Morbidity in parathyroid surgery for renal disease is under reported: a comparison of outcomes with primary hyperparathyroidism

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ABSTRACT

INTRODUCTION Parathyroidectomy is considered to be a safe procedure with low morbidity. However, while this is true for primary hyperparathyroidism, whether it applies to tertiary disease is not so well documented. The aim of this study was to assess the morbidity of surgery for tertiary hyperparathyroidism compared with primary disease and to establish whether there are predictive factors for poor outcomes.

METHODS Data for patients subjected to parathyroidectomy during the period 2007–2015 were retrospectively analysed from a prospectively collected database. Patient age, sex, American Society of Anesthesiologists (ASA) score, renal status, extent of operation and indications for surgery were examined. The complication and mortality rate were compared and independent predictors of outcome were examined.

RESULTS A total of 1079 patients were scheduled for a parathyroidectomy during the study period of whom 158 for renal related hyperparathyroidism (renal group) and 921 for primary disease (non-renal group). There was a significantly higher complication rate in the renal parathyroid group, including a higher mortality (1.3% vs 0.1%, $P = 0.011$), overall complication rate (7.0% vs 2.3%, $P = 0.001$), surgery related complication rate (4.4% vs 1.7%, $P = 0.03$) and systemic complication rate (2.5% vs 0.4%, $P = 0.005$). In patients with ASA score ≤ 2 reoperative surgery (OR 9.25, 95% confidence interval, CI 1.41–60.75), male sex (OR 4.12, 95% CI 1.46–11.63) and renal impairment were (OR 5.86, 95% CI 1.65–20.78) were predictors of worse outcomes. In patients with ASA score ≥ 3 renal impairment, in addition to other variables, were not predictors of complications.

CONCLUSIONS Parathyroidectomy in renal-related disease is associated with a significantly higher risk of morbidity and mortality compared with primary hyperparathyroidism.

KEYWORDS

Parathyroid surgery – Primary hyperparathyroidism – Secondary hyperparathyroidism – Renal – Morbidity

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Introduction

Since the early parathyroidectomies at the beginning of the 20th century, parathyroid surgery has evolved from an unreliable long operation with a low cure rate and high morbidity to what is now perceived to be a safe, reliable routine intervention. Mortality is extremely rare and morbidity is reported to be minimal in specialised centers. In addition to failure to cure, surgery-specific complications that may follow a parathyroidectomy include recurrent laryngeal nerve injury, bleeding, seroma formation, infection and hypoparathyroidism. Systemic complications can also occur, most usually in patients with comorbidities.¹ Surgery

remains the only current definitive cure for primary hyperparathyroidism in its sporadic or syndromic forms. Parathyroidectomy is also used in selected patients with secondary and tertiary hyperparathyroidism that is refractory to medical treatment.

Parathyroid surgery may range from a ‘minimally invasive’ or focused operation where only one gland is identified and removed to bilateral neck explorations where all four glands are visualised and surgery is tailored to the surgical findings.

The aim of this study was to formally address the absence of a comparison in the medical literature between the morbidity of parathyroid surgery in secondary or

tertiary hyperparathyroidism and primary hyperparathyroidism and seek to identify predictive risk factors associated with worse outcomes.

Materials and methods

Study design

The department is a tertiary referral center for endocrine surgery. We retrospectively analysed data collected prospectively in our departmental database. All patients subjected to parathyroid surgery during the period January 2007 to November 2015 were recruited into the study. No patient was excluded from the study. Patients were grouped primarily according to their disease into two groups: a primary (or non-renal) group consisting of patients with primary hyperparathyroidism and a renal group, which included patients with hyperparathyroidism induced by renal impairment or post renal transplant (tertiary) hyperparathyroidism. Patients were also stratified according to their comorbidities using the American Society of Anesthesiologists (ASA) score: patients with ASA scores of 1 or 2 were identified as in the low-comorbidity subgroup, while patients with ASA score of greater than 3 were deemed high comorbidity.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Protocol of interventions

All patients with primary hyperparathyroidism (both sporadic and familial) had their diagnosis established biochemically with serum and urinary biochemistry. Patients deemed surgical candidates with symptomatic disease or qualifying by National Institutes of Health criteria in asymptomatic disease were subjected to localisation studies consisting of a neck ultrasound scan and a sestamibi scan.^{2,5} The parathyroidectomy was tailored to the localisation studies into focused surgery or small incision four-gland visualisation. Concordant preoperatively localised disease was approached via a focused unilateral approach with a central or lateral incision and the removal of the abnormal gland and identification of the normal ipsilateral gland when feasible. Intraoperative parathyroid hormone (PTH) measurement was used as a confirmatory tool for cure using the Miami criteria.⁴ When the disease was not localised, a bilateral neck exploration was performed and the surgery tailored to the operative findings. When a single adenoma was recognised, only one parathyroid gland was removed, whereas in multiple gland disease more than one abnormal gland was removed.

Surgery was performed in patients with secondary and tertiary hyperparathyroidism either with absolute indications (calciophylaxis, post-transplant hypercalcaemia, debilitating bone disease etc.) or loosely according to the K-DOQI guidelines, based on the coexistence of grade 3 renal impairment or greater with symptomatic bone disease, increasing alkaline phosphatase, a calcium to phosphate

product (greater than 4.1) or when PTH was greater than 88 pmol/l despite medical treatment.⁵ The parathyroidectomy was tailored to the patient's condition, with a subtotal parathyroidectomy being the procedure of choice except in patients not on the transplant waiting list. Total parathyroidectomy involved excision of all four glands with or without a thymectomy. A subtotal parathyroidectomy involved identification of all four glands and excision of all except a fragment of the most normal looking gland. Due to this approach, preoperative localisation imaging was not routinely performed for these patients.

Postoperative follow-up protocol

All patient biochemistry was monitored perioperatively and patients were discharged routinely 24 hours after the operation unless delayed by dialysis. The first follow-up appointment was two weeks after the operation when patients were assessed for their parathyroid function, serum calcium levels and local complications related to surgery.

Parameters studied

The parameters studied were patient age, sex and ASA score. Local complications, including recurrent laryngeal nerve injury, hemorrhage, reoperation for any reason, infection and clinically significant seroma formation were recorded when present. Systemic complications, including cardiovascular complications, respiratory complications and mortality were also recorded. The cure rate and the rate of temporary or permanent hypoparathyroidism were not recorded endpoints of the study because comparison between patients with renal impairment and patients with normal renal function is not applicable.

Statistical analysis

Pearson's chi square test was used to compare qualitative parameters between groups. For the comparison of quantitative data and when the distribution was normal Student's t-test was used. A binary logistic regression model was created to compare parameters that were predictive of complications. Parameters that were found to be predictive in univariate analysis were applied to the model of a multivariate binary logistic regression analysis, to identify independent predictors of complications. The level of statistical significance was set to $P < 0.05$. All calculations were made using SPSS version 17.0 for Windows.

Results

A total of 1079 patients were included in the study. The patient demographics are in Table 1. Data were complete for all patients with the exception of the ASA score, which was not documented by anaesthetists in 25% ($n = 276$) of patients. Calculations involving ASA score and classification of patients were therefore based on the patients for whom ASA score was available.

Some 921 patients had primary hyperparathyroidism (non-renal group), while 158 had renal related hyperparathyroidism (renal group), of whom 131 were either

dialysing or in a pre-dialysis stage and 27 were post-renal transplant (Table 2).

When comparing the renal with non-renal groups we found differences in sex distribution. The non-renal group comprised mostly female patients. In addition, we found that patients in the renal group had greater comorbidities, as expressed by both mean ASA score and ASA score

stratification. Most renal patients were offered total or sub-total parathyroidectomy and inevitably the extent of surgery differed between groups but there was no difference in the rate of reoperations between the two groups (Table 3).

There was a significant difference in mortality ($P = 0.021$) between the renal and non-renal groups. One patient from the renal group died from acute myocardial infarction before induction of anaesthesia, so the surgical procedure was not performed. Total complication rate ($P = 0.001$), surgery related complication rate ($P = 0.05$) and systemic complication rate ($P = 0.011$) were significantly higher in the renal group (Table 4). There was no difference in the complication rate between unilateral and bilateral operations (Table 5).

We did not identify a single postoperative complication in post-transplant renal patients; bleeding and overall surgical complications were higher in patients on haemodialysis compared with the rest of the patients within the renal group ($P = 0.035$ and $P = 0.042$, respectively; Table 6).

Multivariate binary logistic regression analysis was performed after stratifying patients according to ASA score ≤ 2 or ≥ 3 . In these patients, age at operation and the extent of operation (unilateral vs bilateral) were not significant independent predictors of complications. However, male sex, reoperative surgery and the presence of renal disease (especially haemodialysis) were associated with higher morbidity. When patients with ASA score ≥ 3 were analysed, none of these variables was an independent predictor of complication incidence. Data are summarised in Table 7.

Discussion

Parathyroid surgery is justifiably perceived as a highly effective operation with low morbidity and near zero mortality. However, this does not apply universally to all indications and patients. Parathyroidectomy patients range from the healthy young patient with multiple endocrine neoplasia to the frail elderly patient with sporadic primary hyperparathyroidism with comorbidities or patients with renal failure ranging from pre- or post-haemodialysis to post-renal transplantation.^{6,7} The extent of the operation may vary from focused parathyroid surgery to bilateral neck exploration and may be performed alone or in combination with thyroid and thymic surgery.^{8,9}

Our data support previous findings that the extent of surgery does not appear to influence the outcomes of parathyroid surgery in primary hyperparathyroidism.¹⁰⁻¹⁵ However, the same parathyroid surgical approach in patients with renal disease is associated with a higher local and systemic risk of complications, although the factors responsible for this difference have not previously been clarified.

While the higher ASA score (despite the trend towards a younger age) in the renal group fits with a higher rate of cardiological complications, this does not immediately explain the higher rate of postoperative bleeding in the renal parathyroidectomy group. When comparing patients on haemodialysis with patients not on haemodialysis (stage

Table 1 Characteristics of the entire study population.		
Variable	Patients	
	(n)	(%)
Age (years)	57.1 ± 14.2	
Sex:		
Male	302/1079	28
Female	777/1079	72
Classification of hyperparathyroidism:		
Primary	921/1079	85.4
Secondary/tertiary	158/1079	14.6
Pathology:		
Sporadic	883/1079	81.8
Renal	158/1079	14.6
Multiple endocrine neoplasia	24/1079	2.2
Familial	8/1079	0.7
Lithium	3/1079	0.3
Carcinoma	3/1079	0.3
American Society of Anesthesiologists (ASA) score	1.9 ± 0.7	
ASA group:		
≤ 2	652/803	81.2
≥ 3	151/803	19.8
Extent of operation:		
Unilateral/focused parathyroidectomy	256/1078	23.7
Bilateral neck exploration	822/1078	76.3
Reoperative parathyroidectomy	86/1078	8.0

Table 2 Severity of renal hyperparathyroidism in the renal group (n = 158).		
Severity of renal impairment	Patients	
	(n)	(%)
Before renal replacement therapy	55/158	34.8
In renal replacement therapy	76/158	48.1
After renal transplantation	27/158	17.1

Table 3 Characteristics of patients according to the presence of renal failure induced hyperparathyroidism.

Variable	Renal group (n = 158)		Non-renal group (n = 921)		P-value
	(n)	(%)	(n)	(%)	
Age at operation (years)	55.5 ± 13.2		57.4 ± 14.3		0.11
Sex (male/female)	77/81		225/696		< 0.001
Extent of operation: ^a					< 0.001
Unilateral neck exploration	3	1.9	185	20.1	
Bilateral neck exploration	146	93	648	70.4	
Parathyroidectomy and other procedure ^b	0	0	10	1.1	
Reoperative parathyroidectomy	8	5.1	78	8.5	0.14
ASA score	2.42 ± 0.70		1.78 ± 0.64		< 0.001
ASA group:					< 0.001
Low comorbidity	65/139	46.8	587/664	88.4	
High comorbidity	74/139	53.2	77/664	11.6	

^aOne patient from the renal group died from myocardial infarction immediately before the induction of anesthesia and thus no surgical procedure was performed.
^bThyroid or sternotomy.
ASA, American Society of Anesthesiologists.

Table 4 Comparison of morbidity and mortality of patients with renal failure-induced hyperparathyroidism and patients with primary hyperparathyroidism undergoing parathyroid surgery.

Variable	Renal group (n = 158)		Non-renal group (n = 921)		P-value
	(n)	(%)	(n)	(%)	
Mortality	2	1.3	1	0.1	0.011
Overall complications	11	7.0	21	2.3	0.001
Recurrent laryngeal nerve injury (temporary)	1	0.6	3	0.3	0.557
Bleeding (haematoma)	4	2.5	6	0.7	0.023
Collection	0	0.0	1	0.1	0.679
Infection	2	1.3	4	0.4	0.194
Other	0	0.0	2	0.2	0.558
Total surgery-related complications:	7	4.4	16	1.7	0.030
Cardiological	3	1.9	2	0.2	0.004
Respiratory	1	0.6	3	0.3	0.557
Total systemic complications	4	2.5	5	0.5	0.011

III and IV renal failure and patients after renal transplantation) the postoperative bleeding and all surgery-related complication rates were significantly higher. However, we noted the absence of complications in the post-transplant renal group, which points to the possibility that the effects of uraemia and/or dialysis contribute to complication risks, although the sample size may be misleading. Schneider *et al.*¹⁴ have reported a higher incidence of surgical complications in patients with end-stage kidney disease

undergoing non-endocrine surgery compared with normal controls and Turgeon *et al.* have reported a higher incidence of surgical and cardiopulmonary complications in patients with renal dysfunction who are undergoing bariatric surgery. The degree of renal impairment and haemodialysis appear to be independent predictive factors for complications.^{15–17}

The multivariate regression analysis demonstrated that the presence of renal impairment, male sex and re-

Table 5 Comparison of morbidity and mortality of patients undergoing unilateral or bilateral neck exploration for parathyroid surgery (after excluding reoperative cases).

Variable	Unilateral (<i>n</i> = 190)		Bilateral (<i>n</i> = 802)		<i>P</i> -value
	(<i>n</i>)	(%)	(<i>n</i>)	(%)	
Mortality	0	0.0	2	0.2	0.491
Overall complications	4	2.1	23	2.9	0.561
Recurrent laryngeal nerve injury (temporary)	1	0.5	2	0.2	0.532
Bleeding (haematoma)	0	0.0	9	1.1	0.142
Collection	0	0.0	1	0.1	0.626
Infection	1	0.5	5	0.6	0.877
Total surgery-related complications	2	1.1	17	2.1	0.335
Cardiological	1	0.5	3	0.4	0.766
Respiratory	1	0.5	3	0.4	0.766
Total systemic complications	2	1.1	6	0.7	0.673

Table 6 Comparison of morbidity and mortality of parathyroid surgery in subgroups of renal failure-induced hyperparathyroidism patients.

Variable	Pre-transplantation (<i>n</i> = 131)		Post-transplantation (<i>n</i> = 27)		<i>P</i> -value	Pre-haemodialysis, post-transplantation (<i>n</i> = 82)		On haemodialysis (<i>n</i> = 76)		<i>P</i> -value
	(<i>n</i>)	(%)	(<i>n</i>)	(%)		(<i>n</i>)	(%)	(<i>n</i>)	(%)	
Mortality	2	1.5	0	0	0.518	1	1.2	1	1.3	0.957
Overall complications	11	8.4	0	0	0.119	3	3.7	8	10.5	0.090
Recurrent laryngeal nerve injury (temporary)	1	0.8	0	0	0.649	1	1.2	0	0	0.334
Bleeding (haematoma)	4	3.1	0	0	0.358	0	0	4	5.3	0.035
Collection	0	0.0	0	0	n/a	0	0	0	0	n/a
Infection	2	1.5	0	0	0.518	0	0	2	2.6	0.139
Total surgery-related complications	7	5.3	0	0	0.219	1	1.2	6	7.9	0.042
Cardiological	8	2.3	0	0	0.427	1	1.2	2	2.6	0.516
Respiratory	1	0.8	0	0	0.649	1	1.2	0	0	0.334
Total systemic complications	4.3	3.1	0	0	0.358	2	2.4	2	2.6	0.939

operative surgery were independent predictors for complications. However, this was not the case when we compared patients with more comorbidities. The increased complication rate in the renal hyperparathyroidism group was mainly due to cardiovascular events and the incidence of bleeding, findings supported by other studies.^{18,19} Postoperative 'uraemic' bleeding can be associated with hypervolaemia and the ubiquitous hypertension present in renal patients. Uraemic platelet dysfunction is also a well-recognised phenomenon in haemodialysis.²⁰

Patients with renal failure on haemodialysis are prone to postoperative infections,^{21,22} but the cause is unclear, although the aetiology of the renal failure itself (such as diabetes mellitus) may often be implicated.¹⁵ The risk of cardiovascular complications is presumably related to the predisposition to thromboembolic events, including stroke, owing to chronic arterial calcification, atherosclerosis, fluid overload, hypertension and congestive heart failure, which are all usually present in patients with these conditions.²⁵

Table 7 Multivariate analysis of prognostic factors of complications after stratification of patients in low comorbidity (LC) or high comorbidity (HC) groups.

Variable	LC group (ASA score ≤ 2)			HC group (ASA score ≥ 3)		
	Odds ratio	95% CI	Significance (P)	Odds ratio	95% CI	Significance (P)
Reoperation	9.25	1.41–60.75	0.02	1.850	0.12–27.67	0.65
No renal impairment	–	–	0.02	–	–	0.63
Moderate renal failure ^a	0.97	0.12–7.94	0.98	.492	0.04–5.10	0.55
Severe renal failure ^b	5.86	1.65–20.78	0.006	1.454	0.32–6.46	0.62
Unilateral vs bilateral neck exploration	0.23	0.03–1.50	0.12	.447	0.03–6.09	0.54
Sex (male)	4.12	1.46–11.63	0.007	1.720	0.43–6.74	0.43
Age at operation	1.00	0.96–1.03	0.95	1.034	0.97–1.09	0.24

^a Pre-haemodialysis and post-transplantation.
^b Haemodialysis.

Haemodialysis independently causes intravascular fluid volume changes, sudden changes in serum electrolytes and, as a result, third-space fluid shifts. These in turn change cardiac preload, cardiac output and result in haemodynamic changes. This is in addition to heparin, which must be administered throughout the session to prevent clotting of the extracorporeal circuit, which in turn increases even further the bleeding diathesis of these patients.²⁵

This is the first study to highlight the increased morbidity of parathyroid surgery in patients having surgery for renal failure-induced hyperparathyroidism compared with surgery for primary hyperparathyroidism. The study has limitations owing to its retrospective nature and incomplete data. While most of the data were prospectively collected from our departmental database, the ASA scores could not be found for all patients and were missing in 25.6% of patients. As a result, multivariate analysis was not performed in the entire patient population but in only 803 patients. In addition, detailed comorbidities of our study population were not available, leading us to use ASA scores as a marker of potential life-threatening comorbidities. Finally, although over 1000 patients were included in the study, a relatively small proportion suffered from renal failure-induced hyperparathyroidism. When combining this with the fact that mortality is very rare in parathyroid surgery, safe conclusions cannot be made concerning this aspect of the study.

Conclusion

In conclusion, although parathyroid surgery is relatively safe, this does not apply universally. Parathyroid surgery in renal failure patients is far more likely to be associated with morbidity, probably due to the effects of renal failure on clotting, the immune and cardiovascular systems and less so on the background comorbidities of the patient group.

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