Cohort study on effects of parathyroid surgery on multiple outcomes in primary hyperparathyroidism

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Abstract

Objectives To assess the effects of surgery compared with conservative treatment (no surgery) for primary hyperparathyroidism. Design Cohort study. Setting Nationwide Danish cohort. Participants 3213 patients, mean age 61 (SD 16) years, with a diagnosis of primary hyperparathyroidism between 1980 and 1999. 1934 (60%) underwent surgery and 1279 (40%) were treated conservatively. Main outcome measures Occurrence of fractures, osteoporosis, kidney or urinary tract stones, acute myocardial infarction, angina pectoris, cardiac arrhythmias, arterial hypertension, heart failure, stroke, acute pancreatitis, stomach or duodenal ulcers, muscle pain, malignant diseases, psychiatric disorders, and mortality. Results At diagnosis of primary hyperparathyroidism, patients who subsequently underwent surgery had a lower prevalence of previous fracture (odds ratio 0.64, 95% confidence interval 0.51 to 0.80), acute myocardial infarction (0.59, 0.42 to 0.83), stroke (0.57, 0.37 to 0.88), psychiatric disorders (0.54, 0.51 to 0.94), and painful muscle disorders (0.44, 0.26 to 0.76), whereas kidney stones (2.49, 1.93 to 3.23) and acute pancreatitis (2.77, 1.33 to 5.76) were more prevalent. After diagnosis, the risks of fractures (hazards ratio 0.69, 0.56 to 0.84) and gastric ulcers (0.59, 0.41 to 0.84) were lower in patients treated surgically than those treated conservatively. Events involving kidney or urinary tract stones were more prevalent in patients treated surgically than patients treated conservatively (1.87, 1.30 to 2.68). Mortality was lower in patients treated surgically (0.65, 0.57 to 0.73).

Conclusions Patients treated surgically for primary hyperparathyroidism have a lower prevalence of fractures and gastric ulcers than patients treated conservatively. The type of treatment had no effect on the occurrence of cardiovascular events.

Introduction

Most intervention studies on the effects of surgery in primary hyperparathyroidism are uncontrolled cohort or before and after trials comparing changes in left ventricular size, fracture rate, bone mineral density, and incidence of kidney stones. They therefore have not evaluated the difference between surgically and non-surgically (conservatively) treated patients. One small randomised study evaluated the effects of surgery and conservative treatment on bone mineral density and found an increase in bone mineral density and quality of life scores in surgically treated patients. We collected data on a large cohort of patients with primary hyperparathyroidism and evaluated the long term outcome of hard end points in surgically treated patients compared with conservatively treated patients.

Materials and methods

Data were obtained from the Danish hospital discharge database. This central national database contains information on patients admitted to hospital according to their unique identification number and type of disease. Any surgical procedures are also recorded.
We retrieved information on patients with a first-time diagnosis of primary hyperparathyroidism from 1 January 1980 to 31 December 1999. We identified 3225 patients; 12 (0.4%) were excluded, leaving 3213 for analysis. Overall, 1934 patients (60%) had undergone surgery and 1279 (40%) had not. Information was obtained on all hospital contacts for these 3213 patients from 1 January 1977 to 31 December 1999. Our primary end points of interest were fractures, osteoporosis, kidney and urinary tract stone events, acute myocardial infarction, angina pectoris, cardiac arrhythmias, arterial hypertension, cardiac insufficiency, stroke, stomach or duodenal ulcers, acute pancreatitis, poorly defined muscular pain, cancer, and psychiatric illness (psychoses and dementia) or neurotic disorders. We assessed whether any such contact had taken place before or after the date when primary hyperparathyroidism was diagnosed. Information was also obtained on whether patients had died or emigrated during this period. Total follow-up time from diagnosis of primary hyperparathyroidism to surgery or conservative treatment (no surgery) for primary parathyroidism was 47 063 (median 15.9) years. The precision of the disease codes is generally considered to be high.\(^1\)\(^,\)\(^2\)

**Statistics**

Crude odds ratios were calculated for all outcomes. We used a Cox proportional hazard model to analyse differences between surgically and conservatively treated patients. We entered as potential confounders in the model, age at diagnosis of primary hyperparathyroidism for patients aged 50 or over compared with those under 50, sex, and presence of the end point in question before the time of diagnosis. We analysed the dataset both with the end points before the time of diagnosis and without. The results were similar for both approaches. We used logistic regression to evaluate difference in the prevalence of concurrent diseases at the time primary hyperparathyroidism was diagnosed, adjusted for age (\(\geq 50\) vs. \(<50\) years) and sex (female vs. male). We compared the observed survival in the cohort of patients with that of the age matched and sex matched normal population using national survival tables. See bmj.com for details.

**Results**

Baseline characteristics at the time of diagnosis in all patients with primary hyperparathyroidism, stratified by treatment, showed that the group who had had surgery were younger and had less comorbidity. The median time from diagnosis to surgery was 0.09 years (31 days), range 0-14 years. We examined the presence and distribution of any end point before diagnosis and the effect of surgery on the occurrence of a variety of end points after diagnosis (see bmj.com). The risk of fractures was 31% (hazard ratio 0.69) lower in surgically treated patients than in conservatively treated patients (table). The risk of death was lower in patients with a history of kidney stones. Prior myocardial infarction, hypertension, cardiac failure, arrhythmia, cancer, fracture, and ulcer were associated with an increased risk of death. Survival was higher in surgically treated patients than in conservatively treated patients (figure). In both groups the observed survival was significantly lower than in the general population. However, the relative loss of expected lifetime was higher among conservatively treated patients than among surgically treated patients (mean 20% or 2.7 years vs. 14% or 2.1 years, \(P<0.01\)) after adjustment for age and sex. The proportion undergoing surgery decreased with time: 66% of patients diagnosed from 1980 to 1989 underwent surgery compared with 56% of those diagnosed between 1990 and 1999 (\(P<0.01\)).

**Discussion**

Surgical treatment for primary hyperparathyroidism led to fewer fractures and episodes of gastroduodenal ulcers and lower mortality than conservative treatment. Surgery was not, however, associated with a change in risk of cardiovascular events.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Hazard ratio (95% CI)*</th>
</tr>
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<tbody>
<tr>
<td>Kidney stones</td>
<td>0.57 (0.46 to 0.71)</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.57 (1.27 to 1.93)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.34 (1.02 to 1.74)</td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>1.06 (0.75 to 1.49)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>2.21 (1.56 to 3.14)</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>1.48 (1.07 to 2.03)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.82 (1.40 to 2.36)</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.34 (0.95 to 1.88)</td>
</tr>
<tr>
<td>Stomach or duodenal ulcer</td>
<td>1.40 (1.09 to 1.79)</td>
</tr>
<tr>
<td>Acute pancreatitis</td>
<td>0.97 (0.57 to 1.64)</td>
</tr>
<tr>
<td>Fracture</td>
<td>1.29 (1.06 to 1.57)</td>
</tr>
</tbody>
</table>

*Cox proportional hazard analysis. Hazard ratios are mutually adjusted. Results not changed by replacing preoperative conditions with Charlson index.

Kaplan-Meier plot of survival in surgically and conservatively treated patients with primary hyperparathyroidism. Death during follow-up occurred in 591 (31%) surgically treated patients and 474 (37%) conservatively treated patients.
Advantages and disadvantages of study
The major advantage of our study is that we looked at a population based representative sample, allowing assessment of multiple outcomes over an extended period. Our study was not randomised, but relied on observational data from an administrative system collected for other purposes. Another major limitation was the lack of information on important confounders such as smoking. Thus bias may have affected the outcomes significantly. Selection bias could have affected the results in several ways. It is unlikely that the population was selected, as all cases of primary hyperparathyroidism in Denmark are managed in hospital and thus are included in the register. Selection bias is, however, a significant factor in deciding who should have surgery and who should be managed conservatively.

Effects of surgery on hard end points
Surgery is the treatment of choice in patients with symptoms of primary hyperparathyroidism. Guidelines recommend that patients with asymptomatic primary hyperparathyroidism undergo surgery when there is a high concentration of serum calcium (>1 mg/dl above normal range), high urine calcium output, and organ involvement (reduced kidney function or reduced bone mineral density). Thus those selected for surgery are more likely to have advanced disease with symptoms in contrast with those selected for conservative management, who will often have asymptomatic disease with a low risk of any end point. This would underestimate any difference between surgical and conservative treatment. On the other hand, some patients may simply be too unwell to tolerate surgery, and this would mean that some of those managed conservatively actually have a higher risk of death than those undergoing surgery. It is also possible that some patients did not want to undergo surgery, particularly those with psychiatric disorders. A trend was, however, shown towards a decrease in occurrence of psychiatric disorders in surgically treated patients.

Information bias seems to pose a smaller problem for fractures and acute myocardial infarction, as the precision of diagnoses was high. Precise data for the validity of certain end points, such as stomach ulcers, were not available. The lower precision of the diagnoses in those not undergoing surgery would tend to underestimate any effect of surgery because some of the patients did not have primary hyperparathyroidism. Although many of the conditions studied are managed in hospital, hypertension, muscle pain, neuroses, and gastric ulcers are often managed by general practitioners and are therefore not reflected in the data presented here. This may lead to a significant underestimation of these types of comorbidity. A special feature of bias is confounding by indication, when patients with urinary tract stones were more likely to undergo surgery than those without after the recommendations from international guidelines. Those who did not undergo surgery were older and had a higher mortality—that is, they may not have been offered surgery owing to their health and comorbidity.

We have already presented the results of a study on patients only surgically treated for primary hyperparathyroidism. Although the risk of fracture was increased before surgery and returned to that of the general population within one year after surgery, it took 10 years or more for the risk of kidney stones to return to that of the general population. Although we tried to adjust for prior kidney stones, this may not have excluded patients with asymptomatic kidney stones, those whose pain was misdiagnosed as simple stomach pain, or those who did not seek medical attention for the pain. Therefore, although some of the basis for recurrent stone formation is removed after parathyroidectomy, other factors may continue to induce stone formation. The risk of being admitted for gastric and duodenal ulcers decreased by 41% after surgery, although patients who underwent surgery tended to have more ulcers before diagnosis than those who did not have surgery. In accordance with our study, previous studies have shown that blood pressure is unchanged after surgery for primary hyperparathyroidism, probably indicating irreversible vascular or renal changes. This may partly explain the absence of treatment effect on overall cardiovascular risk in our study.

The risk of death was smaller in surgically treated patients even after adjustment for several important confounders such as cardiovascular disease, cancer, and hypertension. Those not selected for surgery may have had a shorter expected life span than those selected for surgery. However, surgery did improve survival by decreasing serum calcium and serum parathyroid hormone levels. In our study those with prior kidney stones had a lower risk of death, a finding that agrees with another study. The reason for this remains unclear.

Effect of time
The incidence of primary hyperparathyroidism has remained unclear.
decrease in the proportion undergoing surgery. With the advent of milder cases the difference in the risk of end points between surgically and conservatively treated patients must be larger than if the cases were more balanced. However, the effects of surgery on these mild cases must be expected to be less than those on the more extreme cases in our study.

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Prehospital tracheal intubation in severely injured patients: a Danish observational study

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The value of advanced prehospital life support for patients with severe trauma—for example, endo-
tracheal intubation by ambulance staff—is unclear. Only one randomised controlled trial was found among 2034 papers in a Cochrane review, concluding that advanced trauma life support by ambulance crews should be initiated only as part of rigorously conducted trials.1 A critical review also failed to show benefit and reported success rates for endotracheal intubation from 57% to 92%.5 The review questioned whether prehospital staff could master the required skills. These reviews focus on paramedic based systems.

The helicopter emergency medical services in London is staffed by doctors; the service studied 486 trauma patients intubated without anaesthetics at the scene. One patient (0.2%) survived—after thoracotomy at the scene. The service debated the practice of para-
medics doing endotracheal intubation without anaes-
thesthesia because this is possible only in profoundly unconscious trauma patients with a poor prognosis.

In Denmark, ambulance crews do not intubate, and emergency medicine is not a separate specialty. Anaes-
thetists work in emergency care in and out of hospitals.

We describe the number of severely injured patients having endotracheal intubation with and without anaes-
thetic drugs (hypnotics, analgesics, and muscle relaxants) out of hospital and assess their chances of survival.

Participants, methods, and results

In Aarhus (population 330,000), one mobile emergency care unit, staffed with an anaesthetist, runs in addition to ambulances and is dispatched in the most severe cases. From the databases of the mobile unit and the trauma centre, we identified severely injured patients who were intubated out of hospital (table). We defined a severely injured patient as having an injury severity score greater than 15.

Between 1998 and 2000, the trauma team was acti-
vated in a total of 741 cases, and 220 patients were severely injured. The mobile unit brought 172 of these to hospital, and prehospital intubation was done in 43% (74/172) of severely injured patients. Of these, 84% (62/74) received anaesthetics. Fifty eight per cent (56/62) of patients who were given anaesthetics and 8% (1/12) of patients who were not survived at least six months ($P = 0.003$, Fisher’s exact test).

Comment

Prehospital intubation was done in 43% of severely injured patients, mostly with anaesthesia; only 12 intu-
bations were done without anaesthesia during three years, and although survival was considerably lower in this group, it was not negligible. The helicopter emergency medical service in London found pre-

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