Medication discontinuation after curative surgery for sporadic primary hyperparathyroidism

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Background. Although parathyroidectomy (Ptx) for sporadic primary hyperparathyroidism (PH) improves comorbidities and symptoms, routine Ptx for minimally symptomatic PH remains controversial. Whether successful Ptx translates into discontinuation or dose-reduction of prescribed medications is unknown.

Methods. Consecutive patients undergoing curative Ptx for sporadic PH from January 2007 to April 2009 were compared to patients undergoing thyroidectomy (Tx). We reviewed patient demographics, symptoms, comorbid conditions, and pre- and postoperative medications utilizing the Fisher exact test and t test for comparisons.

Results. Compared to 176 Tx patients, 260 Ptx patients were older (P < .001), more commonly men (P = .006), and had higher preoperative prevalences of every examined PH symptom and comorbid condition. Postoperatively, even minimal PH symptoms improved after Ptx. The mean number of preoperative medications was higher in Ptx patients (4 vs 2.8, P < .001). Discontinuation or dose-reduction of medication occurred in 28 (11%) Ptx patients vs 7 (4%) Tx patients (P = .01). After Ptx, symptom improvement was the predominant reason for beneficial medication changes, and the most common beneficial effect was discontinuation or dose-reduction of chronic analgesics (33%).

Conclusion. PH symptoms are numerous and improve after curative Ptx. Medication use for related symptoms can be beneficially reduced by surgery. Drug profiles should be routinely reviewed and adjusted after parathyroidectomy. (Surgery 2010;148:1113-9.)

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Sporadic primary hyperparathyroidism (PH) is one of the most common endocrine disorders, with an incidence of approximately 22 per 100,000 person-years in the U.S.1 The incidence of PH varies with geographic location, gender, and age, with a peak incidence in women in their 6th decade.2 Parathyroidectomy (Ptx) provides the only cure for PH. Increasingly, studies have shown that truly asymptomatic PH is a rare entity. A number of common medical comorbidities seen in the US have been demonstrated to be associated with PH, including hypertension, hyperlipidemia, nephrolithiasis, osteoporosis, pancreatitis, and peptic ulcer disease.2 Many of the major comorbidities, as well as more nonspecific or “minimal” musculoskeletal, gastrointestinal, and neurobehavioral symptoms, such as depression, have been reported to improve after Ptx. In a recent case-control study, only ~5% of patients did not report an improvement in symptoms after Ptx, yet routine surgery for all patients remains controversial.3

To quantify symptom improvement, the PAS score was developed and validated by Pasieka et al4 who recently documented that improved quality of life, associated with a lower PAS score, can last for up to 10 years after Ptx.5 It is not known if symptom improvement translates into the discontinuation or dose-reduction of medications used to treat PH comorbidities and symptoms. We hypothesized that (a) comorbidity and symptom-associated medication use is more common in patients requiring Ptx for PH than in a control cohort of patients undergoing thyroidectomy (Tx), and that (b) after successful Ptx, these medications may be discontinued or the dosage reduced.

METHODS

A prospective multi-surgeon database was queried for all patients >18 years old with sporadic PH.
undergoing initial Ptx between January 1, 2007 and April 30, 2009. Data review was done under a University of Pittsburgh Institutional Review Board-approved protocol (IRB# PRO09070034). PH was defined as hypercalcemia with an elevated or inappropriately high-normal intact parathyroid hormone (PTH) level.

We considered the symptoms of PH to include: self-reported depression, anxiety, fatigue, bony/joint pain, constipation, short-term memory loss, and nocturia more than once per night. We considered the comorbid conditions of PH to include: osteoporosis, osteoarthritis, peptic ulcer disease (PUD), gastroesophageal reflux disease (GERD), pancreatitis, hypertension, and hyperlipidemia. The indications for Ptx were: any symptom (with the exception of isolated constipation), a comorbid condition (except isolated hypertension, hyperlipidemia, or osteoarthritis) or for asymptomatic patients, the presence of one or more of the 2002 Consensus Criteria: age <50 years, absolute calcium level >1mg/dL above the upper limit of normal, bone demineralization with a T-score <−2.5 at any site, 24-hour urine calcium of >400mg/day, reduction in creatinine clearance of >30%, and/or inability to undergo appropriate surveillance. Other conditions such as fibromyalgia, migraine headaches, and bipolar disorder were noted, but their presence was not an indication for Ptx. Although we performed Ptx when patients elected surgery but did not meet the above criteria, we excluded such patients (n = 3) from the study cohort.

Under the same IRB protocol, we retrieved the same type of data for a cohort of consecutive patients in our practice who had initial Tx (lobectomy or total) for nodular thryomegaly and/or substernal goiter during the same time interval. At their initial preoperative consultation, all Tx and Ptx patients submitted a written yes/no questionnaire about their medical history that included assessment of hypertension, hyperlipidemia, arthritis, nephrolithiasis, PUD, GERD, constipation, anxiety, and depression. Additionally, Ptx patients were verbally interviewed at both their preoperative and 6-month follow-up visits concerning the standard PH-related symptoms, and in addition were specifically asked postoperatively about the issues they had reported preoperatively. Open-ended and/or objective questioning was employed, such as the following: “Does arthritis or bone pain bother you now, and where exactly?”, “Would you say your fatigue is worse, better or the same than it was preoperatively?”, and “How many times do you get up at night to void?” Tx patients were not routinely interviewed in this manner.

All surgery was performed by 1 of 4 endocrine surgeons; intraoperative PTH monitoring, but not neuromonitoring, was routinely utilized during Ptx. A detailed list of current medications, dosages, new medical problems, and new symptoms was recorded at each pre- and postoperative clinic visit for both Ptx and Tx patients. Data collection included patient demographics, perioperative symptoms, medical comorbidities, medication types and dosages, (antidepressants, anxiolytics, Alzheimer’s medications, stool softeners, analgesics, antihypertensives, antilipids, and antacids), and operative conduct, findings, outcomes, and complications.

Except for transient postoperative analgesia (prn acetaminophen with or without codeine, 0–5 days), routine postoperative calcium supplementation (7–10 days for Tx, 6 months for Ptx), and the institution of replacement l-thyroxine when required after Tx, the medications examined in this study were not changed or advised about by the operating team. All study patients were seen 7–14 days postoperatively. Tx patients were seen again at ≥3 months (mean 4.5) and Ptx patients were seen at ≥6 months (mean 8.2). We excluded Tx patients who were not euthyroid at final postoperative follow-up, who were not screened preoperatively for hypercalcemia, and/or who received postoperative radiiodine ablation for thyroid cancer. Patients with incidental papillary microcarcinoma who did not receive postoperative radiiodine ablation were included. All included Ptx study patients experienced a documented biochemical cure, defined as normal levels of calcium and parathyroid hormone at ≥6 months postoperatively.

Continuous variables were expressed as a mean and compared using the Student t test, while discrete variables were compared with the Fisher exact test. Statistical analysis was done using STATA 9.2 (StataCorp, College Station, TX). A P value <.05 was considered significant.

RESULTS

During the study period, 260 patients with sporadic PH received initial Ptx with durable cure. They were compared to 176 patients undergoing Tx. Characteristics of the patients are summarized in Table I. Ptx patients were older than Tx patients (mean age 61 vs 56 years, P < .001) and were also more commonly men (26 vs 15%, P = .006). The majority of Ptx patients (247/260, 95%) reported symptoms associated with PH. Ptx was performed in 13 (5%) study patients who were truly asymptomatic and instead met 1 of the 2002 consensus criteria for surgery. Major operative complications did not differ by group. Ptx patients were followed for a longer mean period of time.

As Table II illustrates, Ptx patients preoperatively had a higher (P < .02) prevalence of comorbidities
and symptoms reportedly associated with PH (99.6%) than did Tx patients (133/176, 76%). Ptx patients were more likely to manifest at least one of the PH-associated comorbidities except PUD, and were more likely to manifest at least 1 of the PH-associated symptoms examined. We also observed an interesting trend toward a higher prevalence of self-reported fibromyalgia among Ptx patients, but the difference did not reach significance.

Following Ptx, 81 (31%) of patients reported symptom improvement by their first postoperative visit. Although a formal survey was not performed again at this visit, Ptx patients described symptomatic improvement(s) in fatigue, mood, and/or joint and bony pain. At >6 months after curative surgery, systematic re-survey of Ptx patients showed that 188/260 (72%) reported improvement(s) in specific preoperative symptoms. As illustrated in the Figure, among 260 Ptx patients, improvements were most frequent for fatigue (45%), followed by bony/joint pain (36%), nocturia (23%), depression (22%), STML (11%), GERD (7%), and anxiety (4%).

Preoperatively, Ptx patients took an average of 4.0 (range, 0–17) medications while Tx patient took an average of 2.8 (range, 0–13) medications ($P < 0.01$, Table I). Table III lists the categories of different medications that were taken preoperatively. Overall, postoperative discontinuation or dose-reduction of study medications (a “beneficial” change) occurred in 28 (11%) Ptx patients compared to 7 (4%) Tx patients ($P = 0.01$). A total of 30 different medications were discontinued (29) or dose-reduced (1) in Ptx patients, compared to only 8 medications that were discontinued among Tx patients. The most common type of medication to be stopped or dose-reduced among Ptx patients was chronic analgesics (10/30, 33%). Two patients were able to stop more than 1 medication (1 stopped an analgesic and a proton pump inhibitor and the other stopped an antidepressant and an antihypertensive). The most common type of medication to be stopped among Tx patients was antacids (2/8, 25%) and only 1 Tx patient was able to discontinue her analgesic.

The clinical details of analgesic medication discontinuation after curative Ptx were informative. Among the 10 beneficial medication changes involving analgesics, 6 patients discontinued nonsteroidal anti-inflammatory agents and 4 patients discontinued narcotics. In addition to her narcotic, 1 patient also was able to discontinue the cyclobenzaprine and pregabalin originally prescribed for “complex regional pain syndrome.” Improvement in depression enabled 3 Ptx patients to discontinue antidepressants postoperatively. Improvement in anxiety allowed 2 patients to discontinue and 1 patient to decrease the dosage of their anxiolytics postoperatively.

### Table I. Patient characteristics by disease type

<table>
<thead>
<tr>
<th>Variable</th>
<th>Parathyroid n = 260</th>
<th>Thyroid n = 176</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age at operation (years) ± SD</td>
<td>61.2</td>
<td>55.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Men (%)</td>
<td>67 (26)</td>
<td>26 (15)</td>
<td>.006</td>
</tr>
<tr>
<td>Mean number preoperative medications (range)</td>
<td>4 (0–17)</td>
<td>2.8 (0–13)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Hematoma (%)</td>
<td>2 (.8)</td>
<td>2 (1.1)</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>Permanent hypoparathyroidism (%)</td>
<td>2 (8)</td>
<td>0 (0)</td>
<td>.52</td>
</tr>
<tr>
<td>Permanent vocal cord paralysis (%)</td>
<td>0 (0)</td>
<td>1 (.01)</td>
<td>.40</td>
</tr>
<tr>
<td>Mean follow-up (months)</td>
<td>8.2</td>
<td>4.5</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*Peptic ulcer disease.
†Gastroesophageal reflux disease.
‡Short-term memory loss.

and symptoms reportedly associated with PH (99.6%) than did Tx patients (133/176, 76%). Ptx patients were more likely to manifest at least one of the PH-associated comorbidities except PUD, and were more likely to manifest at least 1 of the PH-associated symptoms examined. We also observed an interesting trend toward a higher prevalence of self-reported fibromyalgia among Ptx patients, but the difference did not reach significance.

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In the subset of 5 patients who had been diagnosed with fibromyalgia, 80% reported improvement in symptoms after Ptx by the final follow-up visit, and 2 patients felt better within 2 weeks of surgery. One “fibromyalgia” patient was able to stop her antidepressant medication altogether. Among the 4 Ptx patients who discontinued their antihypertensives, mean systolic blood pressures pre- and postoperatively were 159 and 139 mmHg, respectively (P = .20). One Ptx patient discontinued the antilipid gemfibrozil, and her postoperative low density lipoprotein level is now in the normal range; there were 3 patients who discontinued proton pump inhibitors.

We evaluated the initiation of new medications and the dose increase of existing medications (an “adverse” change) after Ptx and Tx, and these results are shown in Table IV. After Ptx or Tx, a total of 38 medications were initiated or dose increased by study patients. Overall, postoperative initiation or dose increase occurred in 25/260 Ptx patients (10%) compared to 8/176 Tx patients (5%, P = .07). However, when we evaluated medication changes by considering only medications prescribed for PH-related symptoms (analgesics, antidepressants, anxiolytics, stool softeners, Alzheimer’s medications) rather than those prescribed for comorbidities (antihypertensives, antilipids, antacids) we found that a beneficial change was more likely after Ptx (n = 21) than after Tx (n = 3, P = .004). For PH-related comorbidity medications, there was no difference observed; beneficial medication changes occurred in 9 Ptx vs 5 Tx patients (P = .79). Thus, after Ptx, symptom improvement was the predominant reason for the observed beneficial medication changes.

Adverse medication changes followed the opposite pattern: after Ptx, there was no significant addition or dose-increase of medication(s) for PH-related symptoms (10 Ptx vs 3 Tx patients, P = .26), and there was a trend towards an adverse change in medications used to treat PH-related comorbidities (18 Ptx vs 5 Tx patients, P = .08.) Thus, after Ptx, the presence of PH-associated comorbidities may predict adverse medication changes. The lack of association of PH-related symptoms to adverse medication change is illustrative; of the 4 patients who started new analgesics after Ptx, 2 actually reported improved bony/joint pain; I was newly on indomethacin for gout; while another was on a new narcotic, but had sustained a traumatic fall 2 months after Ptx. Of the 5 Ptx patients on new or increased doses of antidepressants, 1 already carried the untreated diagnosis of depression preoperatively and a second patient never endorsed depressive symptoms at any time, while it is unclear why she was newly started on sertraline.

DISCUSSION

The alleviation of PH-related symptoms and comorbidities after surgery has been demonstrated by several experts, particularly in the field of endocrine surgery, yet still remains controversial. Roman and Sosa recently reviewed thoroughly the psychiatric and neurocognitive features of PH, emphasizing observed improvements in depression, memory, and concentration post-parathyroidectomy.8 In evaluating 5 specific symptoms considered to be “nonclassic” for PH (irritability, mood swings, depression, forgetfulness and fatigue), Pasieka et al found that 1 and 10 years after Ptx, PH patients reported improvement in all 5 symptoms, which was not the case for a thyroid comparison group.5 We confirm here that widespread improvements in multiple self-reported neurocognitive, musculoskeletal, and gastrointestinal symptoms occur after curative Ptx. Fatigue, bony/joint pain, and depression showed the most notable change; but, symptom improvement, even despite specific preoperative denial of symptomatology, was observed in 21% of study patients overall.

We show here for the first time that patients can discontinue medication after Ptx. Up to 11% of Ptx patients (vs 4% of Tx patients) were able to discontinue or reduce the dose of at least 1 drug that had been used to treat a symptom or comorbidity associated with PH. Analgesics were the most common medication to be favorably changed after Ptx, which is consistent with the symptomatic improvements in bony and joint pain that patients reported. Most of the beneficial medication changes we saw were in the medications used to treat the neurocognitive and musculoskeletal symptoms associated with PH, such as depression,
anxiety, memory loss, and pain. We did not observe a beneficial effect of Ptx upon the medications used to treat PF-related comorbidities. An association between PH and cardiovascular disease has been debated in the literature.\textsuperscript{9-13} Compared to Tx patients, our Ptx patients did have a higher prevalence of hypertension (54\% vs 38\%, $P = .002$) and hyperlipidemia (51\% vs 27\%, $P < .001$); but the Ptx cohort also had more men and was older, which introduces two independent risk factors for both comorbidities. Interestingly, 4 Ptx patients (compared to 2 Tx patients) were able to discontinue their antihypertensive medications after surgery, with an apparent decrease in mean SBP from 159 to 139 mmHg; another 2 Ptx patients were able to discontinue their antilipid drugs, and 1 patient normalized her LDL levels. These data are anecdotal, and the potential effect remains unproven but worthy of further study.

We observed that a number of medications were initiated or dose-increased after surgery, and more often among Ptx patients than Tx patients. However, new analgesics and antidepressants did not always correlate with worsening of bony pain or depressive symptoms after Ptx. The addition of medication(s) was driven by an increased usage of comorbidity-related drugs such as antihypertensives and lipid-lowering agents. This phenomenon would be expected in an older, more male, and aging cohort; and it certainly also is possible that such...
comorbidities are first recognized and/or treated at the time of medical evaluation for hypercalcemia.

Our study has several limitations. The findings are inherently limited by retrospective design and data analysis is plausibly confounded by the Ptx cohort being older, having longer mean follow-up, and having a higher proportion of men. Tx patients also did not undergo the same detailed perioperative verbal survey that the Ptx patients did, and thus the observed higher prevalence of preoperative nocturia, pancreatitis, bone demineralization, STML, fibromyalgia and fatigue among Ptx patients may be overestimated. Because Ptx patients were followed longer, we may also have underestimated symptom resolution and/or beneficial medication change among Tx patients. However in both cohorts, with longer follow-up and further aging, it is possible that additional medication changes would be observed.

Although our numbers were small, an interesting association uncovered in our study is the possible diagnostic confusion or overlap of PH with fibromyalgia. Five patients in our Ptx cohort had a history of fibromyalgia; of these, 4/5 (80%) reported improvement in their fibromyalgia symptoms 6 months after Ptx, and 2 patients (40%) enjoyed a beneficial change in medications that had been prescribed to treat the putative condition. This possible association certainly warrants further study.

In conclusion, the findings of our study confirm the possible association uncovered in our study is the possible diagnostic confusion or overlap of PH with fibromyalgia. Five patients in our Ptx cohort had a history of fibromyalgia; of these, 4/5 (80%) reported improvement in their fibromyalgia symptoms 6 months after Ptx, and 2 patients (40%) enjoyed a beneficial change in medications that had been prescribed to treat the putative condition. This possible association certainly warrants further study, especially given the current significant socioeconomic cost of fibromyalgia in the US.14

In conclusion, the findings of our study confirm that patients with PH are ill at baseline compared to patients undergoing thyroid surgery. We demonstrate that a number of symptoms and comorbidities objectively improve 6 months after curative parathyroid exploration. We further show that after successful parathyroid surgery, significant medication adjustments may be necessary, and recommend that the medications prescribed by physicians to treat PH-associated symptoms and conditions be systematically reviewed postoperatively. Medication dose-reduction or discontinuation can occur after curative Ptx, even in an older population.

REFERENCES

DISCUSSION
Dr Nancy Perrier (Houston, TX): Thank you for a nice set of data. I noticed on 1 of your slides that fatigue was the symptom that you noted that most patients improved on. I wonder, do you have available any of the medications that would relate to that? For instance, it seems to me that there are data out there that sleep is 1 of the most important aspects of the quality-of-life issues of these patients, and that encompasses the fatigue and perhaps even the depression. Although fatigue was so high in your series, I didn’t see fatigue treatment listed in the drugs that you didn’t see fatigue treatment listed in the drugs that you...
Dr Barry Inabnet (New York, NY): Thank you for a great presentation and bringing these data to us. I have a question followed by a comment.

Did you look at the influence of Ptx on glucose homeostasis and diabetes? The reason I ask is that we know that bone remodeling is influenced by the parathyroid system. There are peptides made in the skeletal system, such as osteocalcin, that interact directly with the beta cell to influence glucose homeostasis. We notice that often diabetes or glucose intolerance improves following Ptx. Do you have any data on glucose metabolism in your cohort of patients?

Dr Adrienne L. Melck (Pittsburgh, PA): We certainly know which patients carried the diagnosis of diabetes. It’s not something I particularly looked at in our study. It’s certainly an interesting point and something that I could go back and look at, and the difference between the 2 groups.

Dr Jacob Moalem (Rochester, NY): Did you look at the number or frequency of visits to primary care providers before and after Ptx?

The reason I ask is so many of the referrals that I get for this problem come when a patient gets a new primary care provider or switches providers; so, that may be a confounding variable.

Dr Adrienne L. Melck (Pittsburgh, PA): Unfortunately, we did not look at that; but, that’s an interesting point that we could also include.

Dr Jim Norman (Tampa, FL): We have been following some of these same issues for a couple of years and have noticed a huge difference in the decrease in medication of these patients when we make an attempt to educate the primary care physician that they should look for this opportunity. We’ve also found that the opportunity to decrease their medications, including some of the comorbidities like blood pressure medications, can occur at one or two years after Ptx.

My question to you is, who is changing these medications? Are you making an effort to educate the primary care physicians to look for these opportunities?

Secondly, how long did you follow your data? And if only for 6 months, I believe, then I would encourage you to follow along further, because you may find there are changes in other comorbidities, such as blood pressure medications.

Dr Adrienne L. Melck (Pittsburgh, PA): Thank you for an excellent point and questions. We excluded any changes in medication instituted by the surgical team. So, these were changes made by the PCPs, and I think this is a starting point to educate PCPs that these medication changes are possible.

And, our follow-up was short, 8 months in the Ptx cohort. So I think we may have underestimated the long-term medication changes that are possible. So, certainly, a future study with longer follow-up would be very important.

Dr Rebecca Sippel (Madison, WI): When we talked about the symptom profile and the comorbidities, those were present in 30–60% of patients. A fairly large number of patients had had issues. But, when we looked at the medication reduction, it was a fairly small percent. And, in most of those cases, it was only a reduction in one medication for 1 comorbidity.

It suggests that 1) we are either overstating the symptomatic improvement after Ptx; or 2) these patients aren’t followed long enough; or 3) they are just not getting taken off the medications. How do you think those factors played and which do you think is probably the bigger issue?

Dr Adrienne L. Melck (Pittsburgh, PA): I think, again relating to the last question, it may just be a matter of follow-up. If we follow these patients for longer, we may find more significant changes.

I also think there may be some confounding variable, due to the fact that these Ptx patients have perhaps more complaints and they are more visible in the medical system; and so the comorbidities are being picked up more often. Medications are being started or changed, so that’s playing a role in some of the results received.