

Canadian Association of General Surgeons and American College of Surgeons Evidence Based Reviews in Surgery. 16

Randomized trial of parathyroidectomy in mild asymptomatic primary hyperparathyroidism

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CAGS Evidence Based Reviews in Surgery

The term "evidence-based medicine" was first coined by Sackett and colleagues as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients."¹ The key to practising evidence-based medicine is applying the best current knowledge to decisions in individual patients. Medical knowledge is continually and rapidly expanding, and it is impossible for an individual clinician to read all the medical literature. For clinicians to practise evidence-based medicine, they must have the skills to read and interpret the medical literature so that they can determine the validity, reliability, credibility and utility of individual articles. These skills are known as critical appraisal skills. Generally, critical appraisal requires that the clinician have some knowledge of biostatistics, clinical epidemiology, decision analysis and economics, as well as clinical knowledge.

In October 2005, the American College of Surgeons joined with the Canadian Association of General Surgeons to sponsor a program entitled "Evidence Based Reviews in Surgery (EBRS)," which is supported by an educational grant from ETHICON and ETHICON ENDO SURGERY, both units of Johnson & Johnson Medical Products, a division of Johnson & Johnson, and ETHICON INC. and ETHICON ENDO-SURGERY, INC. divisions of Johnson & Johnson Inc. The primary objective of this initiative is to help practising surgeons improve their critical appraisal skills. During the academic year, 8 clinical articles are chosen for review and discussion. They are selected not only for their clinical relevance to general surgeons but also because they cover a spectrum of issues important to surgeons; for example, causation or risk factors for disease, natural history or prognosis of disease, how to quantify disease (measurement issues), diagnostic tests and the early diagnosis of disease, and the effectiveness of treatment. A methodological article is supplied that guides the reader in critical appraisal of the clinical article. Both methodological and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS Web site. As well, a listserv discussion is held where participants can discuss the monthly article. Members of the College and the Canadian Association of General Surgeons can access Evidence Based Reviews in Surgery through the American College of Surgeons Web site (www.facs.org) or the Canadian Association of General Surgeons Web site (www.cags-accg.ca). All journal articles and reviews are available electronically through the EBRS Web site. We also have a library of past articles and reviews that can be accessed at any time. Surgeons who participate in the monthly packages can obtain continuing medical education credits and/or Royal College of Physicians and Surgeons of Canada Maintenance of Certification credits for the current article only by reading the monthly articles, participating in the listserv discussion, completing the monthly online evaluation and answering the online multiple choice questionnaire. For further information about EBRS, the reader is directed to the ACS Web site or should email the administrator, Marg McKenzie at mmckenzie@mtsinai.on.ca.

In addition to making the reviews available through the ACS and CAGS Web sites, 4 of the reviews are published in condensed versions in the *Canadian Journal of Surgery* and 4 in the *Journal of the American College of Surgery* each year. We hope readers will find EBRS useful in improving their critical appraisal skills and also in keeping abreast of new developments in general surgery. Comments regarding EBRS may also be directed to mmckenzie@mtsinai.on.ca.

Reference

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Selected article

Talpos GB, Bone HG III, Kleerekoper M, et al. Randomized trial of parathyroidectomy in mild asymptomatic primary hyperparathyroidism: patient description and effects on the SF-36 Health Survey. *Surgery* 2000;128:1013-20 [discussion 1020-1].

Abstract

Question: Is quality of life improved in patients who have a parathyroidectomy for mild asymptomatic primary hyperparathyroidism? **Design:** A randomized controlled trial. **Setting:** Single centre trial, Henry Ford Health System, Detroit, Mich. **Patients:** Fifty-three patients (42 women, 11 men) with confirmed asymptomatic primary hyperparathyroidism defined as follows: persistent albumin-adjusted serum calcium level of 10.1–11.5 mg/dL (2.5–2.9 mmol/L) from at least 3 measurements over a period of at least 3 months with an intact parathyroid hormone level that was greater than 20 pg/mL (> 2.1 pmol/L) and no other cause of hypercalcemia. **Interventions:** Patients were randomly allocated to receive either careful observation ($n = 28$) or surgery ($n = 25$). Those in the surgery group underwent a standard parathyroidectomy with bilateral approach by a single experienced surgeon who had performed over 600 parathyroid procedures before the study. **Main outcome measure:** Nine domains of the SF-36 Health Survey were measured to assess health-related quality of life. **Results:** The parathyroidectomy group had significantly better quality of life in 2 of the 9 domains of the SF-36: social functioning ($p = 0.007$) and role functioning — emotional ($p = 0.012$). **Conclusions:** Improved quality of life is seen after a parathyroidectomy for mild asymptomatic primary hyperparathyroidism and supports surgical management of mild primary hyperparathyroidism.

Commentary

Primary hyperparathyroidism (PHPT) is a common endocrine disease with a prevalence reported to be as high as 1 in 1000.¹ It was the introduction of automated, multi-channel, routine screening of total serum calcium concentrations in the early 1970s that led to a dramatic increase in the recognition of this disease. Where specific symptoms and clinical consequences of PHPT exist, there is little controversy about the need to operate. However, today, only a minority of patients with PHPT present with the “classic” symptoms of “aching bones, kidney stones, abdominal groans and psychic moans.” Most patients are considered “asymptomatic” and present with a constellation of vague nonclassic and subclinical signs and symptoms,² including mental depression, pain and decreased energy levels, decreased ability to complete daily tasks and decreased social interaction. It is because of the difficulty in quantifying and evaluating the nonclassic symptoms exhibited by these “asymptomatic” patients with PHPT that controversy surrounds the role of parathyroidectomy for their treatment. In 1991, the US National Institutes of Health (NIH) sponsored a consensus conference to set criteria for indications for parathyroidectomy in patients with mild disease.¹ These criteria were updated unofficially in 2002 by another NIH conference.³ The most important criteria for parathyroidectomy included age (< 50 yr), bone disease (osteoporosis, T score < 2 or other manifestation), kidney disease (abnormal creatinine, decreased creatinine clearance or kidney stones) and severe neuromuscular symptoms (weakness). Most endocrine surgeons, however, find these “NIH criteria” too conservative, because they exclude many patients with mild disease who might benefit from parathyroidectomy.³

Several retrospective and some prospective studies^{4,5} have shown that many patients have nonclassic symp-

toms and these symptoms significantly affect patients’ objectively measured quality of life. However, the key question is whether patients with asymptomatic PHPT benefit from parathyroidectomy. The study by Talpos and colleagues aims to answer this question by using a wellness survey, the SF-36 Health Survey, to assess outcome in patients with asymptomatic, mild hypercalcemia (serum calcium concentration 10.1–11.5 mg/dL [2.5–2.9 mmol/L]) randomly allocated to surgery or nonsurgical treatment. It was performed by a group with a lot of experience with the disease (1201 patients seen over 3 years).

Although the methods section appears extensive, most of that section is devoted to an exhaustive description of the patient inclusion and exclusion criteria. The strength of a randomized trial is its ability to control for possible bias. Blinding of randomization and blinding of outcome assessment are 2 important elements to minimize bias. The method of randomization is not described, and one cannot ascertain whether there was concealment of the randomization scheme. Furthermore, the timing of randomization is not stated, but there were few crossovers (none in the control group and 3 [12%] in the treatment arm) suggesting that randomization occurred close to the time of surgery. Blinding of patients and surgeon to treatment assignment is virtually impossible in a trial comparing surgical with nonsurgical treatment. However, precautions can be taken to ensure blinding of the assessors of patient outcome, but again there is no mention that this was done in this trial. One can only hope that the exhaustive attention to clinical detail and follow-up, evident in the publication, was also applied to the trial methodology. Unfortunately, however, the validity of the results may have been compromised by a lack of control of bias. Similarly, it does not appear that a sample size was calculated a priori, and there is

no mention of what were considered to be the primary and secondary outcomes.

The authors do describe the findings at surgery and patient clinical outcomes in detail. They are also to be congratulated that follow-up was complete. However, they fail to include a table summarizing the baseline characteristics of the 2 groups. It is also unclear why a large proportion of the patients who received surgery were found either at initial or subsequent surgery to harbour multiple gland disease (31%) and whether this may affect the generalizability of the results.

One of the strengths of the study is the use of a validated instrument, namely, the SF-36 health questionnaire, to measure outcome. The advantage of using the SF-36 is that it has been used in many other clinical settings, allowing the results to be compared with those for individuals with non-parathyroid disease. It has also been found to be reliable and valid. The major disadvantages are that the SF-36 was not developed specifically to measure acute changes following operation and it is not disease specific. A specific wellness tool for patients with PHPT, the Parathyroid Assessment of Symptoms (PAS) score, has been developed and validated in a multicentre PHPT cohort. It has also been used in a study that showed that asymptomatic patients exhibit significant improvement after parathyroidectomy.⁶

Upon first reading, it would seem that this randomized controlled trial confirms the results of previous non-randomized studies: parathyroidectomy improves quality of life of pa-

tients with mild PHPT because there is an improvement in 2 of 9 SF-36 domains. However, upon closer scrutiny, the results are less compelling. There is a reasonable likelihood that 1 or even 2 of the 9 domains of the SF-36 might show a statistically significant difference due to chance. This concern might have been minimized if the level of statistical significance had been adjusted (i.e., Bonferroni correction). In addition, given the information available from the paper by Burney and colleagues,⁵ the investigators could have planned which SF-36 results they expected to change and indicated a priori that those were the first and secondary outcomes. A final issue is that we do not know how much change in SF-36 domain score is required to be a “clinically significant” difference.

Overall, the authors should certainly be commended for attempting to carefully limit the target population and for performing a randomized controlled trial. However, the data appear weak in the face of an unclear randomization scheme, a lack of blinding and no consideration of the possibility of a type I error due to multiple comparisons. We are thus led to conclude that a larger, more methodologically rigorous, multicentre randomized controlled trial is necessary to address this issue. The results of this study provide support for performing such a trial. Furthermore, they provide evidence in the larger context that surgery may be warranted in this condition. There are data showing that parathyroidectomy improves life expectancy, especially in young patients with PHPT. This study and other recent work

certainly support the notion that “asymptomatic primary hyperparathyroidism” is a medical misnomer and that there is a need to revise the indications for surgery in the NIH-sponsored consensus conference guidelines for the surgical treatment of PHPT.

Competing interests: None declared.

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