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Randomized Controlled Trial Shows Biofeedback to be Superior to Alternative Treatments for Patients with Pelvic Floor Dyssynergia-type Constipation

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Abstract

Purpose—To determine whether biofeedback is more effective than diazepam or placebo in a randomized controlled trial for patients with pelvic floor dyssynergia-type constipation, and whether instrumented biofeedback is necessary for successful training.

Methods—One hundred seventeen patients participated in a 4-week run-in (education and medical management). The 84 who remained constipated were randomized to Biofeedback (n=30); Diazepam (n=30); or Placebo (n=24). All patients were trained to do pelvic floor muscle exercises to correct pelvic floor dyssynergia during 6 biweekly 1-hour sessions, but only Biofeedback patients received electromyography feedback. All other patients received pills 1-2 hours before attempting defecation. Diary data on cathartic use, straining, incomplete bowel movements, Bristol stool scores, and compliance with homework were reviewed biweekly.

Results—Before treatment, the groups did not differ on demographic (average age 50, 85 percent females), physiologic or psychologic characteristics, severity of constipation, or expectation of benefit. Biofeedback was superior to diazepam by intention to treat analysis (70 percent *vs.* 23 percent reported adequate relief of constipation 3 months after treatment, $\chi^2 = 13.1$, $p < 0.001$), and also superior to placebo (38 percent successful, $\chi^2 = 5.7$, $p = 0.017$). Biofeedback patients had significantly more unassisted bowel movements at follow-up compared to Placebo ($p = .005$), with a trend favoring biofeedback over diazepam ($p = .067$). Biofeedback patients reduced pelvic floor electromyography during straining significantly more than diazepam patients ($p < 0.001$).

Conclusions—This investigation provides definitive support for the efficacy of biofeedback for pelvic floor dyssynergia and shows that instrumented biofeedback is essential to successful treatment.

Keywords

biofeedback; constipation; dyssynergia; dyssynergic defecation; electromyography

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Introduction

Reports of the prevalence of constipation in the US range from 4 percent[1] to 27 percent.[2] Constipation has an adverse effect on quality of life[3,4] and is associated with increased work absenteeism[5] and health care costs.[6,7] The estimated cost of laxatives alone is over $4 million annually in the United States.[8] Medical management is ineffective in an estimated 89 percent of patients with chronic constipation,[9] and a significant number of these treatment failures seek and receive a subtotal colectomy (7 percent) or sigmoid resection (17 percent).[10]

The cause of constipation for many patients is unknown and identified as idiopathic constipation. The two primary mechanisms known to cause constipation are slow transit constipation, defined as delayed movement of stool throughout the colon, and pelvic floor dyssynergia, which is defined as impaired ability to evacuate the rectum caused by paradoxical contraction or failure to relax the pelvic floor during attempts to defecate.[11] Pelvic floor dyssynergia is believed to be responsible for up to 50 percent of constipation.[12,13]

When patients with pelvic floor dyssynergia do not respond to conservative interventions such as dietary recommendations, bowel scheduling, and medications, biofeedback is frequently recommended.[14] Biofeedback utilizes electronically amplified recordings of pelvic floor muscle contraction to teach patients how to relax pelvic floor muscles and to strain more effectively when they defecate.[15]

A collaboration between our laboratory and Chiarioni's has established that pelvic floor biofeedback benefits patients with pelvic floor dyssynergia but not patients with slow transit constipation,[16] and in a randomized controlled trial our two groups showed that biofeedback is more effective than the laxative, polyethylene glycol, for treatment of pelvic floor dyssynergia.[17] These studies tested a comprehensive training program that combined instrumented biofeedback with patient education and daily pelvic floor muscle exercises. It is not known whether instrumented biofeedback training (*i.e.*, visual or auditory displays of electronically amplified physiologic activity) is necessary *vs*. whether good patient education alone would be sufficient, as has been suggested by Norton *et al*.[18] for the treatment of fecal incontinence. The aims of this study were to determine (1) whether biofeedback is more effective than the muscle relaxant diazepam (5 mg given orally one hour prior to attempted defecation) and also more effective than placebo, and (2) whether instrumented biofeedback is a necessary component of successful training. This was a randomized controlled trial.

Methods

Patients

Patients were recruited from a consecutive series of chronically constipated patients who were referred by their physicians to the University of North Carolina Motility Laboratory between December, 2000 and November, 2004. Referral was for diagnostic testing by anorectal manometry and intra-anal surface electromyography to determine whether the patient had pelvic floor dyssynergia. Adult patients who were found to have pelvic floor dyssynergia on diagnostic testing were contacted by investigator SH, screened to insure that they met inclusion criteria, and invited to participate if they were eligible. This study was reviewed by the university's Institutional Review Board and by the advisory board of the General Clinical Research Center. It was initially approved May 4, 1999, and reapproved annually thereafter. All subjects provided written consent after full disclosure of the experimental procedures.

Inclusion criteria

The patient had to fulfill Rome II diagnostic criteria for pelvic floor dyssynergia[11] which are (1) two or more symptoms of functional constipation for at least 12 weeks in the past year; (2) manometric, electromyography, or radiologic evidence for inappropriate contraction or failure to relax the pelvic floor muscles during attempts to defecate; (3) evidence for inadequate propulsive forces during attempts to defecate; and (4) evidence of incomplete evacuation. Inclusion criteria 2-4 were ascertained from the anorectal manometry and electromyography tests. Exclusion criteria were (1) current use of diazepam; (2) previous experience with biofeedback for constipation; (3) known allergies or sensitivities to diazepam or other benzodiazepines, (4) inability to comply with medication precautions (*i.e.*, avoidance of the use of alcohol or other sedating medications (benzodiazapines and Zolpiem), and the operation of heavy machinery); (5) current pregnancy or at risk of becoming pregnant (if subject is female, premenopausal, and sexually active, she must be using a medically approved birth control method to prevent pregnancy); and (6) seizure disorder, psychotic disorder, or severe cognitive impairment.

Design

This was a randomized controlled trial involving three phases (Fig. 1): run-in, treatment, and follow-up. Patients who met the criterion for successful treatment after the run-in phase were excluded from the training phase. The remaining patients were randomly assigned to three groups: biofeedback, diazepam, or placebo. The trial was partially blinded: both the investigators and the patients knew whether the patients were assigned to biofeedback or to pills, but neither the investigators nor the patients knew whether patients assigned to the pill groups received diazepam or placebo.

Diazepam was chosen as an active comparator (control group) because it has been commonly used in our clinical practice as an adjunctive treatment for pelvic floor dyssynergia. The rationale for this practice is that the goal of most treatments for pelvic floor dyssynergia is relaxation of the striated pelvic floor muscles, whether through biofeedback,[19,20] surgical division of the puborectalis muscle,[21] or botulinum toxin injection[22]. Diazepam is a skeletal muscle relaxer which is known to be effective in muscle spasticity,[23] and unlike the other commonly used muscle relaxer, baclofen,[24] it does not cause constipation as a side-effect. Diazepam has the additional theoretical advantage that it reduces anxiety, which may contribute to pelvic floor dyssynergia in some patients.[11]

The primary outcome was a report of adequate relief of constipation at 3 months follow-up.[25] The primary efficacy assessment was delayed to this point because (1) patients enrolled in behavioral treatments sometimes continue to improve following the end of training,[26,27] and (2) sustained improvements in symptoms provide a better measure of the efficacy of treatment than does an end of treatment measure. The question used to assess adequate relief was, “Compared to before you started the study, have you experienced adequate relief of constipation?” Patients could only respond “yes” or “no”.

Run-in

This phase consisted of four weeks during which all patients were provided with education and medical management. Education included information on the physiology of defecation and the normal range of bowel movements, including a review of their manometry test results and the use of drawings of pelvic floor anatomy to illustrate the concept of pelvic floor dyssynergia. Patients were instructed not to strain excessively (less than 50 percent of maximum effort), and they were instructed to keep diaries recording unassisted bowel movements, assisted bowel movements (defined as bowel movements occurring within 12 hours of taking laxatives or suppositories), straining, and the feeling of incomplete

evacuation. All patients were also instructed to attempt defecation by sitting on the toilet for 10 minutes after dinner and to take stool softeners (ducosate sodium 100 mg) as needed to maintain normal stool consistency (which was defined as a rating of 4 on the Bristol stool scale).[28] Patients also received recommendations regarding changes in diet (increased fiber), water/diuretic intake, and general physical exercise to improve stool consistency. A detailed treatment manual describing this educational intervention is available from the corresponding author.

During the run-in phase, the 12-week treatment phase, and during follow-up, patients were allowed to take a bisacodyl suppository if they had gone for 72 hours without a bowel movement. However, they were not permitted to take more than two suppositories in any one week. The rationale for allowing patients to take laxatives as an escape was that those patients who did not benefit from treatment would otherwise tend to drop out or to take laxatives surreptitiously. In the data analysis, the use of escape medication was tracked by distinguishing between assisted and unassisted bowel movements.

Patients who reported adequate relief of constipation at the end of run in were excluded from the training phase of the study and were scheduled for a follow-up evaluation 3 months later, while patients who did not report adequate relief at the end of run-in were randomized to one of three treatments and progressed to the training phase.

Training Phase

Treatments compared in this study were: 1) electromyography biofeedback training to teach relaxation of the pelvic floor muscles during straining to defecate, 2) use of a 5 mg dose of diazepam to relax skeletal muscles (taken one-two hours prior to scheduled attempt to defecate each evening), or 3) use of a placebo tablet in place of diazepam. Patients came for 6 biweekly visits scheduled over a 3-month period. The duration of the training visits were the same for patients in all three groups (approximately 50 minutes).

Independently of the training strategies group to which they were randomly assigned, during the training phase all patients were shown a video of a normal defecogram study (barium paste being evacuated during defecation with proper relaxation of pelvic floor muscles), and two examples of pelvic floor dyssynergia in which evacuation of barium paste was impeded by inappropriate contraction of pelvic floor muscles. All patients were trained to perform pelvic floor exercises by verbal instructions, and they were asked to practice these strategies several times daily. This included instructions to push adequately but not excessively (less than half of their maximum effort) and to perform Kegel exercises. The Kegel exercises were used to help the patient develop awareness of the difference between tensing and relaxing pelvic floor muscles, as well as serving as an example of what not to do during attempted defecation. Patients were also instructed to continue run-in interventions which focused on stabilizing stool consistency and timed toileting following dinner. All patients were taught to relax their whole body when attempting to defecate, to use either a forward leaning or an upright posture, and to discontinue counterproductive postural strategies they may have developed. Patients were also coached to modify their attitudes towards defecation, *i.e.*, to stop pushing if they detected that they were contracting their pelvic floor muscles, and then try again. They were instructed that if they were unsuccessful when pushing correctly over a 10-15 minute period, they should give up and try again later. Patients were instructed to attempt to defecate following dinner every day, in addition to whenever an urge to defecate was perceived. They were instructed to use the skills they had learned during pelvic floor muscle retraining visits to correct pelvic floor dyssynergia. All patients kept a daily diary which included daily straining efforts, feelings of incomplete evacuation, Bristol stool scale ratings for each BM, identification of unassisted bowel movements *vs.* assisted bowel movements, and a comments section designed for patients to

record their thoughts on what influenced the success of defecation efforts. The investigator reviewed these diaries data with the patient at each clinic visit.

Biofeedback Treatment

In addition to the training strategies mentioned above, patients in this group received instrumented biofeedback using an acrylic anal plug containing three longitudinally-oriented metal plate electrodes (Self-Regulation Systems Incorporated, Redmonds, Washington, USA). electromyography activity was amplified, filtered to eliminate low frequency electromyography activity from the smooth muscle and high frequency activity representing ambient electrical noise, then averaged and displayed so that patients could see the recording. This recording reflects both the external anal sphincter and puborectalis muscles. A second channel of electromyography was recorded from electrodes applied to the skin overlying the abdominus rectus muscles. For this channel, the two active electrodes were positioned in a vertical line with the first situated 2 cm below the umbilicus and the second placed 5 cm below the first. A reference electrode was placed midway between these two active electrodes. The patient watched a computer monitor displaying the abdominus rectus electromyography on the top and the pelvic floor electromyography immediately below it. A 2-channel Sandhill® Insight GI motility/biofeedback system computer (Sandhill® Scientific Incorporated, Highlands Ranch, Colorado, USA) was used to record and display these signals.

Each 50 minute biofeedback training session was done while the patient was covered with a sheet and sitting on a chair to simulate defecation postures. At the beginning of each biofeedback session, resting electromyography from both the pelvic floor and the abdominus rectus was recorded for 3 minutes. The patient was then instructed to relax, squeeze, or strain gently for a series of 10-second trials. The therapist conducting the session set target lines on the computer monitor for the abdominus rectus electromyography tracing to indicate that straining should go up to this line. He also established targets for relaxing the pelvic floor electromyography tracing below appropriate levels during straining. The therapist altered the target lines in a standard shaping procedure (rewarding successively better approximations to the desired response) in such a way that the patient succeeded on at least 50 percent of trials.

Training strategies for pill groups

Patients in the pill groups ingested a diazepam (5mg) or placebo pill one hour prior to dinner, with instructions for proper defecation attempts following dinner. Side-effects and contraindications for taking the diazepam were discussed with each patient in both pill groups. Patients were encouraged to contact the therapist if they experienced any unexpected side effects or had any concerns about taking the pills. Both the patients and therapist were blind as to which pill each patient received. At biweekly clinic visits, the therapist addressed adherence with taking the pills and discuss any reasons for non-adherence.

To summarize, the only differences in treatment strategies for patients in the three groups were related to whether they received instrumented biofeedback or a pill; patients in all groups received an intensive educational intervention, pelvic floor muscle exercises, and the use of stool softeners and diet manipulations to modify stool consistency.

Follow-up Evaluations

Patients completing the treatment phase of the study were scheduled to return for a 3-month follow-up evaluation regardless of their symptomatic improvement. During this three-month period, patients were instructed to continue to practice relaxing and pushing gently during bowel movements. Kegel exercises and pills were discontinued. All patients were instructed

to continue using bisacodyl suppositories if they had no bowel movement for 72 hours. Prior to the scheduled 3-month follow-up evaluation, all patients were sent a diary to keep for the two weeks before their visit, and they were instructed to avoid the use of laxatives during this two-week interval. During the follow-up evaluation they were asked to undergo repeat anorectal manometry and electromyography testing, and to complete posttreatment questionnaires. After completing their 3-month follow-up visit, all patients were contacted by telephone by the same investigator (SH) and asked, whether they experienced adequate relief of constipation. Patients who did not report adequate relief at 3 months follow-up or who failed to return for follow-up evaluation at 3 months were labeled treatment failures and were provided with information on alternative treatment and dismissed from the trial. Those who reported adequate relief were scheduled for 6-month and 12-month follow-up evaluations. Collection of follow up data is continuing. The primary data for this report is the 3 month follow-up evaluation.

Dependent Variables

All patients in the randomized treatment trial completed a treatment credibility questionnaire[29] to assess their expectation of benefit. This questionnaire was administered at the beginning of their second training visit after they had been exposed to one treatment visit and two weeks of practice.

The primary outcome measure of this investigation was the patient's response to the question, “Compared to before you started the study, have you experienced adequate relief of constipation?” [25] This was administered as a single item questionnaire at the 3-month follow-up visit as well as at 6 month and 12 month follow-up visits. Patients who withdrew from the trial prior to completion of the training or who did not return for follow-up evaluation were counted as treatment failures (*i.e.*, no adequate relief) and were included in all of the intent-to-treat analyses. Secondary outcomes are listed below.

Unassisted bowel movements—defined as any bowel movement that was not preceded within 12 hours by use of a laxative or suppository.

Assisted bowel movements—defined as any bowel movement that did occur within 12 hours of taking a laxative or suppository.

Straining—On their diaries patients were asked to rate the intensity of straining for each bowel movement on a 0-10 numerical scale in which 10 represented the maximum possible.

Other diary measures—Patients were also asked to record use of laxatives and whether they had a sensation of incomplete evacuation for each BM.

Patient Assessment of Constipation Symptoms (PAC-SYM):[30]—The PAC-SYM is a validated 12-item questionnaire used to assess symptoms of constipation over the previous month. It was completed at study enrollment, end of run-in, end of treatment, and at 3 months follow-up. The PAC-SYM provides a single index of the severity of constipation.

Patient Assessment of Constipation Quality of Life questionnaire (PAC-QOL):[31]—The PAC-QOL is a validated 28-item questionnaire used to assess the impact of chronic constipation on the quality of the patient's life over the past month. It was completed at study enrollment, end of run-in, end of treatment, and at 3 months follow-up. The PAC-QOL is scored for 4 domains (Worries and Concerns, Satisfaction, Psychosocial Discomfort, and Physical Discomfort).

Health Related Quality of Life measured with the SF-36:[32]—The SF-36 is a standardized, 36-item measure of the impact of illness on quality of life that is not specific to a single disease. It is used to make comparisons across diseases and comparisons to the general population using tables published in the manual for the test.

Moderator variables

Attitudes Toward Treatment:[29]—This 7-item questionnaire is used to assess the patient's expectation of benefit from a treatment to which they have had an initial exposure (*i.e.*, it is a credibility scale). The questionnaire was administered at the beginning of the second treatment visit as a way of gauging whether patients in the diazepam and placebo groups had an expectation of benefit that was comparable to patients in the biofeedback group.

Spielberger State-Trait Anxiety Inventory (STAI-2):[33]—This is a standardized scale measuring the overall tendency to experience anxiety.

Beck Depression Inventory (BDI):[34]—This is a 24-item, standardized questionnaire used to measure the severity of symptoms of depression over the past week.

Sexual and Physical Abuse Scale:[35]—This validated 12-item checklist was used to identify patients with a history of sexual or physical abuse and to characterize the type of abuse.

Physiological Variables

Anorectal manometry—All patients underwent a diagnostic anorectal manometry study prior to enrollment in the study. With the patient's permission, data from this study were used as baseline measures for evaluating the outcomes of the intervention. Anorectal manometry was repeated at the end of training and at the 3-month follow-up to investigate the mechanism of treatment effects. Anorectal manometry was performed using a Sandhill® Scientific (Highlands Ranch, Colorado, USA) physiologic recorder. Pelvic floor electromyography was also measured at rest, squeeze, and during straining to defecate. See the Biofeedback Treatment section for a description of the technique.

Whole gut transit time was measured by the Sitzmark technique at baseline. The protocol was to have patients ingest a gelatin capsule containing 24 radio-opaque rings daily for 5 days and to receive a single abdominal radiograph on the sixth day to determine how many markers remained in the abdomen. The interpretation of this examination is based on the assumption that over a period of days, the number of markers ingested comes into equilibrium with the number excreted, so that the number of markers remaining in the bowel on Day 6 can be taken as an estimate of average whole gut transit time in hours.

Sample size and power—Prior to study initiation, we estimated the number needed per group for 80 percent power to detect between group differences, to be 50. However, after approximately 30 patients per group had completed the 3 month follow-up, an interim intent-to-treat analysis was performed on the primary outcome variable with alpha set at a conservative 0.01. This showed the biofeedback group to be significantly better than the two pill groups combined (the blind had not been broken), and enrollment in the trial was consequently closed. Once enrollment stopped, patients who were already enrolled in run-in or treatment phases of the study continued until completed.

Data Analysis

Comparability of groups at randomization

To insure that the groups were not different prior to treatment, the biofeedback, diazepam, and placebo groups were compared by separate analyses of variance (ANOVAs) with respect to (1) demographic variables, (2) symptoms of constipation at the end of run-in, (3) physiologic variables at enrollment, and (4) credibility ratings measured after the first treatment visit. These analyses were limited to patients who were allocated to treatment, *i.e.*, those who did not report adequate relief of constipation at the end of run-in.

Effects of education and conservative medical management during run-in

The proportion of patients who reported adequate relief at the end of run-in and the proportion of those patients who continued to report adequate relief 3 months later at follow-up was calculated. In secondary analyses, we also calculated changes in the frequency of unassisted bowel movements by comparing the two weeks prior to enrollment (assessed by retrospective questionnaire) to the frequency of unassisted bowel movements during the last two weeks of run-in (assessed by diary).

Treatment efficacy analysis

The primary analysis was an intent to treat analysis of the proportion of responders (patients reporting adequate relief at 3 months follow-up) in the biofeedback group compared to the diazepam group and (separately) to the placebo group. All patients allocated to a treatment group were retained in these analyses; drop outs during treatment were assumed to be non-responders. Chi squared tests were used, and significance was defined by a Bonferoni adjusted p-value of .025. The CONSORT guidelines (www.consort-statement.org)[36] were followed in reporting the results of the trial (see Fig. 2). These guidelines dictate full disclosure of what happens to all patients approached about enrollment in the study and reasons for nonparticipation.

Secondary analyses of efficacy utilized analysis of covariance (ANCOVA) for the following dependent variables: unassisted bowel movements, assisted bowel movements, average straining rating, frequency of reporting a sensation of incomplete evacuation, PAC-SYM, and PAC-QOL. The covariate was the pretreatment values for these variables. All secondary measures were evaluated in intent-to-treat analyses. We used the principle of the last observation carried forward for patients who withdrew or were withdrawn from the study at any time. This avoids overestimating the benefits of treatment caused by a greater tendency for patients who have not benefited to drop out during follow-up. Per protocol data (limited to those patients that completed training) was assessed as well.

Mechanism of treatment effects

To determine whether improvements in constipation following treatment were mediated by changes in the physiologic mechanisms believed to be responsible for pelvic floor dyssynergia, we carried out an analysis of covariance (ANCOVA) with baseline push electromyography values as the covariate. We predicted that the largest changes in pelvic floor electromyography would occur in the biofeedback group.

Results

Recruitment

Out of 184 patient meeting inclusion criteria and invited to participate, 67 (36 percent) declined, and 117 were enrolled in the run-in (Fig. 2). Of the patients declining participation,

approximately 49 percent cited travel difficulties (too far or no transportation), 19 percent were “too busy”, 10 percent wanted alternative treatments, 10 percent cited other health reasons, and 10 percent gave no reason.

Effects of education and conservative medical management during run-in

Eighteen (15 percent) of the 117 patients who were enrolled in the run-in phase reported adequate relief at the end of run-in and 15 patients (13 percent) withdrew from run-in (Fig. 2). Patients who reported adequate relief were scheduled for follow-up 3 months later and were not continued into the treatment phase of the study.

Substantial symptom improvements occurred during the run-in intervention. The average increase in unassisted bowel movements during run-in for all subjects combined was 3.8 per week ($p < 0.001$). Run-in responders increased unassisted bowel movements by 4 per week, whereas patients who did not report adequate relief (and progressed to the training phase) increased unassisted bowel movements by 2.6 per week during the run-in. Similarly, the average decrease in assisted bowel movements during run-in for all patients combined was 4.35 ($p < 0.001$). Run-in responders decreased laxative assisted bowel movements by over 6 per week, while patients progressing to training reduced assisted bowel movements by 2.6 per week.

Treatment efficacy

Eighty-four patients (85 percent female) remained constipated and dissatisfied with their treatment at the end of run-in and progressed to the treatment conditions to which they had been randomly assigned. No significant differences were found among treatment groups at baseline or end of run-in prior to the treatment phase of the study with regard to demographic and medical history variables (Table 1) or physiologic, psychologic, quality of life measures (PAC-QOL, SF-36), symptom severity, or health care utilization measures (Table 2). Importantly, these groups also had a similar expectation of benefit at the beginning of their second treatment session, which followed initial exposure to their respective treatment protocols: Average scores on the Attitudes Towards Treatment scale were 53 for biofeedback, 51 for diazepam, and 49 for placebo (ANOVA, $p = 0.27$).

Primary Outcome Measure

Figure 3 shows that at 3 months follow-up more than twice as many patients in the biofeedback group reported adequate relief as compared to both the diazepam group and the placebo group. These comparisons were both statistically significant in the intent to treat analysis. Seventy percent of biofeedback patients *vs.* 23 percent of diazepam patients ($\chi^2 = 13.1$, $p < 0.001$), and 38 percent of placebo patients ($\chi^2 = 5.7$, $p = 0.017$) reported adequate relief (Fig. 3).

In a per protocol assessment (*i.e.*, analysis limited to those who completed treatment), a greater proportion of biofeedback patients reported adequate relief compared to diazepam patients (91.3 percent *vs.* 30.4 percent, respectively, $\chi^2 = 17.9$, $p < 0.001$) or placebo patients 91.3 percent *vs.* 46.5 percent, respectively, $\chi^2 = 10.9$, $p = 0.001$). Only two patients completing biofeedback training failed to report adequate relief compared to 15 and 11 patients in the diazepam and placebo groups respectively.

Secondary Outcome Measures

Clinical Outcomes

Between-group comparisons of unassisted bowel movements and assisted bowel movements at 3 months follow-up support the primary outcome analysis. There was a significant

treatment group effect on increases in unassisted bowel movements (ANCOVA, F = 4.37, p = .016) and a trend (p = .165) for treatment group effect on decreases in assisted bowel movements. Univariate Contrasts showed that patients in the biofeedback group had significantly more unassisted bowel movements compared to patients in the placebo group (p = 0.005), with a trend in favor of the biofeedback patients having more unassisted bowel movements than patients in the diazepam group (p = .067). Similarly, biofeedback patients had fewer assisted bowel movements compared to diazepam patients or compared to placebo patients, though these differences were not significant. Other secondary outcome measures from the symptom diary, namely straining and feeling of incomplete evacuation, did not differ between groups at 3 months follow-up.

Quality of life

At baseline, all but one subscale of the SF-36 were significantly lower (p < .001, t-test) than population norms [Physical Functioning, Role-physical, Bodily Pain, General Health, Social Functioning, Role-emotional, Mental Health, and reported Health Transition, (Vitality, p = 0.23)], reflecting significant impairment in QOL for patients suffering from constipation. However, there were no between-group differences prior to treatment on the summary scores for the SF-36 or PAC-QOL, nor on any of the subscales for these questionnaires. At 3 months follow-up, the biofeedback group tended to have higher summary scores on the SF-36 and lower summary scores on the PAC-QOL compared to the other two groups (Table 2: both differences reflect better quality of life in the biofeedback group), but these differences were not statistically significant. At 3-month follow-up the biofeedback group reported significantly better General Health and were more satisfied with bowel function than patients in either of the pill groups (ANOVAs, F = 3.17, p = 0.049, and F= 3.2, p = 0.047, respectively).

Physiological mechanism of treatment changes

Figure 4 shows the average values for pelvic floor electromyography when straining to defecate; the aim of biofeedback training was to reduce this activity. Between-group comparisons of push electromyography values at 3 months follow-up showed that there was a significant treatment group effect on increases in push values (ANCOVA, F = 8.02, p = 0.001). Baseline push electromyography values were used as the covariate in this analysis. Univariate Contrasts show that patients in the biofeedback group exhibited significantly lower electromyography activity during straining as compared to the diazepam group (p<. 001), and there was a trend for push values for patients in the biofeedback group to be lower than for patients in the placebo group (p < .16).

Discussion

This investigation provides definitive support for the efficacy of biofeedback treatment for patients with pelvic floor dyssynergia constipation. Three months after the end of training, the proportion of patients reporting adequate relief of constipation was significantly greater for patients receiving biofeedback compared to patients treated with a skeletal muscle relaxer, diazepam, or patients treated with placebo tablets. Adequate relief is a patient-reported global outcome measure which was recommended by the Rome III multinational working team for the design of treatment trials as the preferred outcome measure in treatment trials for the functional gastrointestinal disorders[25]. Based on an intent-to-treat analysis in which patients who dropped out were listed as treatment failures, 70 percent of patients randomized to biofeedback reported adequate relief compared to 23 percent of patients treated with diazepam and 38 percent of patients treated with placebo tablets. If the analysis was limited to patients who completed all 6 training sessions, 91 percent of

biofeedback patients achieved adequate relief of constipation. Clearly biofeedback was more effective than these alternative treatments.

The superiority of biofeedback was also shown by multiple secondary outcome variables that were derived from a daily symptom diary. Patients in the biofeedback group, when compared to diazepam and placebo treated patients, reported more unassisted bowel movements and fewer laxative assisted bowel movements at 3 months follow-up.

An unanticipated finding was that fewer of the patients treated with diazepam (the active control condition), reported adequate relief compared to the placebo group. This is believed to be the result of side-effects of diazepam, as reflected in a higher drop out rate in the diazepam group (7/30) compared to the placebo group (4/24; Fig. 2). Drop outs were regarded as treatment failures in the intent to treat analysis.

This is not the first randomized controlled trial to address the effectiveness of biofeedback for the treatment of pelvic floor dyssynergia; a collaborative study between our laboratory and Chiarioni's group,[17] showed biofeedback to be superior to laxatives for the treatment of pelvic floor dyssynergia, and Rao and colleagues reported a study comparing biofeedback to sham feedback and to standard medical care which showed biofeedback to be more effective than sham biofeedback.[37] The current study extends the Chiarioni study and the unpublished Rao study in a number of important ways, as discussed below:

Non-Specific Effects

One of the primary aims of this study was to rigorously control for nonspecific aspects of treatment and to determine whether instrumented biofeedback training is necessary to successful treatment. In previous studies, biofeedback training was combined with a number of nonspecific treatment components that may have contributed to patient improvement; these nonspecific elements of biofeedback training included increased contact with the health care provider, patient education, lifestyle modification (*e.g*., advice regarding diet and exercise), and in some studies the provision of stool softeners or laxatives and pelvic floor exercises. It is important to know whether the most expensive and least available component of this training program is necessary, namely biofeedback training by a specially trained provider using electronic devices to amplify muscle activity and convert it to a visual or auditory display. It has been suggested that instrumented biofeedback is not necessary to the successful treatment of another pelvic floor disorder, fecal incontinence.[18]

The run-in phase of our study was intended to control for the effects of good medical management. All patients enrolled in the study were provided with fiber and stool softeners to improve constipation, advice on diet and exercise, education on the physiologic mechanisms for pelvic floor dyssynergia, and advice on ways to prevent outlet dysfunction type constipation by attempting a bowel movement after a meal at a regular time of day, positioning themselves appropriately on the toilet seat, and not straining excessively. These were all considered to be elements of good clinical management that could be provided by health care providers without special training or equipment. We found that this systematic application of good clinical management produced adequate relief of constipation for 15 percent of patients despite a history of failed medical management, and these patients continued to report adequate relief when they were reevaluated at the three month follow-up. They were not enrolled in the treatment phase of the study. Moreover, among the patients who did not experience adequate relief from good clinical management, there was nevertheless a significant increase in the frequency of unassisted bowel movements and a significant decrease in the frequency of assisted (laxative induced) bowel movements during the run-in phase of the study. Clearly, the systematic delivery of good clinical management

can benefit many patients, and we have developed a treatment manual to facilitate primary care providers being able to do this more effectively.

During the treatment phase of the study, the focus shifted from whether good medical management was sufficient to whether behavioral training without instrumented biofeedback was sufficient. The educational component of training was intensified by using videos of defecography examinations from both normal subjects and patients with pelvic floor dyssynergia to teach patients what they were doing wrong. All patients were taught pelvic floor muscle exercises and instructed to practice these daily, and they were taught to adopt a more passive approach to defecation in which, if they were not successful after 10 minutes, they should stop trying and try again later. All patients also kept detailed diaries in which they recorded what they believed might have caused them to have more difficulty or more success with evacuation on some days, and a clinical psychologist reviewed these diaries with the patient at the beginning of each treatment session and coached them on coping strategies. Because these intensive behavioral treatments were provided to all patients, the only thing which distinguished the biofeedback treatment group from the two control groups was the provision of instrumented biofeedback training. The finding that two to three times as many patients in the biofeedback group achieved adequate relief as compared to the two control groups provides compelling evidence that instrumented biofeedback is an essential component of successful treatment.

Expectancy/placebo effects

The studies by Chiarioni *et al.*[17] and Rao *et al*.[37] attempted to control for expectancy effects by including an alternative treatment such as laxative therapy or sham biofeedback. However, neither of these studies evaluated whether patients in fact had the same expectation of benefit from these treatments. It is possible that subjects would have a low expectation of benefit from laxatives because they have previously failed to benefit from laxatives. We therefore employed diazepam as an active control because a skeletal muscle relaxer is a plausible treatment for pelvic floor dyssynergia, and in fact it is a treatment that we have provided clinically in the past. Moreover, we tested the credibility of all treatments using the validated Attitudes Towards Treatment scale[29] after the patients' first exposure to each of the treatments and were able to show that the patients in the diazepam group and the patients in the placebo group had an equal expectation of benefit when compared to the biofeedback patients. Thus, we can confidently state that the differences in the proportion of patients reporting adequate relief of constipation are not the result of placebo or expectancy effects.

Mechanism of biofeedback training effects

An important measure of the validity of a clinical trial is to show that the active treatment is working in the intended manner (*i.e.*, by showing that biofeedback modifies pelvic floor electromyography responses during straining to defecate), and that the controls conditions do not produce similar changes in the process measure.[38] The biofeedback group showed greater reductions from baseline in the electromyography activity of the pelvic floor during efforts to defecate as compared to the two control groups. This supports the validity of the trial and suggests that the clinical benefits seen in the biofeedback subjects were related to their learning to relax the pelvic floor muscles during defecation.

Health Related Quality of Life

Pelvic floor dyssynergia patients reported significant impairment in quality of life at baseline compared to population norms. Group differences at 3-month follow-up revealed a trend (not statistically significant) for more improvement in quality of life for biofeedback patients compared to diazepam or placebo patients. Moreover, on the subscales for General

Health and satisfaction with bowel function, the biofeedback patients showed significantly less impairment than patients in either of the pill groups at three months follow up.

Limitations of the Investigation

All patients with pelvic floor dyssynergia at the diagnostic evaluation (that consented to participate) were included in this investigation, including patients with slow transit constipation, and it has been reported[15] that patients with severely delayed transit are less responsive to biofeedback. Although it is possible that studying a more homogenous population by excluding patients with slow transit might have yielded different results, the lack of association between transit times and treatment outcome in this study suggests that this would not be the case.

As with most behavioral intervention, the therapist was not blind to treatment interventions (except to pill content). Also, patients were not blind to alternative treatments. However, we used the credibility scale to show that the patients' expectation of benefit did not differ among groups. In addition, separate investigators provided treatment and interpreted anorectal manometry reports. Because diary data and physiologic data support the results of the primary outcome data, it is unlikely that experimenter bias or expectation bias influenced the results of this investigation.

Implications for clinical practice

This study confirms that biofeedback is a highly effective treatment for pelvic floor dyssynergia and shows that this should be the first line treatment for this type of constipation. We have also shown that the machines are necessary – instrumented biofeedback is an essential element of successful training. At present, however, there is a shortage of practitioners who are trained to provide this form of biofeedback, and there are few clinics where biofeedback instruments are available and where this form of biofeedback can be obtained. The shortage of available service providers may be, in part, the result of the absence (until now) of randomized controlled trials showing biofeedback to be effective,[13] which led third party payers to withhold payment for this form of treatment. It is hoped that this emerging body of evidence for the efficacy of biofeedback for pelvic floor dyssynergia constipation will contribute to an improvement of this situation.

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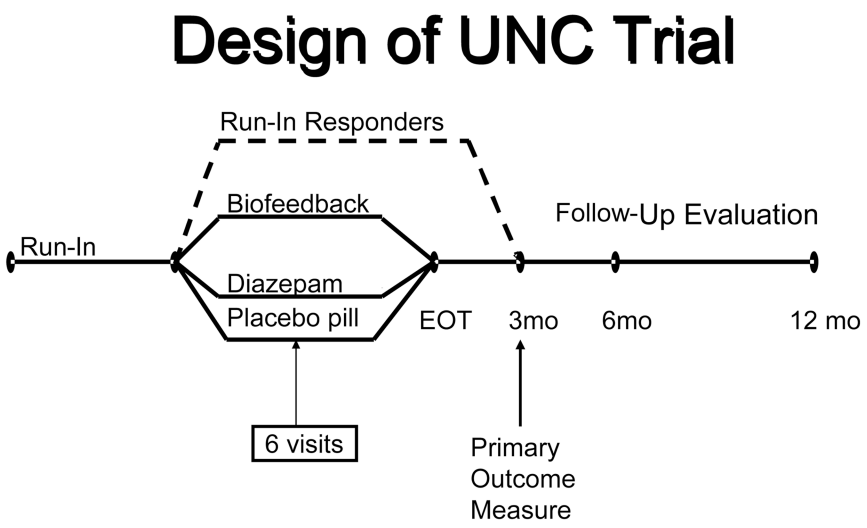

Figure 1. Schematic of study flowchart

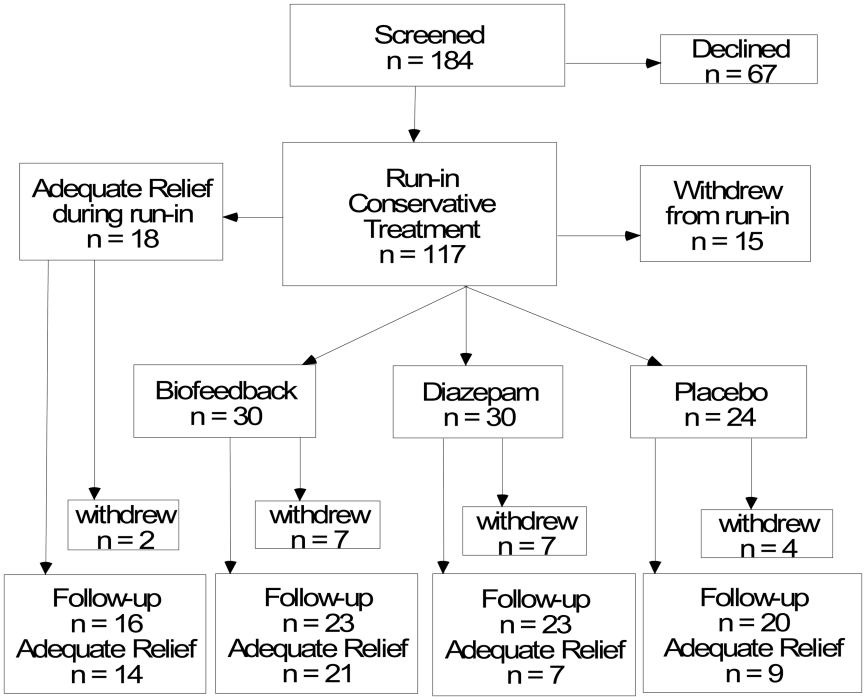

Figure 2. Consort guidelines flow-chart

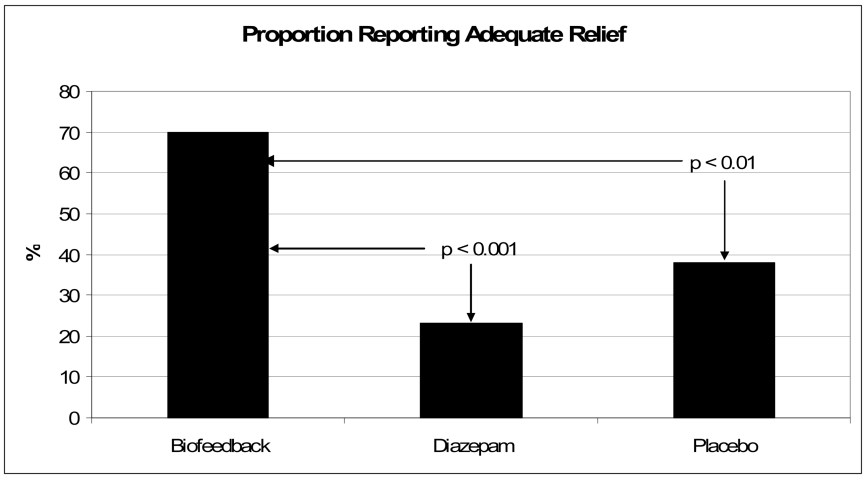

Figure 3.
Primary Outcome Measure using a Chi Squared analysis comparing the proportion of subjects reporting adequate relief at 3-month follow-up in the biofeedback group compared to the diazepam and to the placebo groups.

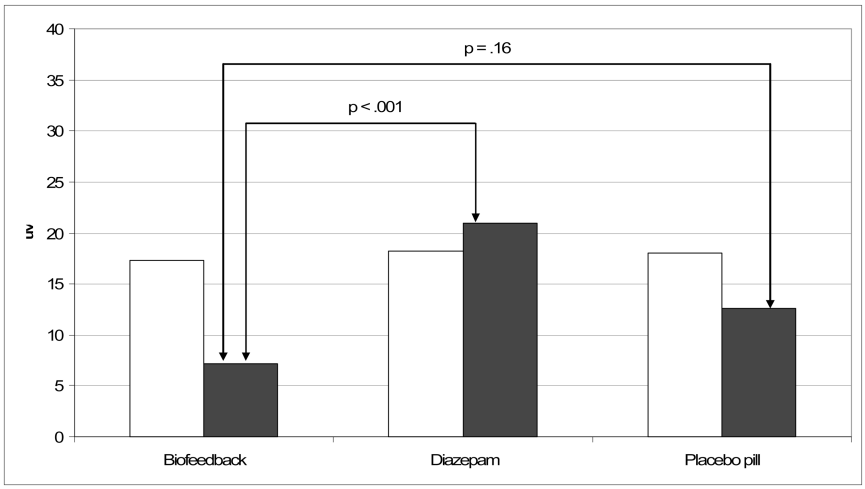

Figure 4.
Pelvic floor electromyography values (microvolts) during simulated attempts to defecate (baseline electromyography = white, 3-month follow-up electromyography = black).

Table 1

Baseline	Biofeedback	Diazepam	Placebo
Sample size	30	30	24
Age	51.4	51.7	46.1
Symptoms (years)	14.0	14.5	19.0
Physician visits (past 6 months)	5.0	5 .5	5.3
BDI (range 0-63)	10.9	11.3	11.8
STAI-2 (range 20-80)	38.8	40.7	40.6
History of sexual abuse (percent of subjects)	0.47	0.24	0.21
History of physical abuse (percent of subject s)	0.3	0.17	0.21
Sitzmarks (range 0-120 transit hours)	70.1	74.2	81.6

BDI: Beck Depression Inventory scores

Spielberger Stait-Trait Anxiety Inventory

Table 2

	End of Run-in			3-month		
	Biofeedback	**Diazepam**	**Placebo**	**Biofeedback**	**Diazepam**	**Placebo**
UBM (range 0-7)	4.2	3.4	3.1	*4.63	3.25	2.4
ABM (range 0-7)	1.0	2.0	1.7	0.58	1.93	1.4
Incomplete BM (range 0-10)	7.95	6.73	7.1	4.83	5.65	5.69
Strain (range 0-10)	6.75	6.0	7.58	4.0	4.3	4.31
Bristol score (range 0-7)				3.52	3.55	3.38
PAC-QOL (range 0-4.53	2.4	2.5	2.5	1.9	2.3	2.2
SF-36 (range – 0-100)	41.9	40.4	41.6	47.8	44.5	44.5
Push EMG (BL uv)	17.3	18.2	18.0	#7.14	21.0	12.56
Rest (BL uv)	9.1	6.0	8.6	5.9	7.1	5.5
1st Sensation (BL mmHg)	19.7	15.5	20.0	15.4	15.0	17.9

*Biofeedback *vs.* placebo pill group, $p < 0.01$

#Biofeedback *vs.* Diazepam group, $p < 0.001$

UBM: unassisted bowel movements

ABM: assisted bowel movements

BM: bowel movement

EMG: electromyography

PAC-QOL: Patient Assessment Quality of Life scale

SF-36: Short Form-36 Health Status Questionnaire

uv: microvolts

mmHg: millimeters of mercury