SPECIAL ARTICLE

Canadian Association of General Surgeons, the American College of Surgeons, the Canadian Society of Colorectal Surgeons, and The American Society of Colorectal Surgeons: Evidence-Based Reviews in Surgery – Colorectal Surgery

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for the members of the Evidence-Based Reviews in Surgery Group

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

The Canadian Association of General Surgeons and the American College of Surgeons jointly sponsored a program entitled "Evidence Based Reviews in Surgery" (EBRS), supported by an educational grant from Ethicon Inc. and Ethicon Endo Surgery Inc. and Ethicon Endo Surgery. The primary objective of this initiative is to help practicing surgeons improve their critical appraisal skills. Beginning in 2007, EBRS also included a module covering topics in colorectal surgery. Each academic year, six clinical articles are chosen for review and discussion. The articles are selected not only for their clinical relevance to colorectal surgery, but also to cover a spectrum of methodologic issues important to surgeons; for example, causation or risk factors for disease, natural history or prognosis of disease, quantifying disease (measurement issues), diagnostic tests and the diagnosis of disease, and the effectiveness of treatment. Both methodologic and clinical reviews of the article are performed by experts in the relevant areas and posted on the EBRS-CRS website. As well, a listserv discussion is held where participants can discuss the monthly article. Members of the Canadian Association of General Surgeons (CAGS), and the American College of Surgeons (ACS), can access Evidence-Based Reviews in Surgery–Colorectal through the Canadian Association of General Surgeons website (www.cags-accg), the American College of Surgeons website (www.facs.org), the Canadian Society of Colon and Rectal Surgeons (CSRCS) website (www.cscrs.ca), and The American Society of Colon and Rectal Surgeons (ASCRS) website (www.fascrs.org). All journal articles and reviews are available electronically through the website. Surgeons who participate in the current (modules) packages can receive continuing medical education and/or maintenance of certification credits by completing an evaluation and a series of multiple choice questions. For further information about EBRS-CRS, readers are directed to the CAGS, ACS, CSCRS, and ASCRS websites or should e-mail the administrator, Marg McKenzie at mmckenzie@mtsinai.on.ca.

In addition to making the reviews available through the CAGS and the ACS websites, a condensed version of the reviews will be published in *Diseases of the Colon & Rectum*. We hope readers will find EBRS useful in improving their critical appraisal skills and in keeping abreast of new developments in general surgery. Comments about EBRS may be directed to mmckenzie@mtsinai.on.ca.

SELECTED ARTICLE

Leroi AM, Parc Y, Lehur PA, *et al.* Efficacy of sacral nerve stimulation for fecal incontinence. Results of a multicenter double-blind crossover study. Ann Surg 2005;242:662–9.

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QUESTION: Does sacral nerve stimulation effectively improve fecal incontinence in patients with fecal incontinence?

DESIGN: Randomized, double-blind, controlled crossover trial.

SETTING: Multicenter setting within France.

PATIENTS: Thirty-four patients (31 women; median age, 57 years; range, 33–73 years) who had fecal incontinence (FI) to solid or loose stool at least once per week.

INTERVENTIONS: Before permanent implantation, all patients underwent temporary percutaneous stimulation to assess their response. After permanent implantation, patients were randomly assigned in a double-blind crossover design to stimulation ON or OFF for a one-month period. While still blinded, the patients chose the period of stimulation (ON or OFF) that they preferred. The mode of stimulation corresponding to the selected period was continued for three months (final period).

MAIN OUTCOMES: Frequency of FI and urgency episodes, delay in postponing defecation, Cleveland Clinic Continence Score, feeling of improvement, preference for ON or OFF, quality of life, and manometric measurements.

RESULTS: In the crossover portion of the study, the self-reported frequency of fecal incontinence episodes was significantly reduced during the ON *vs.* the OFF period ($P = 0.03$), and this symptomatic improvement was consistent: 1) with the patient's feeling of greater improvement during the ON *vs.* the OFF period ($P = 0.02$); and 2) with the patient's preference ($P = 0.02$) for the ON *vs.* the OFF period. In the final period of the study, the frequency of fecal incontinence episodes decreased significantly ($P = 0.005$) in patients with the stimulator ON. The ability to postpone defecation ($P = 0.1$), the Cleveland Clinic Continence Score ($P = 0.0004$), quality of life ($P < 0.05$), and anal sphincter function improved significantly.

CONCLUSION: Sacral nerve stimulation is effective in improving outcome and quality of life in patients with fecal incontinence.

COMMENTARY: Fecal incontinence is unfortunately relatively common throughout the world with a prevalence of 2% to 11% depending on the population studied. Treatment of underlying gastrointestinal disorders improves many patients' symptoms. Sphincter repair results in improvement for approximately 80% of patients in the short term, but the results deteriorate over time. The current management of patients with fecal incontinence due to a weak, intact anal sphincter is unsatisfactory. These patients have no truly curative options. Bowel management routines, antegrade and retrograde irrigation techniques, sphincter-strengthening exercises, and biofeedback may improve quality of life, but rarely, if ever, reestablish normal continence. Colostomy can improve quality of life, but it is not a popular alternative.

The Secca procedure, injectable sphincter bulking agents, stimulated muscle transpositions, artificial bowel sphincter (ABS), and sacral nerve stimulation (SNS) have been advocated, but some carry a significant morbidity.

Sacral nerve stimulation was initially used for urinary incontinence. Clinicians found that many patients with concomitant bowel symptoms noted improvement in both their urinary and bowel symptoms. The beauty of the procedure is its simplicity and the availability of a test phase before insertion of the permanent stimulator. Under local anesthesia with sedation, testing is done to determine the optimal location for the stimulation lead. Patients then undergo a test period of temporary percutaneous stimulation; implantation of the permanent stimulator is performed if patients note at least a 50% reduction in fecal incontinence episodes. Minimal morbidity has been reported. However, the stimulator is expensive.

The study by Leroi and colleagues attempts to define the efficacy of sacral nerve stimulation and determine whether the benefit can be explained by the placebo effect. Thirty-four patients with an intact anal sphincter and severe fecal incontinence (incontinence to solid or liquid stool at least once per week), in whom conservative management failed, underwent insertion of a sacral nerve stimulator after temporary percutaneous stimulation. Only those with a significant response to temporary stimulation went on to permanent placement of the sacral nerve stimulator.

This study used a crossover design. Crossover trials are appropriate to evaluate therapies that are not permanent, have a predictable duration of effect, and do not interact with each other. Diseases evaluated by use of crossover methods should be chronic diseases that are stable over time. In crossover studies, individual patients receive all forms of treatment in successive time periods, and, thus, treatment assignment is not randomized. Instead, the order in which patients receive the treatments is randomized. In this study, the order in which patients had the sacral nerve stimulator activated and inactivated was randomized. After an adaptation period of one to three months, 27 of them participated in a crossover study of one month with the stimulator activated and one month with the stimulator inactivated. The patients and clinicians were blinded to the crossover periods. At the completion of the crossover study, patients then chose which period (activated or inactivated) they preferred for the final three-month study period.

In crossover studies, there is always concern that there may be a carry-over effect, so most crossover studies have a washout period that allows the effect of a therapy to completely dissipate before crossing over to the new therapy or placebo. In this case, there was no washout period. Thus, patients who were randomly assigned to activation in the first study period had up to three months of continuous stimulation before the active period, and up to four

months of continuous stimulation before the inactive period. In contrast, those randomly assigned to inactivation in the first phase of the study had one month less stimulation before the inactive period and had one month without stimulation before the active period. There is some evidence (although the evidence is inconsistent) that sacral nerve stimulation may result in a relatively long-term improvement in incontinence in some patients even after only brief stimulation. Thus, the failure to have a sufficient washout period may have resulted in differences between the groups at the beginning of the treatment periods. In addition, results in the inactive periods may reflect residual effects of stimulation. However, although this was a concern, the authors found no significant order or time effects. It is important to evaluate order effects and time effects in crossover studies to determine whether there is an interaction between what order the treatments were given and what the length of time the treatment was given and the effectiveness of the treatment.

The authors do not present a CONSORT diagram (a diagram now required by most journals publishing results of clinical trials that accounts for all patients who were randomly assigned). However, it appears that of the 34 patients entering the study, 7 were excluded before the random assignments; 3 of the 27 patients who were randomly assigned were excluded because of "protocol violation." Furthermore, variable numbers of patients are included in the measurement of outcomes and ten patients, including four who had explanations for complications, did not complete the trial.

A statistically significant decrease was found in the frequency of episodes of fecal incontinence when the stimulator was activated compared with when then stimulator was inactivated ($P = 0.03$). The authors do not report the precise difference in episodes of fecal incontinence between the time periods; however, in Figure 2A, the reader can see that the absolute difference was small (the median number of episodes of fecal incontinence per week was approximately 0.5 when the stimulator was activated compared with 1.5 when the stimulator was inactivated), in particular, when the range of episodes in the groups is considered (range, 0–11 episodes). In addition, because there may have been persistence of the effect of SNS into the inactive time period, the true estimate of the effectiveness of sacral nerve stimulation cannot be determined with any precision from this study. No differences in median urgency episodes, median delay in postponing defecation, or severity of incontinence as measured by the Cleveland Clinic Score were found when comparing the active and inactive time periods. This study demonstrated no significant differences in anal resting pressure, squeeze pressure, or duration of voluntary contraction, but it is interesting that squeeze pressure was increased compared with baseline in both stimulation ON and OFF periods. As is often found in FI studies, there was no or very weak correlation between symptom improvement and changes in manometric parameters.

Despite the fact that only small differences were found when the stimulator was active and inactive in terms of the objective parameters measured, more patients perceived an improvement in fecal incontinence when the device was activated (89%) compared with inactivated (63%), $P = 0.02$, and more patients expressed a preference for activation of the stimulator (18/27) than inactivation (6/27) or had no expressed preference (3/27), $P = 0.02$.

A major part of the rationale for this study and the study design was to exclude a placebo affect for SNS in the treatment of neurogenic FI. The authors claim success, "our trial has shown that the clinical benefit derived [from] SNS was not due to a placebo affect . . . " Still, the placebo effect, or possibly the "neuronal plasticity effect" (first paragraph of the discussion section) was fairly impressive: The median frequency of incontinence episodes decreased by 76% during the OFF period, 63% of patients had improvement during the OFF period; FI scores and defecation postponement improved whatever the mode of stimulation. Nine of 24 patients expressed either a preference for stimulation OFF or expressed no preference for OFF or ON. These data provide strong support for the need to have control groups in this kind of investigation.

Although this study raises as many questions as it answers, it is a beginning. Fecal incontinence is hard to study. Defining success is particularly difficult. Continence diaries, scoring systems, quality-of-life scales, and physiologic assessments are all imperfect. Thus, kudos to this team of investigators for trying! As well, the options for neurogenic fecal incontinence are not attractive. The ABS and stimulated muscle transpositions have a small role to play; these treatments are limited by morbidity, cost, and results that are good but not excellent. Less invasive procedures like Secca and sphincter injection appear to yield very modest improvement, but more high-quality, placebo-controlled trials are needed. As for the risk/benefit analysis for SNS, the risks are relatively low: four patients had the device removed because of complications. This rate is consistent with the SNS literature and is lower than what is seen with the ABS device, which has an explantation rate in the 30% to 40% range. On the other hand, the results are modest. Achieving modest results in the management of this difficult problem is par for the course. There is no economic analysis in this report, but in general, making people continent is cost effective; it is also a nice thing to do.

Currently, sacral nerve stimulation is approved in the United States only for urinary incontinence. The efficacy study on fecal incontinence with one-year follow-up has been submitted to the Food and Drug Administration with approval expected this year. Now is the optimal time to sort out the true efficacy and role of sacral nerve stimulation. It appears to be very beneficial for some patients, but

the mechanism of action, long-term outcome, and optimal patient selection is still unknown.

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REFERENCE

1. Evidence Based Medicine Working Group. Evidence-based medicine. JAMA 1992;268:2420–5.