesis-stimulating agents (ESAs), becomes almost universal in secondary hyperparathyroidism (2HPT) of Chronic Kidney Disease (CKD) patients [1], and represents a risk factor for unfavourable cardiovascular outcomes. Decrease in renal erythropoietin production, and/or its release, is one of its main causes and, in most patients, medical therapy, with ESAs, is required, determining an increase in collateral effects and healthcare costs. Severity of 2HPT seems to be involved in A degree, since more elevated iPTH levels decrease red blood cells (RBC) survival [2], cause bone marrow fibrosis [3] and inhibit erythropoietin production [4]. Moreover, the hemodialysis (HD) procedure – exposure to the hemodialysis membrane and the

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extracorporeal circulation – may determine a RBC survival decrease [1]. In the medical management of CKD, the optimal treatment of A remains a topic of active research, and available literature data about surgical or medical effects are still controversial in terms of ideal target levels [5]. According to the most recent FDA alert [6], target hemoglobin levels in HD patients should be not more than 11 g/dl, given the high risk of cardiovascular events linked to ESA therapy. Several studies demonstrated that parathyroidectomy (Ptx) improves endogenous erythropoietin levels, ameliorates A, reducing the need for exogenous ESAs [7-10]. These studies were mostly performed in the last decade of the previous century; improved hemodialysis techniques and medical therapy have greatly changed the general management of these patients.

Therefore, aim of this retrospective study was to assess Ptx results in 30 severe 2HPT hemodialysis patients, observed in the last few years, affected by mild or moderate A, and preoperatively treated by a variable doses of ESAs. iPTH, Hb levels, and ESA requirement, were compared pre and postoperatively, and at 6 and 12 months follow-up. In most cases, a successful Ptx determined an increase in RBC and Hb levels, reduced ESA requirement both at 6 and 12 months, decreasing medical costs.

## Materials and Methods

Data were retrospectively collected from 30 consecutive patients (11♂and 19♀), affected by 2HPT of CKD, on standard three-weekly HD, observed between January 2004 and January 2009. All patients gave informed consent to participate in the study. According to the Royal College of Physicians (UK) National Clinical Guideline Centre[11], Hb level ≤ 8 mg/dl, ≤ 10 g/dl, ≤ 12 g/dl in female patients or ≤ 13 g/dl in male patients, were classified as severe, moderate or mild A respectively.

The 1.06-6.89 pmol/L range was taken as reference of normal iPTH level based on which eu- (1.06-6.89), hypo- (< 1.06), aparathyroidism (0) and persistence or relapse ( > 6.89) of disease were determined.

Hypocalcemia was considered to be present when serum calcium was < 1.99 mmol/L (normal value= 2.09-2.54 mmol/L).

Ptx was considered successful when postoperative iPTH level was < 26.52 pmol/L.

High-resolution neck ultrasonography, ENT examination, technetium- 99m-sestamibi scintigraphy of the neck and mediastinum, were the main preoperative diagnostic procedures. Hemoglobin (Hb) levels, RBC, hematocrit and erythropoietin dosing were evaluated pre and 6-12 months after surgery, since Ptx effects on erythropoiesis occur at least three months after surgery; to minimize the dilution effect on laboratory assays, all blood samples were obtained before dialysis. Intact parathyroid hormone (iPTH), serum calcium (Ca), serum phosphate (P), alkaline phosphatase (ALP) and $FT_3$, $FT_4$, TSH, thyroglobulin were measured along with fine needle biopsy of the thyroid nodules. The Liaison NTact PTH Assay (DiaSorin Inc-Stillwater, MN, USA), based on chemiluminescence immunoassay (CLIA), was used for the quantitative determination of iPTH (Coefficient of variation: CV% intra assay 1.7-3.7; CV% inter assay 2.6-5.9; limit of detection 0.07 pmol/L).

Patients were addressed to our Institution from regional HD centres, and indications to surgical procedure were set according to both K/DOQI 2003 guidelines and Tominaga [12,13].

Regarding the surgical procedures, 15 patients underwent total parathyroidectomy (TP) and another 15, on the kidney transplant waiting list, underwent total parathyroidectomy with autotransplantation (TPai) of 9-15 fragments of non- nodular glandular tissue, in 3 subcutaneous pockets of the non-dominant forearm.

In 12 out of 30 patients (40%) with thyroid gland disease, 8 total thyroidectomy and 4 hemithyroidectomy procedures were performed. In all cases, 4 parathyroid glands at least were removed (the nature of the tissue was confirmed via intraoperative histological examination).

Only in a few cases, a HD treatment was required immediately after surgery, due to an electrolyte imbalance. The majority of patients required intravenous administration of calcium, due to postoperative hypocalcemia.

Patients who underwent autoimplantation completed long-term follow-up monitoring of iPTH from the implantation site and from the contralateral arm, in order to evaluate the gradients.

The patients included in the study did not receive kidney transplantation in the intervening period between surgery and evaluation.

### Statistics

Data were reported as the mean ± standard error of the mean (SEM). A paired t Student test was performed [14]. All calculations were performed using the software package GraphPad Prism, Version 5.0 for Windows (GraphPad Software, San Diego, CA, USA). Statistical significance is considered at $p < 0.05$.

## Results

### Demographics

Patient mean age was 51.5 ± 10.89 years, and mean dialysis vintage was 12.93 ± 8 years. Mean preoperative iPTH was 142.08 ± 64.01 pmol/l, and mean serum calcium level was 2.50 ± 0.45 mmol/l. All patients reported diffuse pruritus, arthromyalgia and mood alterations, while cardiovascular disease (defined as signs of cardiac hypertrophy at the EKG) was found in 60%. No case of calciphylaxis was reported. Twelve patients (40%) suf-

fered from coexisting thyroid pathology. None of them had iron deficiency or external blood loss and a mild or moderate A (Hb level 7 - <12 gr/dl), was observed. The ESA treatment regimen consisted in three-weekly recombinant human ESA (alfa-erythropoietin) injections - 5.200 ± 3824.48 IU, in 29/30 patients. 1/30 patients was treated with alfa darbepoetin 30 (30 μgr/every 15 days). Preoperative RBC count, Hb levels, ESA dosing are reported in Tables I and II.

### Surgical outcomes

TP and TPai were followed by similar functional outcomes. Surgical treatment produced a benefit in terms of itching, a substantial improvement in clinical osteoarticular symptoms as well as in mood patterns first, and later in sleep disorders [15-19], an increase in muscular strength, which were associated to a statistically significant reduction in PTH levels (Fig. 1), ESA need (Fig. 2) and improvement of Hb levels (Figure 3). With regard to twelve-months Hb levels, 26/30 pts (86.6%) showed a significant increase and 5 (19.2%) of them had a Hb level >12 gr/dl. No significant variations were reported in 4/30 pts (13.3%).

Regarding the postoperative ESA dosage, 27/30pts (90%) did not need drug treatment, whilst 3/30 pts (10%) needed a lower dosage.

No significant peri- or postoperative complications were observed. None of the patients was found to be aparathyroid.

Eighteen patients (60%) required intravenous postoperative administration of calcium gluconate due to hypocalcemia, which was occasionally severe, with a minimum value of 1.42 mmol/L, but was never associated with hypocalcemic seizures.

The definitive histological examination confirmed the hyperplasia of the removed glands; 2 patients (6.6%) had 5 hyperplastic glands; 8 patients (26.6%) had an associated multinodular goiter, 2 (6.6%) an adenomatous goiter and 2 (6.6%) papillary carcinoma.

In every case iPTH levels were ≤ 26.52 pmol/L during a 12 months follow-up. Tables 3-4 show immediate (on postoperative day 1) and one year TP-TPai functional results.

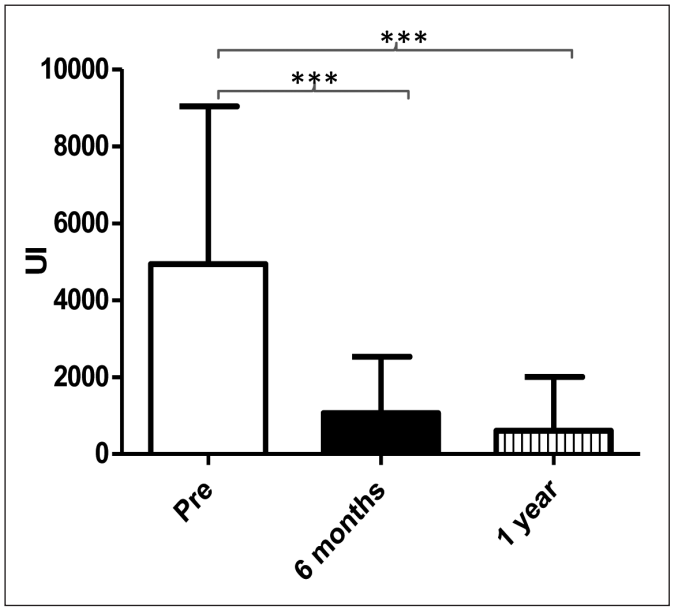


Fig. 1: Preoperative, 6 months and 1 year after surgery mean iPTH levels [t test (n = 30) pre vs 6 months ***p< 0.0001;pre vs 1 year ***p:0.0001].

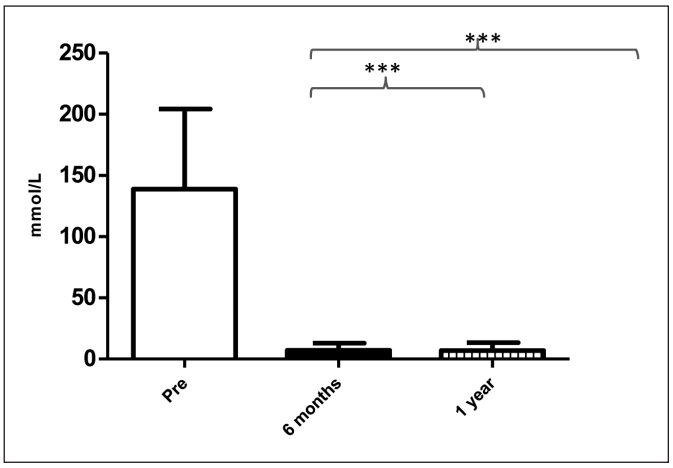


Fig. 2: Preoperative, 6 months and 1 year after surgery mean ESA requirement [t test (n = 30) pre vs 6 months *** <0.0001; pre vs 1 year *** p< 0.0001].

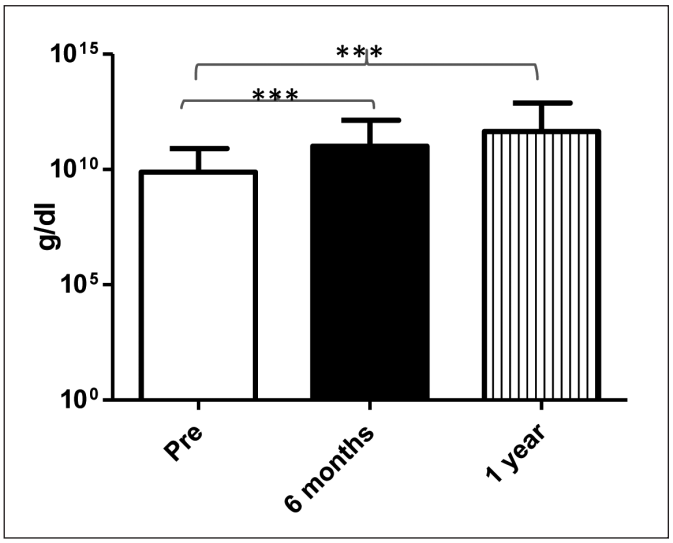


Fig. 3: Preoperative, 6 months and 1 year after surgery mean hemoglobin levels [t test (n = 30) pre *vs* 6 months *** p<0.0001; pre *vs* 1 year *** p<0.0001]. Values are expressed as power of 10 in order to better visualize differences.

After one year Computed Bone Mineralometry and skeletal x-rays showed a clear regression of osteodystrophy in all patients, irrespective of the procedure carried out. No long-term pathological fractures were reported.

## Discussion

Most available studies, inherent to Ptx or medical therapy effects on renal A, have been published between 1980 and 2000, and remain controversial relatively to outcome evaluation. After this time, during which improved HD techniques and medical therapy have greatly changed the general management of CKD patients, we can find only scant analyses in the literature[7,8,10,20-22]. In addition, an FDA alert has been issued in June 2011, warning that excessive ESA treatment with a target > 11 g/dl Hb is fraught with an higher cardiovascular risk[6]. We therefore evaluated the role of Ptx on chronic A and ESA requirement in HD patients, observed in the last years, also comparing functional TP or TPai results.

In the present study, successful Ptx for 2HPT of CKD determined a considerable improvement of A, reducing exogenous ESA need in most patients (27/30pts - 90%), consequently reducing collateral effect and medical costs. In our analysis, TP and TPai were followed by similar functional outcomes. Retrospective analysis and small number of patients are the main limits of the study.

According to KDIGO guidelines[23], Ptx is indicated in patients affected by severe, not responding to medical therapy, 2HPT of CKD, and A represents a secondary indication, that becomes absolute when it becomes resistant to medical treatment [13].

Surgical treatment, required in approximately 1-2 % of patients each year[24], associated in expert hands with minimal morbidity and excellent cure rates, can offer a higher long-term survival rate, as well as a better quality of life (QoL), also improving bone mineral density[3,8,15,16,25]. Ptx is effective in controlling pruritus, osteoarticular and neuromuscular symptomatology, especially mood and sleep disorders [15-17].

Cardiovascular complications, due to "vascular ossification", seems to be irreversible and, probably, when initial signs are present, it should be considered an early indication to surgery.

Ptx ameliorates also A, a typical finding in 2HPT of CKD, which is determined by different causes [3,4]. Decreased endogenous renal erythropoietin production, bone marrow fibrosis, reduced erythropoiesis due to calcitriol level reduction, decrease RBC survival, HD procedure, and resistance to ESAs are the main investigated factors. As a consequence, exogenous recombinant human erythropoietin is needed, and is, at the present, very effective in correcting A in most patients[1].

Since 1980, ESAs are in fact routinely indicated in medical treatment of CKD in HD patients, improving the QoL [22,26,27,28], thereby causing an increase in healthcare costs (Table V). Nevertheless, according to Foley, in the management of CKD, clinical trials on A do not permit to identify the most efficacious, safe and cost-effective ESA therapeutic strategies[5]. Response to medical

TABLE I - *Pre-operative and 6 months and 1 year after surgery TPai data.*

| | Pre operative | 6 months | 1 year |
|---|---|---|---|
| iPTH (mmol/L) | 141.39 ± 62.27 | 7.14 ± 5.84 (***) | 7.34 ± 7.30 (***) |
| Hb (g/dl) | 10.01 ± 1.33 | 10.48 ± 0.91 (*ns*) | 11.56 ± 0.7 (***) |
| Hct (%) | 33.36 ± 2.32 | 33.87 ± 1.87 (*ns*) | 37.95 ± 3.17 (**) |
| RBC (x$10^6$/µL) | 3.46 ± 0.45 | 3.60 ± 0.33 *(ns)* | 4.41 ± 0.62 (***) |
| ESA requirement (UI) | 6133.33 ± 4773.07 | 2571.42 ± 903.50 (***) | 3000 ± 1414.21 (***) |

TPai= Total parathyroidectomy + subcutaneous autoimplantation; iPTH=Intact parathyroid hormone; Hb=Hemoglobin; HCT=Hematocrit; RBC= Red blood cell; ESA = Erythropoiesis-stimulating agent; t test p value pre vs 6 months and pre vs 1year (***p< 0.0001, **p<0.001)

TABLE II - *Pre-operative and 6 months and 1 year after surgery TP data.*

| | Pre operative | 6 months | 1 year |
|---|---|---|---|
| iPTH (mmol/L) | 130.01 ± 71.14 | 7.08 ± 6.05 (***) | 6.47 ± 5.61 (***) |
| Hb (g/dl) | 9.8 ± 0.98 | 11.3 ± 1.12 (**) | 11.72 ± 1.61(***) |
| Hct (%) | 35.61 ± 1.80 | 36.34 ± 2.18 (*ns*) | 37.95 ± 3.17(*ns*) |
| RBC (x$10^6$/µL) | 3.83 ± 0.57 | 4.24 ± 0.53 (*ns*) | 4.24 ± 0.82 (*ns*) |
| ESA requirement (UI) | 3733.3 ± 2711.5 | 2800 ± 1095 (*ns*) | – |

TP= Total parathyroidectomy; iPTH=Intact parathyroid hormone; Hb=Hemoglobin; HCT=Hematocrit; RBC= Red blood cell; ESA= Erythropoiesis-stimulating agent; t test p value pre vs 6 months and pre vs 1 year (***p< 0.0001 **p<0.001)

TABLE III - *Ptx postoperative day 1 results.*

| | Eupara | % | Hypopara | % | Persistence | % |
|---|---|---|---|---|---|---|
| TP | 11/15 | 73.3 | 3/15 | 20 | 2/15 | 13.3 |
| TP ai | 10/15 | 66.6 | 3/15 | 20 | 2/15 | 13.3 |

Ptx= Parathyroidectomy; TP= Total parathyroidectomy; TPai= Total parathyroidectomy + subcutaneous autoimplantation

TABLE IV - *Ptx one year results.*

| | Eupara | % | Hypopara | % | Persistence | % |
|---|---|---|---|---|---|---|
| TP | 10/15 | 66 | – | – | 5/15 | 33.3 |
| TP ai | 9/15 | 60 | 1/15 | 6.6 | 2/15 | 13.3 |

Ptx= Parathyroidectomy; TP= Total parathyroidectomy; TPai= Total parathyroidectomy + subcutaneous autoimplantation

TABLE V - *Mean ESA costs in Italy.*

| Drug active principle | Mean dose/week | Mean cost/week | Mean cost/month |
|---|---|---|---|
| Epoetin alfa | 12000 UI | 198,45 € | 793,8 € |
| Epoetin beta | 12000 UI | 150 € | 600 € |
| Darbepoetin | 40 mcg | 143,19 € | 572,76 € |
| Methoxy polyethylene glycol-epoetin beta | 12.5 mcg | 42 € | 167,67 € |

treatment is variable, depending on poorly known factors, and, A requiring an administration of ESAs > 300 IU/Kg per week to reach or maintain a target Hb concentration, within 4 to 6 weeks of treatment, is considered as being resistant. Further pathogenetic factors, such as iron-deficiency, infections, aluminium overload, malnutrition, immunosuppression were considered [9,24,25].

The role of iPTH as a uremic toxin on erythropoiesis, has been a topic of several interesting studies. High serum iPTH levels are involved in decreasing RBC survival [2], and determining bone marrow fibrosis [3,29], which is followed by a reduction in RBC progenitor number. ESA response is inversely related to serum iPTH levels [7] as well, and higher ESA dosing, in patients showing higher PTH levels, and a more severe bone marrow fibrosis, was demonstrated [29]. According to Meytes [4], iPTH seems to have an inhibiting effect on erythropoietin release, and, moreover, by stimulating bone marrow fibrosis, improving hemolysis and decreasing marrow erythroid progenitors, may also induce ESA hyporesponsiveness [30]. Vitamin D deficiency is also involved, and administration of calcitriol can successfully improve renal A [22,31].

Most of surgery effects on renal A and ESA requirement data, published before 2000, were contrasting, not straightforward, and researches were mainly based on small series. However, recent studies showed that Ptx may decrease the need for ESAs and correct or improve A[7,8,21]. Ptx ameliorates A also in patients with a significant ESA treatment resistance, improving erythropoietin production and overall nutritional status. Surgery may infact determine progressive weight gain, decrease of gastric acid secretion, a better fat turnover, daily activity and improving patient appetite [2-22]. An increase of Hb level in 50% of patients submitted to Ptx is reported [7,8,32], as well as a postoperative increase in serum endogenous erythropoietin levels [33,34]. Zingraff [3] reported an Htc increase associated to a decrease of bone marrow fibrosis in Ptx patients; similarly, Goicoechea [35] showed a decreased postoperative ESA need. Also Coen [36] confirmed the efficacy of Ptx on A control. Brancaccio[9] affirmed that "progressive hyperparathyroidism carries a progressive resistance of bone marrow to ESA treatment and early control of PTH secretion is crucial for preventing worsening of anemic status".

In the last years, the interest of literature has focused on this issue, especially because of calcimimetics widespread use, which was very effective either on iPTH decrease or on A control, reducing bone marrow fibrosis [37,38]. A comparison study of Ptx vs calcimimetics effects on chronic A is eagerly awaited.

With regard to our analysis, in patients undergoing a successful Ptx, surgery was associated to a remarkable increase of overall QoL, along with a regression of pruritus, osteoarticular, muscle and neurological symptomatology, with a very low morbidity rate. A significant improvement of A, and a lower need of ESA dosing, determining a significant reduction of healthcare costs,

were observed regardless of preoperative serum iPTH concentrations and of surgical procedure (TP or TPai).

## Conclusions

In case of renal A, a more aggressive treatment of 2HPT should be indicated. When it is associated to well known symptoms (renal osteodystrophy, pruritus and muscle weakness), A represents a secondary indication to Ptx, not only when medical treatment fails, since surgery, associated to a very low complication rate, may reduce ESA requirement, and increase RBC and Hb levels, decreasing medical costs.
Ptx is especially recommended in more severe anemia, resistant to ESA treatment, on the contrary to the last decade of the last century, when it was not considered as an independent indication for surgical intervention [39]. Therefore, we propose that it should be considered a major indication, with the same clinical weight of the more commonly regarded symptoms.
Nevertheless, further studies on larger series of patients, managed by a new and more effective medical treatment irrespective to the past, are needed, in order to obtain a more accurate statistical analysis on the effects of surgical treatment on A and ESA need in HD patients by medium and long-term follow-up.


## Riassunto

L'anemia (A), talora resistente al trattamento farmacologico, rappresenta un fattore di rischio cardiovascolare comune ai pazienti dializzati affettti da iperparatiroidismo secondario (IPS). L'elevazione del paratormone determina infatti una ridotta sopravvivenza dei globuli rossi, una fibrosi midollare ed una inibizione della secrezione endogena di eritropoietina. In passato, numerosi studi hanno dimostrato che la paratiroidectomia (PTx) nel paziente dializzato aumenta i livelli di eritropoietina migliorando l'A e riducendo la necessità di un trattamento farmacologico. Nello studio retrospettivo, condotto negli ultimi anni, gli Autori hanno valutato gli effetti della PTx sull'A e la necessità di eritropoietina esogena nei pazienti in emodialisi affetti da IPS. Tra il 2004 e il 2009, 30 pazienti affetti da IPS resistente alla terapia medica, sono stati sottoposti a PTx totale (15 casi) e PTx totale con autoimpianto sottocutaneo (15 casi). I livelli sierici di iPTH, emoglobina, il numero di globuli rossi e la dose di eritropoietina preoperatori venivano confrontati con quelli osservati 6-12 mesi dopo chirurgia. In ogni paziente la PTx determinava una notevole riduzione dell'iPTH con incremento dell'emoglobina nell'86.6% dei casi. 27/30 pazienti (90%) non richiedevano più somministrazione postoperatoria di eritropoietina. L'analisi dei risultati ottenuti dimostra che, indipendentemente dal tipo di intervento, la PTx determina un'incremento dell'emoglobina migliorando l'A nella gran parte dei casi e consentendo una riduzione della spesa sanitaria relativa alla somministrazione di eritropoietina. Nei pazienti in emodialisi affetti da IPS, l'A dovrebbe essere attentamente considerata come fattore determinante nell'indicazione al trattamento chirurgico.


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