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Conservative three-quarter versus subtotal seven-eighths parathyroidectomy in secondary hyperparathyroidism

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ABSTRACT

Keywords:

End-stage renal disease
Chronic kidney disease
Parathyroidectomy
Secondary hyperparathyroidism
Hypoparathyroidism

Objective: There is at present no consensus concerning surgical techniques for secondary hyperparathyroidism (SHPT) in end-stage renal disease (ESRD). Although both subtotal and total parathyroidectomy provide low rates of recurrence, they may induce hypoparathyroidism, damaging the bone and cardiovascular systems. The aim of our study was to compare 3/4 and 7/8 parathyroidectomy in this population and to discuss the potential benefit of more conservative treatment.

Study design: Prospective observational study in a university teaching hospital between 2010 and 2014.

Methods: The study included 34 consecutive ESRD patients with SHPT: 19 underwent 3/4 parathyroidectomy (group A*3/4) and 15 underwent 7/8 parathyroidectomy (group B*7/8). Serum intact 1-84 PTH levels (before and 6 months after surgery) and hospital stay were compared between the two groups.

Results: Before surgery, PTH levels were similar between the two groups. At month 6 following surgery, median PTH levels were significantly higher in group A*3/4 than in group B*7/8 (109 versus 24 pg/mL, respectively; $P < 0.0006$). Hospital stay was shorter in group A*3/4 (4.79 versus 6.80 days, respectively; $P = 0.008$). Postoperative hypoparathyroidism requiring long-term calcium and 1 α (OH) D3 treatment was reported in 5% of patients in group A*3/4 and 26% of patients in group B*7/8 ($P = 0.04$).

Conclusions: In this preliminary study, 3/4 conservative parathyroidectomy seemed effective and safe, with less reported morbidity than 7/8 parathyroidectomy, as assessed by lower rates of irreversible hypoparathyroidism and shorter hospital stay.

Level of evidence: 3b, individual case-control study.

1. Introduction

Secondary hyperparathyroidism (SHPT) in end-stage renal disease (ESRD) is due to several mechanisms, including increased serum fibroblast growth factor 23 (FGF23) and low circulating 1,25(OH)₂D levels [1,2]. This dysregulation leads to persistent low serum calcium concentrations, which induce high serum parathyroid hormone (PTH) levels related to hyperplasia of the four parathyroid glands, in most cases. Despite improvements in the medical management of patients with SHPT, some develop progressive bone disorders characterized by osteofibrosis with bone

pain and spontaneous fractures, erythropoietin-resistant anemia, myopathy, arthropathy, and soft-tissue calcifications with calciphylaxis, worsening prognosis.

Partial or total parathyroidectomy (PTx) to decrease hyperplastic parathyroid tissue mass is indicated in ESRD, especially in the setting of persistent high PTH levels, hypercalcemia and hyperphosphatemia despite well-conducted medical therapy [3] and/or when patients experience complications such as calciphylaxis, fractures, bone pain or pruritus. Expected benefits of PTx include improved quality of life, with alleviation of symptoms, prevention of calciphylaxis, and improvement of anemia and mineral density [4]. However, although total PTx in ESRD patients has no influence on cardiovascular outcomes, onset of chronic hypoparathyroidism was reported to decrease survival [5,6].

Several treatment aspects are controversial. Preoperative parathyroid gland localization procedures are not well established and depend upon PTH monitoring, and type of surgical procedure,

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especially between subtotal and total PTx with or without cryopreservation or transplantation [7]. There is controversy between total PTx (radical PTx) versus subtotal PTx indications, and there are no studies defining the amount of remnant parathyroid tissue that must be left in situ (i.e., the amount of parathyroid tissue that should be removed) in subtotal PTx, and notably in 7/8 PTx. Total PTx, with or without autotransplantation, has been shown to prevent recurrent or persistent SHPT [8,9]. However, most implanted parathyroid glands proved nonfunctional [7], and 25% rates of irreversible hypoparathyroidism and 25% rates of disease persistence are reported with subcutaneous autotransplantation [10]. Relocation of cryopreserved glands is also rarely successful [11]. Hypoparathyroidism and hypocalcaemia are the most common complications after total PTx [12]. The consequences of chronic hypoparathyroidism for bone metabolism in ESRD patients are not well established. In normal adults, bone mass is regulated by a balance between resorption and formation in a tightly regulated process of remodeling, in which PTH is one of the key regulators. A reduction or absence of circulating PTH can lead to abnormal bone dynamics with initially decreased bone resorption coupled to a reduction in bone formation. Chronic hypoparathyroidism thus requires massive calcitriol and calcium substitution to correct hypocalcemia, which may induce vascular calcification, calcific uremic arteriopathy (CUA) or calciphylaxis [13–15].

In our experience, onset of hypoparathyroidism is not a rare event following 7/8 PTx. We therefore decided shift to 3/4PTx (conservative PTx) and to compare this new procedure with the former one, using PTH level at 6 months following PTx as the main criteria. We hypothesized that a more conservative PTx could decrease the occurrence of hypoparathyroidism while reducing serum PTH levels within recommended KDIGO target values [3].

2. Methods

2.1. Patients (Fig. 1)

Nineteen consecutive patients underwent conservative PTx (3/4PTx) for SHPT in our center between 2010 and 2013 (group

A*3/4) (). This group was compared to a population of 15 patients who underwent conventional 7/8 subtotal PTx between 2004 and 2009 (group B*7/8). All procedures were performed by the same surgeon.

All patients had a longstanding history of chronic renal failure requiring hemodialysis. Patients who underwent renal transplantation within 6 months following PTx ($n = 10$: 5 in group A*3/4 and 5 in group B*7/8) were excluded from analysis, as were patients in whom follow-up was performed in other centers ($n = 9$: 3 in group A*3/4 and 6 in group B*7/8).

2.2. Surgical indication

Hyperparathyroidism was assessed the month before surgery by high serum intact PTH (iPTH) levels using radioimmunoassay kits (Cisbio International and Immunodiagnosics Systems Ltd). Surgery was indicated according to the KDIGO criteria [3]: failure of > 6 months medical management of HPT (despite calcium, calcimimetics, calcitriol (1.25 dihydroxycholecalciferol) supplements, or phosphate binders) with hypercalcemia or hyperphosphatemia and PTH > 800 pg/mL, calciphylaxis with documented elevated PTH levels, osteoporosis (T score > 2.5 SD below mean, pathologic fracture), and symptoms of osteomalacia (pruritus, bone pain, severe vascular calcifications, myopathy).

2.3. Radiological assessment

Before surgery, parathyroid glands were localized both by high resolution ultrasonography in the presence of the surgeon, and dual-phase dual-isotope iodine-123/technetium-99m sestamibi scintigraphy in our institution, to detect the number and the position of the hyperfunctioning parathyroid glands [16]. Results of these preoperative investigations (scintigraphy and ultrasonography) were important to decide both which parathyroid gland should be preserved during surgery (i.e. the least hyperfunctioning), and the most hyperfunctioning parathyroid glands that should be removed.

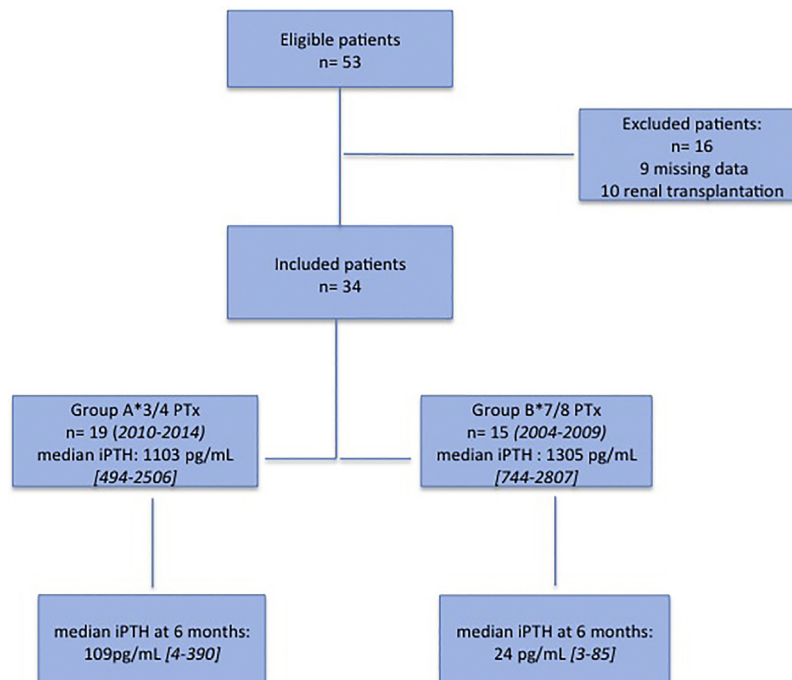


Fig. 1. Flowchart. Results of median iPTH before and after parathyroidectomy in the two groups. Interquartile range in brackets.

2.4. Surgical procedure

All surgical procedures were performed by the same surgeon (SP), under general anesthesia, through a transverse collar incision with a retrothyroid approach. Inferior laryngeal nerve monitoring (Neurosign® 400, Inomed GmbH, Feningen, Germany) was systematically used to test the first inferior laryngeal nerve visualized before dissection of the other side [17].

All pre-localized glands were identified without complete dissection before their excision; the most normal parathyroid gland, identified preoperatively by scintigraphy (the least hyperfunctioning) and ultrasonography (the smallest), or intraoperatively, was left vascularized in situ (in 3/4PTx), or half was removed (7/8 PTx). The 3 most hyperfunctioning parathyroid glands assessed by scintigraphy and/or by ultrasonography were usually identified intraoperatively and removed. When only 3 parathyroid glands were identified intraoperatively, dissection of part of group VI was performed [18] (ipsilateral paratracheal and superior mediastinal neck dissection); if the 4th parathyroid gland was finally not found, only two-thirds (equivalent to 3/4PTx) or five-sixths (equivalent to about 7/8 PTx) of the glands was removed. The remaining gland was marked with a nonabsorbable thread to facilitate any reoperative detection. No intraoperative iPTH measurement was performed.

Histological analysis of frozen sections confirmed presence of parathyroid tissue, before definitive analysis.

2.5. Postoperative supplementation

Postoperatively, all patients received oral calcium and 1-alpha-hydroxy-cholecalciferol (1alpha(OH)D3), in addition to 1.75 mmol/L calcium dialysate during the first postoperative days. In the immediate postoperative period, intravenous calcium gluconate was systematically delivered in group B*7/8, and exceptionally in group A*3/4, and prolonged if the total calcemia remained <1.7 mmol/L despite oral supplements. Patients were commonly discharged when their level of calcium was >1.8 with supplementation, depending on the center in which the hemodialysis were performed.

2.6. Monitoring and hospital stay

Serum iPTH levels monitoring was performed systematically before surgery and at month 6. Measurement of total and/or ionized calcemia was performed both during hospital stay and after discharge by referent nephrologists in order to adapt calcium and vitamin D supplements when necessary, but was not a study parameter since measurements were not performed at the same time in the two groups of patients.

Hospital stay (from first postoperative day) was compared between the two groups.

Complications such as laryngeal nerve injury, infection, or wound hematoma were reported.

2.7. Analysis

Analysis of iPTH before surgery and at month 6 and hospital stay were compared between the two groups. The results are reported as median values with 25–75% interquartile range for quantitative data. Comparisons between two groups were tested by Mann-Whitney non-parametric test for quantitative data and Chi² test for qualitative data (GraphPad Prism V.7, San Diego, CA). *P*-values <0.05 were considered statistically significant.

2.8. Ethical considerations

The study was approved by the “Commission d’Évaluation et de Recherche Observationnelle en Oto-Rhino-Laryngologie” (Ethics Committee of the Society of Otolaryngology, France). Data were strictly anonymous.

3. Results

The study population included 14 women and 20 men (sex ratio 1.43). They were aged from 23 to 66 years with a mean age of 44 years. The two groups were similar regarding age and gender. All patients were ESDR under hemodialysis. As shown in Figs. 1 and 2, preoperative serum iPTH level was similar in the two groups. Tables 1 and 2 report pre- and postoperative iPTH in the two groups.

The four parathyroid glands were identified in all patients during surgery, with sizes in accordance with scintigraphy or ultrasonography, except two patients in group A*3/4 (Table 1). In these two patients, 2 of the 3 identified glands were removed, and PTH at month 6 was within the target range (105 and 174 pg/mL, respectively). In all patients, parathyroid tissue was confirmed on frozen sections, and histopathologic findings confirmed the diagnosis of hyperplastic parathyroid glands. Two patients in group B*7/8 (patients 4 and 11) and 1 patient in group A*3/4 (patient 2) experienced a severe postoperative hypocalcemia related to a hungry bone syndrome (Tables 1 and 2). These patients required intravenous calcium gluconate and 1.75 mmol/L calcium dialysate in the immediate postoperative period, before their substitution with oral calcium and 1alpha(OH)D3.

Hospital stay was shorter in group A*3/4 (4.79 versus 6.8 days; *P*=0.0086).

Six months following surgery, iPTH had significantly decreased in both groups (*P*<0.0001), with significantly higher values in group A*3/4 (median 109 pg/mL versus 24 pg/mL in group B*7/8, *P*=0.0006) (Figs. 1 and 2). 86% (13/15) versus 31% (6/19) of patients in group B*7/8 and A*3/4 respectively (*P*=0.0013) exhibited iPTH <50 pg/mL; hypoparathyroidism requiring long-term calcium and 1alpha(OH)D3 treatment was reported in 4 patients (26%) in group B*7/8 and in only 1 patient (5%) in group A*3/4 (patient 2) (*P*=0.04). The relatively high level of PTH in group A*3/4 (>300 pg/mL) did not require revision of parathyroidectomy, as bone biomarkers were improved.

No wound infection was observed. One patient in group B*7/8 showed hematoma at day 3, which was successfully drained. Intraoperative neuromonitoring of the inferior laryngeal nerve was

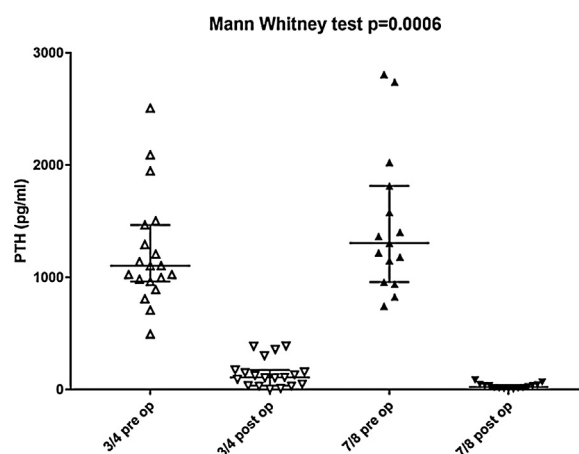


Fig. 2. iPTH variations in groups A*3/4 and B*7/8 before surgery and postoperatively, at 6 months. Medians, with interquartile range between horizontal bars.

Table 1
Characteristics of patients with 3/4 parathyroidectomy (group A*3/4).

n = 19	Gender	Age	Pre-iPTH	Surgery	Post-iPTH	H stay
1	F	60	1139	3/4	157	6
2	M	28	963	3/4	34	14
3	M	52	891	3/4	390	5
4	F	41	2091	3/4	49	4
5	M	51	1105	3/4	132	4
6	M	43	1465	3/4	31	4
7	M	46	808	3/4	123	4
8 ^a	M	55	1291	2/3	105	4
9	M	58	494	3/4	151	4
10	M	55	1024	3/4	109	4
11 ^a	F	59	983	2/3	174	6
12	F	57	1024	3/4	32	4
13	M	45	2506	3/4	358	5
14	M	54	1103	3/4	104	4
15	M	55	997	3/4	303	2
16	M	38	708	3/4	93	4
17	F	27	1207	3/4	4	4
18	M	49	1502	3/4	12	6
19	F	25	1946	3/4	387	4

Intact Parathyroid hormone (iPTH) (pg/mL). Pre-iPTH (pg/mL): Preoperative iPTH; Post-iPTH (pg/mL): Postoperative iPTH (pg/mL); H stay: hospital stay in days.

^a Only 3 parathyroid glands were found during surgery in patients 8 and 11.

Table 2
Characteristics of patients with subtotal parathyroidectomy (group B*7/8).

n = 15	Gender	Age	Pre-iPTH	Post-iPTH	H stay
1	F	36	1814	3	5
2 ^a	F	66	1181	3	14
3	M	38	1305	85	4
4	F	46	2023	13	5
5	F	26	942	35	5
6	F	36	744	17	7
7	M	53	1219	34	5
8	M	56	1578	65	14
9	M	38	2740	17	12
10	M	57	1148	13	6
11	M	58	2807	35	5
12	M	33	827	24	4
13	M	23	1401	41	7
14	F	32	1364	43	4
15	F	25	957	7	5

Intact Parathyroid hormone (iPTH) (pg/mL). Pre-iPTH (pg/mL): Preoperative iPTH; Post-iPTH (pg/mL): Postoperative iPTH (pg/mL); H stay: hospital stay in days.

^a Patient 2 required prolonged parenteral calcium replacement before oral relay.

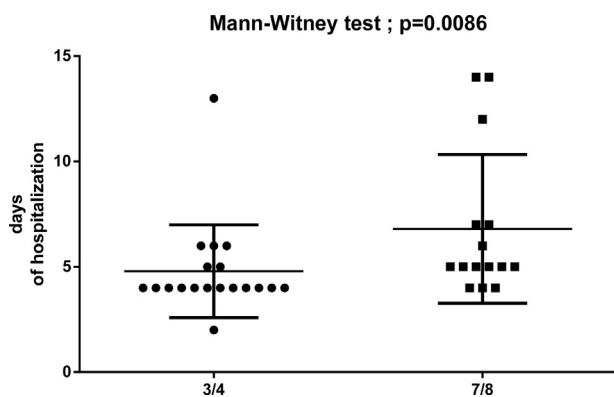


Fig. 3. Hospital stay in groups A*3/4 and B*7/8.

positive in all cases. However, a transient unilateral inferior laryngeal nerve paralysis (lasting 3 months) was reported in 1 patient in group A*3/4 (Fig. 3).

4. Discussion

The aim of our preliminary study was to evaluate the outcomes of conservative PTx (3/4 PTx) compared to subtotal PTx (7/8 PTx) in

SHPT and to assess the prevalence of hypoparathyroidism in relation to the type of procedure. Assessment was based on iPTH assay at month 6, which is the essential marker of parathyroid function. PTH levels decreased dramatically in the B*7/8 PTx group, with more frequent onset of irreversible hypoparathyroidism, although iPTH levels decreased in both groups; no patients in group A*3/4 required PTx revision surgery. However, follow-up in our preliminary study was limited to 6 months, whereas events such as renal transplantation are frequent in these patients over the long term. In addition, patients who underwent 2/3PTx probably still had a whole fourth gland in situ, which has an impact on postoperative PTH levels, but may be considered as accessory since not hyperfunctioning on scintigraphy, not located on ultrasonography and not identified during surgery; the choice of 2/3PTx is justified, PTH being only 105 and 176 pg/mL at month 6 (patients 8 and 11 in group A; Table 1).

This was the first study to assess iPTH status in conservative PTx, and it should be borne in mind that there is no consensus on the surgical management of renal hyperparathyroidism [4], whereas KDIGO provides guidelines for medical management and criteria for surgical indications [3]. It is a challenging clinical problem to propose surgical management in renal hyperparathyroidism. Although the main objective is to lower postoperative PTH levels, recent studies have shown that excessive decrease resulting in severe

hypoparathyroidism is associated with increased cardiovascular mortality when levels fall below 47 pg/mL in a stage V chronic kidney disease population [19]; the hypoparathyroidism impairs bone dynamics, with vascular calcifications related to the administration of high doses of calcium and active vitamin D. A prospective multicenter study including 2,164 patients treated with high calcium dialysate reported excess cardiovascular mortality [14]. These data and the present results are thus in favor of conservative PTx in SHPT.

Our results strongly support the view that a more conservative parathyroid surgery in SHPT, by 3/4 (or 2/3) PTx, is preferable to 7/8 PTx, achieving PTH levels within target values, with lower risk of recurrent hypoparathyroidism. In case of PTH concentration above target values, based upon calcium status, vitamin D compounds and/or calcimimetic agents may also be given. When revision surgery is required, the risk of inferior laryngeal nerve paralysis appears lower than the risk of chronic hypoparathyroidism encountered after 7/8 PTx; hypoparathyroidism is not reversible, with no PTH substitution available. Within our population, in the group A*3/4, no patients required second surgery for persistent significant hyperparathyroidism at a relatively short 6 months' follow-up. Moreover, landmarking with nonresorbable thread near the inferior laryngeal nerve facilitates localization of in case of potential revision surgery. Furthermore, removal of part of a non-dissected gland (in 3/4PTx) is certainly easier than the removal of remnant tissue from a gland already sectioned with opened capsule (in 7/8PTx), since the latter usually requires removing part of the thyroid gland (as remnant parathyroid tissue comes in close contact with it). Secondary removal of part of the remnant parathyroid gland left is possible in persistent hyperparathyroidism; in contrast, severe hypoparathyroidism is irreversible.

In order to select the parathyroid gland to be conserved (i.e., the least hyperfunctioning/hyperplastic) in conservative PTx, complementary tools such as scintigraphy and ultrasonography are mandatory. This procedure avoids complete dissection of the remaining gland, thus limiting postoperative fibrosis which would substantially increase inferior laryngeal nerve lesions in case of second surgery.

Lower and shorter doses of oral calcium and vitamin D were required after 3/4PTx, thus presumably limiting risk of long-term vascular and soft-tissue calcification [13–15]. However, the duration of postoperative vitamin D and calcium replacement is also dependent on the duration of both dialysis and SHPT before surgery, as the magnitude of calcium depletion within bones largely explains the duration of calcium supplementation. Accordingly, a high preoperative PTH level is known to be a predictor of high postoperative calcium requirements [20].

Shorter hospital stay following 3/4 rather than 7/8 PTx further suggests that 3/4 PTx decreases short-term morbidity or alternatively facilitates monitoring, as surgical complications were similar between the two groups. This difference in time period may, however, constitute a bias, although calcium and 1alpha(OH)D3 substitution protocols were identical. Patients were discharged when 1.75 mmol/L dialysate was no longer necessary, at which point they were more quickly relayed with oral calcium and 1alpha(OH)D3.

This conservative PTx approach also appears to be a good option in kidney transplant recipients, since iatrogenic hypoparathyroidism following subtotal PTx in this population is at risk of graft dysfunction [19], related to hypercalciuria. Unilateral or "focused PTx", on the hyperfunctioning parathyroid gland(s), has been previously advocated [21–25]. Surgical management of SHPT needs to progress in grafted patients with history of parathyroid hyperplasia [26].

Study limitations: this small study was observational and not randomized, hence with low level of evidence. Our surgical

strategy change – from subtotal to conservative PTx – was the result of an exchange of views between surgeons and nephrologists, and the awareness that irreversible hypoparathyroidism following PTx is associated with worse prognosis, as autotransplanted or reimplanted parathyroid glands following total PTx are not successful [7,11]. Follow-up was also short; assessment at 6 months was chosen in view of the frequent onset of major adverse events, including renal transplantation, in the longer term. Medical management following surgery was performed by general practitioners and nephrologists and thus may also induce some bias related to the use of calcium vitamin D and/or calcimimetics; unfortunately these data and ionized calcium measurements were unavailable. PTH level was the parameter studied, as providing a good reflection of residual parathyroid function, and since it was systematically assayed before surgery and at month 6 in the two groups, unlike total calcemia levels, which provide little information and were not available for all patients at the time of the study, as nephrologic follow-up was sometimes performed outside our center. In future, 6-month biological follow-up including ionized calcium and PTH will be performed, with longer term follow-up of bone mineral density by bone biomarkers, and of PTH profile. Further work is required to assess the long-term follow-up, especially for bone mineralization (especially by studying bone biomarkers) and SHPT recurrence.

5. Conclusion

Though this pilot study requires confirmation by higher-powered multicenter controlled studies with longer follow-up, our data demonstrate the safety and efficacy of 3/4 conservative PTx to treat SHPT in dialyzed patients, as assessed by 6-month plasma PTH values and shorter hospital stay. Thus, conservative PTx appears as a safe alternative to maintain bone dynamics and avoid vascular and valvular calcifications in ESRD [13].

Disclosure of interest

The authors declare that they have no competing interest.

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