



## Subtotal Parathyroidectomy versus Total Parathyroidectomy and Autotransplantation in Secondary Hyperparathyroidism: A Randomized Trial

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In a randomized study subtotal parathyroidectomy (sPTX) was compared with total parathyroidectomy and autotransplantation of fresh tissue (PTX + AT) in 40 patients with severe secondary hyperparathyroidism (HPT). After surgery both groups were followed at  $19 \pm 6$  months (PTX + AT) and  $19 \pm 7$  months (sPTX) and at  $43 \pm 9$  months (PTX + AT) and  $40 \pm 7$  months (sPTX). There were 17 patients alive in each group at the time of the second follow-up. After sPTX, 2 patients required re-operation because of recurrent disease originating from the remaining parathyroid gland in the neck and another 2 patients were hypercalcemic at follow-up. After PTX + AT both serum calcium and alkaline phosphatase normalized significantly more often ( $p < 0.03$ ) than after sPTX. Re-operations were not required in this group. Radiological signs also improved significantly more after PTX + AT, as did clinical signs like pruritus ( $p < 0.005$ ) and muscle weakness ( $p < 0.04$ ). These results and the fact that in recurrent disease a re-operation at the autograft in the forearm is simpler than a re-operation in the neck, lead to the recommendation that PTX + AT should be considered as the method of choice in the surgical treatment of secondary HPT.

About 5% of patients with chronic renal failure treated with long-term dialysis require surgery for secondary hyperparathyroidism (HPT) [1]. Hyperfunction of all parathyroids is usual and has to be taken into account when planning surgery. Subtotal parathyroidectomy (sPTX) in secondary HPT was first advocated in 1960 [2]. Eight years later, Averyd [3] reported total parathyroidectomy with autotransplantation (PTX + AT) of fresh parathyroid tissue as a feasible technique. Since that time, there has been no definitive answer to the question of which method is superior. Even meta-analysis of published data (Tables 1 and 2) does not provide the answer due to poorly designed or incomplete studies [4]. Retrospective analysis and incomplete and indeterminate periods of follow-up predominate. In addition, most studies have concentrated on laboratory findings, particularly pre-operative and postoperative serum calcium levels, without taking into account clinical symptoms or the degree of radiologically detectable renal osteopathy as part of the indication for surgery. There are a few reports on direct comparisons of both operative techniques but these were performed either as consecutive studies or without a prospec-

tive randomized trial [5-9]. We report the first prospective randomized study to examine the respective merits of these 2 operations.

### Material and Methods

In 1984 and 1985, 40 patients underwent surgery for secondary HPT. Patients were allocated to one of the treatment groups according to a balanced random permutation. sPTX and PTX + AT each were performed in 20 patients. Clinical data are summarized in Table 3. The groups were similar in age, sex, time period of chronic renal failure, and dialysis. At the time of parathyroidectomy, 38 patients were on chronic hemodialysis, 1 patient had a functional renal graft, and 1 patient was in the predialysis stage of chronic renal failure.

The frequency and severity of clinical symptoms including bone pain, pruritus, and muscle weakness as well as radiological signs of renal osteopathy in routine roentgenograms of the hand skeleton were documented in both groups (Table 4).

The indication for surgery was hypercalcemia in 12 patients undergoing sPTX and in 17 patients having total PTX + AT. In all others surgery was based on severe renal osteopathy with bone pain and positive roentgenographic findings as well as pruritus in the presence of normocalcemia (range of pre-operative serum calcium, 2.25 mmol/l to 2.6 mmol/l). Serum concentrations of parathyroid hormone (PTH) were measured but are not reported here since different assays with different normal ranges were used. Also the PTH levels are rather insignificant for establishing the indication for surgical intervention in secondary HPT.

In the group undergoing sPTX, all parathyroid tissue was removed except for a 60 mg to 80 mg piece of 1 gland that had a good blood supply. The weight of the remaining tissue was estimated by weighing a piece of the same size cut from a resected gland. Four parathyroids were found in 19 cases and 5 glands in 1 case in which  $4 \frac{1}{2}$  glands were resected. The mean weight of all glands removed per patient was 5.6 g (range, 0.7 g to 25 g). Extended surgery included thymectomy in 5 patients and thyroid resection for concomitant nodular goiter in 2 patients.

Four parathyroid tumors were excised in all 20 patients in the

**Table 1.** Results of total parathyroidectomy and autotransplantation in secondary hyperparathyroidism.

Author, year (reference)	No. of pts.	Hypocalcemia	Hypercalcemia	Improvement of bone pain
Wells, 1979 (9)	100	0	3	85
Spelsberg, 1980 (16)	17	2	2	13
Thompson, 1980 (17)	14	1	1	14
Diaz-Buxo, 1981 (18)	50	0	3	36
Diethelm, 1981 (19)	61	0	2	61
Max, 1981 (20)	16	0	2	14
Klempa, 1982 (21)	41	1	4	—
Rothmund, 1983 (1)	100	7	3	82
Welsh, 1984 (22)	15	0	1	11
Albertson, 1985 (5)	10	1	1	8
Kinnaert, 1985 (23)	31	0	3	3
McCarron, 1985 (24)	19	0	0	19
White, 1986 (25)	12	0	5	—
Korzets, 1987 (26)	19	0	5	—
Alexander, 1988 (27)	110	0	12	—
Tagaki, 1988 (8)	128	0	8	128
Niederle, 1989 (28)	35	1	2	34
Henry, 1990 (29)	152	0	4	—
Total	920	13 (1.4%)	61 (6.6%)	504 of 596 (85%)

**Table 2.** Results of subtotal parathyroidectomy in secondary hyperparathyroidism.

Author, year (reference)	No. of pts.	Hypocalcemia	Hypercalcemia	Improvement of bone pain
Hognestad, 1977 (30)	14	3	1	14
Cordell, 1979 (6)	36	11	3	—
Swanson, 1979 (31)	22	0	2	20
Blake, 1983 (32)	33	1	2	19 of 20
Welsh, 1984 (22)	8	0	1	8
Delmonico, 1984 (33)	32	2	3	—
Tagaki, 1984 (8)	20	0	1	—
Zdon, 1984 (34)	14	2	0	11
Albertson, 1985 (5)	22	1	0	21
Neale, 1985 (36)	12	3	0	10
Sitges-Serra, 1987 (37)	26	1	1	—
Johnson, 1988 (38)	61	0	6	13 of 27
Henry, 1990 (29)	79	0	2	—
Total	379	24 (6.3%)	22 (5.8%)	116 of 140 (83%)

PTX + AT group. In each patient 20 tissue pieces 1 to 2 mm<sup>3</sup> were implanted into a forearm muscle. The mean weight of all glands was 5.4 g (range, 1.5 g to 12 g). Extended surgery included cervical thymectomy in 7 patients and subtotal thyroidectomy for nodular goiter in 3 patients. Resection of the thyro-thymic ligament was undertaken in all operations in both groups.

In all 40 operations, frozen sections of all glands confirmed the diagnosis intra-operatively. Resected tissue was routinely cryopreserved for possible reimplantation.

Patients were treated and followed by referring dialysis centers after discharge. Between 1986 and 1988, a standardized questionnaire was sent to these centers. The postoperative course, current levels of serum calcium and alkaline phosphatase, clinical symptoms, radiological changes of the hand skeleton, and potential dose of supplemental calcium or vitamin D metabolites were documented along with possible re-operation that might have performed elsewhere. All questionnaires were answered. Comparisons were made using the chi<sup>2</sup> test.

**Table 3.** Clinical data of 40 patients in randomized study.

	sPTX (n = 20)	PTX + AT (n = 20)
Male/female	8/12	8/12
Age (mean yrs)	44.8	45.0
Time period of renal failure (mean yrs)	11.1	10.7
Time period of chronic hemodialysis (mean yrs)	6.6	7.3
Kidney transplant (no. of pts.)	1	—
Pre-dialysis (no. of pts.)	1	—
On chronic hemodialysis (no. of pts.)	18	20

sPTX: subtotal parathyroidectomy; PTX + AT: total parathyroidectomy and autotransplantation.

## Results

The first follow-up examination was carried out 19 ± 7 months (sPTX) and 19 ± 6 months (PTX + AT) after surgery. Thirty-

**Table 4.** Pre-operative symptoms and radiological signs of secondary hyperparathyroidism.

	sPTX (n = 20)	PTX + AT (n = 20)
Bone pain	12 (60%)	16 (80%)
Pruritus	11 (55%)	12 (60%)
Muscle weakness	7 (35%)	6 (30%)
Radiological signs of renal osteopathy	19 (95%)	18 (90%)

sPTX: subtotal parathyroidectomy; PTX + AT: total parathyroidectomy and autotransplantation.

eight patients could be followed; 2 patients having PTX + AT had died. Between operation and first follow-up, one patient of the latter group and 2 further patients with sPTX received kidney transplants and had normal renal function at follow-up. The second follow-up was at  $40 \pm 7$  months (sPTX) and  $43 \pm 9$  months (PTX + AT). At that time, another patient in the PTX + AT group had died and 3 patients in the sPTX group. Five of 17 patients after sPTX and 4 of 17 patients after PTX + AT had received functioning kidney transplants; the remaining 25 patients were still on maintenance hemodialysis.

No patient required supplemental therapy for hypofunction of the remaining parathyroid tissue. Three patients in each group received low doses of vitamin D metabolites for treatment of their renal osteopathy. No cryopreserved parathyroid tissue was reimplanted in either group and no re-operations were performed for autograft hyperfunction in the PTX + AT group.

Pre-operative levels of serum calcium and alkaline phosphatase are shown in Figures 1 and 2. Both parameters normalized in most patients. Significant differences were evident at the second follow-up date however, between the 2 groups. In 2 patients after sPTX the detection of hypercalcemia led to re-operation. In both cases the parathyroid remnant was enlarged. A further 2 patients were hypercalcemic because of suspected cervical recurrence. After sPTX, therefore, therapeutic failure occurred in 4 patients, compared with no recurrence after PTX + AT. A significant difference ( $p < 0.03$ ) exists in favor of PTX + AT. The same significance ( $p < 0.03$ ) is achieved comparing the levels of alkaline phosphatase including the 4 patients showing elevated levels in Figure 2 and those 2 patients with cervical re-operation who both had elevated serum alkaline phosphatase levels before re-operation (6 of 17 patients following PTX + AT versus 1 of 17 patients following sPTX).

In parallel with these biochemical improvements, bone pain, pruritus, muscle weakness, and radiological signs of renal osteopathy normalized more often in the group with PTX + AT compared to the sPTX group (Table 5). This was statistically significant for renal osteopathy at the time of the second follow-up [ $p < 0.05$  (11 of 16 patients with sPTX versus 5 of 15 patients after PTX + AT)], for pruritus [ $p < 0.005$  (5 of 11 patients with sPTX versus 10 of 10 patients with PTX + AT)] and for muscular weakness [ $p < 0.04$  (1 of 5 with sPTX versus 5 of 6 patients with PTX + AT)], but not for bone pain (Table 5).

## Discussion

The goals in surgical treatment of secondary HPT are normalization of serum calcium levels and improvements of the

clinical symptoms and radiological signs of renal osteopathy. Each of these can be used to assess outcome and make comparisons between different surgical strategies. A simple analysis of serum calcium levels alone is inadequate. Although there is a correlation between postoperative normalization of calcium metabolism and improved clinical and radiological findings, this is not always the case. In addition, some normocalcemic patients require surgery for severe clinical symptoms [4]. It is important, therefore, that each factor be considered since each plays a role in the decision making process leading to surgery. Finally, both the number and extent of re-operations should be considered when evaluating alternative techniques.

Irreversible hypercalcemia is the most frequent indication for surgery, which should still be advocated in the absence of clinical symptoms or radiological changes since these are expected to occur with time. The only reason to postpone parathyroid surgery is when kidney transplantation is expected within a short period of time. Then, provided the kidney transplant functions normally, serum calcium levels return to normal and symptoms of secondary HPT disappear in most cases [10].

Hypercalcemia was the most frequent indication for surgery in this series. As shown in Tables 1 and 2, both sPTX and PTX + AT lead to normocalcemia in most patients. There were, however, 4 recurrences after sPTX. This led to re-operation for a hypertrophied cervical remnant of parathyroid tissue in 2 patients before the second follow-up investigation. The other 2 patients await re-operation. It is unlikely that a fifth parathyroid gland is the source of the recurrence since both patients had a cervical thymectomy at the time of initial operation. It is probable that continuous growth of the parathyroid remnant explains their recurrent hypercalcemia. During the period of this study hypercalcemia could not be detected in the group undergoing PTX + AT. Cases requiring re-operation can, however, occur [11]. Transplant hyperfunction may be associated with hypertrophy of the forearm fragments. In these instances ultrasonography visualizes the fragments as echopoor areas and palpation may reveal small nodules [12]. A further source for a recurrence can be any parathyroid left *in situ* at the time of initial operation, especially if less than 4 parathyroids were excised.

A further possible complication is persistent hypocalcemia which was present in 1 patient in each group at the time of second follow-up. Borderline values of 2.0 mmol/l and 2.1 mmol/l were merely clinically occult, leading to low dose therapy with oral calcium and not requiring reimplantation of cryopreserved autologous tissue.

Rates of hypocalcemia calculated from compiled data (Tables 1 and 2) reveal a 4 fold increase after sPTX compared to PTX + AT. Also, the reliability of these studies may be limited as it is still probably true that sPTX does not provide better protection for this complication than PTX + AT. This implies that even in sPTX parathyroid tissue should be cryopreserved so that reimplantation can be carried out should persistent symptomatic postoperative hypocalcemia become manifest. Moreover, not only in our own experience but also in published reports, autotransplantation of fresh and cryopreserved tissue is an apparently safe procedure to prevent persistent hypocalcemia as well as a recurrence of secondary HPT [11].

Improved clinical symptoms is another criterion by which to

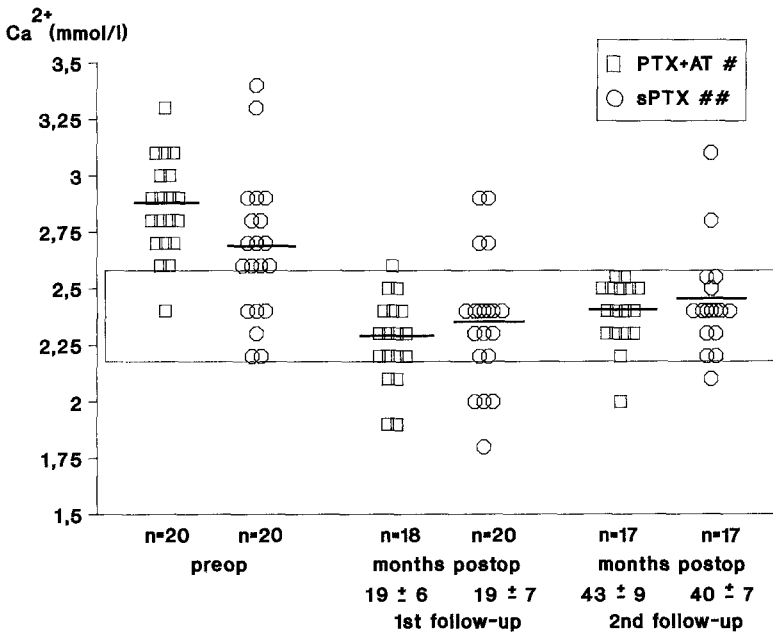


Fig. 1. Serum calcium levels measured pre-operatively and at follow-up in both patient groups. sPTX: subtotal parathyroidectomy; PTX + AT: total parathyroidectomy + autotransplantation.

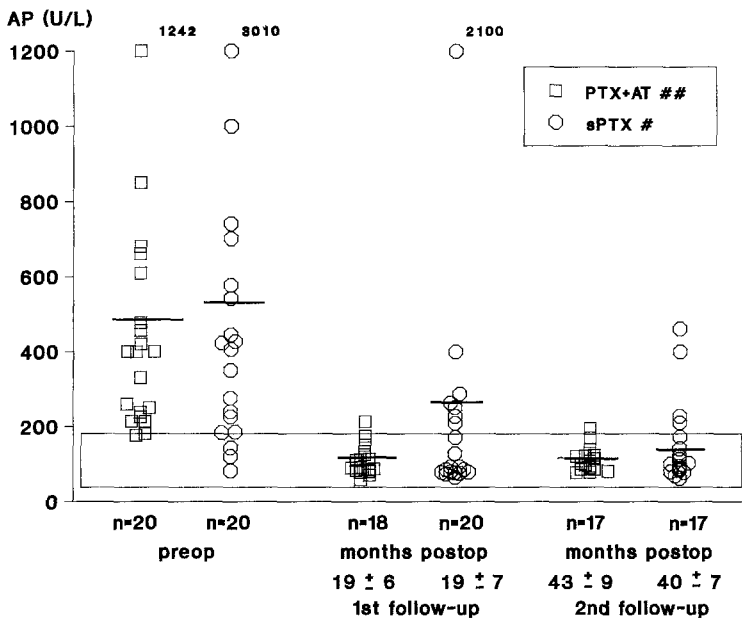


Fig. 2. Alkaline phosphatase values measured pre-operatively and at follow-up in both patient groups. sPTX: subtotal parathyroidectomy; PTX + AT: total parathyroidectomy + autotransplantation.

judge the success of surgery. The most frequent symptom is bone pain, which presents as dull back pain or as arthralgias at the ankles, hips, or shoulders. Bone pain is the result of decalcification as a consequence of renal osteopathy. Pruritus associated with secondary HPT is possibly caused by high PTH levels [13] or possibly by calcium-phosphate complexes deposited in the skin. Muscle weakness is another common symptom which can be an indication for surgery.

Previous studies show that postoperatively bone pain subsides in most patients, no matter which operative technique is used (Tables 1 and 2). In this series, there was a small, though statistically insignificant, difference favoring PTX + AT. In published studies there have been no reliable data concerning the influence of surgical methods on pruritus and muscle weakness. In our investigation, however, we found a significant difference in favor of PTX + AT.

The third feature used to evaluate surgical outcome is improvement of the radiological signs of renal osteopathy. Pathognomonic signs are subperiosteal resorption and acro-osteolysis of the phalangeal bones as evidence of osseal resorption by fibro-osteoclasia. The radiological signs were improved more frequently ( $p < 0.05$ ) after PTX + AT than after sPTX. Some estimation of bone metabolism is also reflected in alkaline phosphatase levels. If a hepatic source is excluded, then elevated alkaline phosphatase levels in the presence of radiological signs of renal osteopathy indicate increased bone metabolism and this provides a strong argument for parathyroidectomy. The return of alkaline phosphatase values to normal levels occurred significantly more often after PTX + AT than after sPTX.

Summarizing the 3 target parameters, normocalcemia, improvement of clinical symptoms, and radiological changes, this

**Table 5.** Postoperative improvement of clinical symptoms and radiological signs.

	Subtotal PTX		Total PTX + AT		Statistical significance <sup>a</sup>
	First follow-up	Second follow-up	First follow-up	Second follow-up	
Bone pain	7/12 (58%)	8/13 (61%)	14/15 (93%)	13/15 (87%)	n.s.
Pruritus	7/11 (63%)	5/11 (45%)	9/11 (82%)	10/10 (100%)	$p < 0.005$
Muscle weakness	2/5 (40%)	1/5 (20%)	6/6 (100%)	5/6 (83%)	$p < 0.04$
Radiological signs of renal osteopathy	4/16 (25%)	5/15 (33%)	11/18 (61%)	11/16 (69%)	$p < 0.05$

PTX: parathyroidectomy; AT: autotransplantation; number of patients with symptom/total number of patients; n.s.: not significant.

<sup>a</sup>At time of second follow-up.

study shows that all 3 parameters demonstrate significant differences in favor of PTX + AT. There are no comparable observations reported in the literature. In part, these differences are due to recurrences observed in 4 patients after sPTX. This finding, however, does not explain all of the differences in postoperative complaints and radiological findings. One explanation could be that the amount of parathyroid tissue remaining is more difficult to estimate in sPTX than when performing PTX + AT. Twenty parathyroid particles 1 mm to 2 mm in length consistently reflect a weight of 60 mg to 80 mg tissue. This is about the amount necessary to provide a normal calcium metabolism in these patients. Even an experienced surgeon may find it difficult to estimate the correct size of the parathyroid remnant in sPTX, particularly where the subtotally resected gland is exposed incompletely in order to not jeopardize its blood supply, or where the gland is situated deep in an incisura of a thyroid lobe. This potentially results in greater amounts of tissue being left *in situ* than after PTX + AT. Conversely, if the parathyroid remnant is too small or its blood supply is compromised, then this might lead to a higher rate of hypocalcemia after sPTX (Table 2) compared to PTX + AT (Table 1). Blood supply from original vessels and the preserved innervation of the cervical gland remnant might also be of importance, since autotransplants are denervated and nourished by a slowly sprouting capillary system arising from the surrounding tissue [4].

The authors also discussed among themselves whether they might be biased, since they had used PTX + AT routinely for years, or whether they might be better trained in PTX + AT than in sPTX. All that can be said is that the 2 authors who performed all of the operations (M.R. and P.K.W.) tried objectively to see if there was a real difference in outcome. Both were trained in sPTX in more than 50 cases of primary hyperplasia among more than 400 operations for primary HPT within recent years. It seems therefore unlikely that significant personal bias was introduced.

The incidence and extent of re-operations also merit consideration. In this study re-operations were required only after sPTX which was always due to hypertrophy of the cervical remnant. This is secondary to chronic renal failure with continuous stimulation of function and growth of the remaining parathyroid tissue. The same mechanism applies to the autotransplant in the forearm in patients after PTX + AT where, in cases of symptomatic hypertrophy, surgery is indicated. Cervical re-operations are more invasive, require greater surgical expertise, and are associated with a higher morbidity than the excision of an autograft in the forearm. Even if the incidence of recurrence was similar, this aspect would be another strong

argument for performing PTX + AT as the method of choice in the surgical treatment of secondary HPT.

Cervical re-operations may still be necessary after PTX + AT when parathyroid glands are left *in situ* either in the neck or in the mediastinum [1, 12, 14, 15]. In most of these cases fewer than 4 parathyroids were found during the initial operation. Although this has not been reported after sPTX, it may be assumed that it can happen after both procedures. This should not therefore be used as an argument for one or another procedure since it can be avoided by an adequate knowledge of typical and ectopic sites of the parathyroid glands and by routine thymic tongue resection in secondary HPT.

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#### Résumé

Dans une étude randomisée, la parathyroïdectomie subtotale (sPTX) a été comparée à la parathyroïdectomie totale avec autotransplantation (PTX + AT) chez 40 patients ayant une hyperparathyroïdie secondaire sévère (HPT). Après l'opération, les deux groupes de patients ont été revus deux fois: à  $19 \pm 6$  et à  $43 \pm 9$  mois pour le groupe PTX + AT, et à  $19 \pm 7$  et à  $40 \pm 7$  mois pour le groupe sPTX. Dix-sept patients étaient en vie dans chaque groupe à la deuxième visite de contrôle. Après sPTX, deux patients ont dû être réopérés en raison de tissu parathyroïdien résiduel; deux autres patients sont restés hypercalémiques. Après PTX + AT, la calcémie et le taux de phosphatases alcalines se sont normalisés plus souvent ( $P < 0.03$ ) qu'après sPTX. Aucune réopération n'a été nécessaire dans le groupe PTX + AT. De même, les signes radiologiques, les signes cliniques tels le prurit ( $p < 0.005$ ) et la faiblesse musculaire ( $p < 0.04$ ) se sont améliorés plus souvent de façon significative dans le groupe PTX + AT. Ces résultats et le fait que lors des récurrences, une autogreffe à l'avant-bras est plus simple qu'une réexploration cervicale, nous amène à préconiser la PTX + AT comme méthode de choix dans le traitement chirurgical de l'HPT.

#### Resumen

En un estudio randomizado se compararon la paratiroidectomía subtotal (sPTX) con la paratiroidectomía total con autotrasplante de tejido fresco (PTX + AT) en 40 pacientes con hiperparatiroidismo secundario severo (HPT). Ambos grupos

fueron valorados dos veces después de la cirugía; a los  $19 \pm 6$  meses (PTX + AT) y  $19 \pm 7$  meses (sPTX) y a los  $43 \pm 9$  meses (PTX + AT) y los  $40 \pm 7$  meses (sPTX). Se encontraron 17 pacientes vivos en cada grupo en el momento de la segunda valoración. Después de sPTX 2 pacientes requirieron reoperación por enfermedad recurrente originada en la glándula paratiroides remanente en el cuello y otros 2 aparecieron hipercalcémicos. Después de PTX + AT tanto el calcio sérico como la fosfatasa alcalina se normalizaron significativamente con mayor frecuencia ( $p < 0.03$ ) que después de sPTX; no se requirieron reoperaciones en este grupo. Los signos radiológicos también mejoraron significativamente con mayor frecuencia después de PTX + AT, tal como lo hicieron signos clínicos tales como prurito ( $p < 0.005$ ) y debilidad muscular ( $p < 0.04$ ). Estos resultados, junto con el hecho de que en la enfermedad recurrente una reoperación sobre el autoinjerto en el antebrazo es más simple que una operación en el cuello, da lugar a recomendar que la PTX + AT es el método de escogencia en el manejo quirúrgico del sHPT.

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