Combination therapy with biofeedback, loperamide, and stool-bulking agents is effective for the treatment of fecal incontinence in women - a randomized controlled trial

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Combination therapy with biofeedback, loperamide and stool-bulking agents is effective for the treatment of fecal incontinence in women – a randomized controlled trial.

Short title: Treating fecal incontinence

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ABSTRACT

Objective. Biofeedback and medical treatments have been extensively used for moderate fecal incontinence (FI). There is limited data comparing and combining these two treatments. The objective of this study was to evaluate the effect of biofeedback and medical treatments, separately and in combination.

Material and Methods. Sixty-four consecutive female patients, referred to a tertiary centre for FI were included. The patients were randomized to start with either biofeedback (4–6 months) or medical treatment with loperamide and stool-bulking agents (2 months). Both groups continued with a combination of treatments, i.e. medical treatment was added to biofeedback and vice versa. A two-week prospective bowel symptom diary and anorectal physiology were evaluated at baseline, after single- and combination treatments.

Results: Fifty-seven patients completed the study. Median number of leakage episodes during two weeks decreased from 6 to 3 ($p < 0.0001$) from baseline to completion. The patients showed a significant (1) decrease in number of leakages without forewarning ($p = 0.04$); (2) decrease in number of stools with urgency ($p = 0.001$); (3) decrease in number of loose stool consistency and (4) an increase in rectal sensory thresholds, both for maximum tolerable rectal pressure and first sensation (<0.01). The combination treatment was superior to both single treatments in terms of symptoms and functions. There was no significant difference between the two groups at any time point.

Conclusions: The combination therapy with biofeedback and medical treatment is effective for symptom relief in FI. The symptom improvement was associated with improved fecal consistency, reduced urgency, and increased rectal sensory thresholds.

Keywords: anorectal manometry, biofeedback, incontinence, pelvic floor exercises

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INTRODUCTION

Fecal incontinence (FI) affects 2.2–15.3% of an adult general population [1-4]. The prevalence increases with age [5], and after 50 years of age, prevalence rates up to 22% in women have been reported [2]. In elderly living in institutions, the prevalence has been found to range between 10% and 50% [4]. Whitehead et al reported that most participants with FI suffered from 1 to 3 leakages per month [3]. However, almost 3% of the women suffered from FI at least once a week and a frequency of one or more FI episodes per day was reported by nearly 1% of the women. They also found that liquid stool incontinence was the most common type of FI [3]. Its pathophysiology is complex and often overlapping mechanisms such as pelvic floor weakness [6,7] and altered bowel habits, such as diarrhea [8] or urgency to defecate [9], concur. Other risk factors are obstetric injuries, age, and other medical conditions [6,8].

Medical treatment such as loperamide and stool-bulking agents have been recommended for treatment of FI [10,11]. Dietary fibers and stool-bulking agents are common adjuncts to loperamide. Methylcellulose in combination with loperamide was found to be effective for short-term treatment of FI [12]. However, in another study, there was no additional treatment effect when fiber was added to loperamide [13]. The combination treatment with pelvic floor muscle exercises and medical treatment has been found to be effective in one study [14].

Biofeedback is used frequently to treat patients with FI and it has been advocated as a first-line therapy for patients with mild to moderate FI who have not responded to simple dietary advice or medication [15]. Heymen et al showed in a randomized

controlled trial that manometric biofeedback therapy in combination with pelvic floor muscle exercises is superior to pelvic floor muscle exercises alone when treating FI [16]. In most studies, both medical- and biofeedback therapy have been used in combination and it has not been possible to assess the treatment effect of either therapies separately.

The present study aimed to evaluate the separate effects, as well as the combination of, standardized biofeedback therapy to standardized medical treatment with loperamide and stool-bulking agents in women with FI.

MATERIALS AND METHODS

Study setting

The randomized controlled trial included two study arms with a modified crossover design and the patients were randomized to either start with biofeedback therapy (A) (4–6 months) or medical treatment (B) (2 months). After completing their first treatment period, the two treatments were combined. As biofeedback therapy is behavioral in its nature, a classical crossover design of the trial with "wash-out" periods between treatments was not appropriate. A CONSORT DIAGRAM of the study protocol is shown in Figure 1.

Prior to the first visit to the hospital a symptom diary was mailed to the patients and they were instructed to record their FI symptoms, bowel habits and gastrointestinal symptoms prospectively on a 24-h diary during 2 weeks. Before consideration of enrolment into the study, a senior colorectal surgeon (OH) assessed all the patients' medical history and performed a physical examination and an endoanal ultrasonography. Rectal volumes, sensational thresholds, and anal sphincter function were evaluated.

After completing the first treatment period (either biofeedback therapy or medical treatment) the patients again recorded their FI symptoms and the anal sphincter function was measured. Patients then continued with a second treatment period, which consisted of a combination of biofeedback therapy and medical treatment, i.e. patients who initially were allocated to medical treatment had biofeedback therapy added to their treatment and vice versa. After the second treatment period patients once again recorded

FI symptoms, rectal volumes, sensational thresholds, and anal sphincter function were measured.

Patients

Sixty-nine consecutive female patients with FI were prospectively evaluated at the Anorectal Physiology Unit, University Hospital of Linköping, between May 2002 and March 2005. Surgeons, gastroenterologists and primary-care physicians referred patients to a tertiary center for FI for evaluation and treatment. Young women who suffered from severe FI symptoms and had anatomical anal sphincter injuries were referred directly to surgery and not enrolled in the study by the senior colorectal surgeon who assessed all the women at the first visit. Thus, 64 female patients were enrolled in the study.

The inclusion criteria were as follows:

- Patients older than 18 years of age;
- Patients with at least one episode of FI during a period of 2 weeks as recorded by bowel function diary;
- Patients from whom written consent was obtained.

The exclusion criteria were as follows:

- Previous congenital or acquired spinal injury, spinal tumor, or spinal surgery;
- Presence of neurological diseases or peripheral vascular disease;
- Insulin-dependent diabetes mellitus;
- Congenital anorectal malformations;

- Recent colorectal or gastrointestinal surgery;
- Presence of external full-thickness rectal prolapse;
- Inflammatory bowel disease;
- Chronic diarrhea;
- Any past or present stimulator use of tibial nerve or sacral nerve stimulations;
- Ongoing pregnancy;
- Any malignant disease such as cancer.

Randomization

The randomization sequence was computer generated prior to study start. Sequenced, non-opaque envelopes were used for randomization; 33 were randomized to start with biofeedback therapy (group A), and 31 to start with medical treatment (group B).

Evaluation

The primary endpoint of the study was to assess the effect of biofeedback treatment and medical treatment and the combination of these two treatment options on the number of FI over a period of 2 weeks.

Gastrointestinal symptom diary

Patients recorded their bowel habits and symptoms prospectively on validated diary cards for 14 days before being enrolled in the study [17]. Along a 24-h time axis they recorded bowel movements, stool consistency, and defecatory symptoms (urgency, straining, and feeling of incomplete evacuation). Additionally they recorded every incontinence episode defined as bowel contents on protective aid or underwear. They

were asked to describe every leakage event: (a) consistency of the leakage content; (b) whether they were aware of the leakage; (c) and if it was accompanied with a forewarning. The consistency of stools was defined as "fluid/mucus" (soiling), "loose," "normal," or "hard." Patients also recorded the number of days with incontinence to gas.

Endoanal ultrasonography

Three-dimensional endoanal ultrasonography (3D-EAUS) was performed at the initial evaluation to visualize the anatomy of the internal and external anal sphincter. All 3D-EAUS were performed by a single investigator (OH). During the procedure, the women were placed in the left lateral position with hips and knees flexed to 90°. 3D-EAUS was performed using a Falcon 2101 ELX scanner (B-K Medical, Herlev, Denmark) with a mechanical rotational transducer, 13 MHz scanning frequency (type 2050, B-K Medical), that provides a 360° axial view of the anal canal. The probe was positioned just above the puborectalis muscle and the 3D acquisition was then performed. All 3D volumes were archived on an external hard disk for later offline analysis on PC with the help of dedicated software (BK3Di, BK Medical).

Rectal volumes and sensational thresholds

All of the anorectal measurements were performed by a single operator (nurse). A mechanical barostat system, earlier described by Hallböök & Sjödahl [18] was used to measure rectal volume changes during isobaric distensions. With the patient in the left lateral position, a noncompliant polyethylene bag (maximal volume 520 ml) attached to a polyethylene tube was inserted into the rectum. The tube was connected to the barostat

and held in position by the operator. A conditioning distension of 10–20 cm H_2O was performed before measurement start. Intermittent phasic isobaric stimulations with a distension duration of 60 sec were used. The time interval between distensions was approximately 30–40 sec. Visceral sensitivity was tested by phasic rectal balloon distensions (ascending method of limits). Pressure increments were 10 cm H_2O, with the exception of the first pressure that was 5 cm H_2O. Due to the purely mechanical nature of the barostat, the baseline pressure between each distension step was near zero. Subjects were instructed to identify three sensation thresholds: first sensation, urge to defecate, and maximal discomfort.

Anal sphincter function

A microtransducer system was used with the station pull-through technique to assess the anorectal pressure profile. The catheter had a diameter of 1.7 mm. It was introduced into the rectum and the resting and squeeze pressures were recorded at defined distances from the anal verge by manual station pull-through technique. Function of the sphincters was expressed as both maximum resting and squeeze pressure. The area under the resting and squeeze pressure curves, 0–5 cm from the anal verge, was calculated. Details of this method have been described previously [18].

Biofeedback therapy (A)

The biofeedback therapy consisted of (a) patient education and behavioral instructions and (b) pelvic floor muscle training sessions with biofeedback.

(a) Patient education and behavioral instructions

During the first session the therapist explained both anatomy and physiology of the gut, anorectum, and the pelvic floor. Patients were also taught optimal behaviour when emptying the bowel. During the following sessions this education was repeated when required.

(b) Biofeedback therapy

Two physiotherapists, specially trained in pelvic floor disorders, instructed the women in biofeedback. The biofeedback was performed using a surface electromyometer (Davicon M44 or MyoTrac) with an anal plug attachment. The augmentation of electrical activity in the muscles during squeeze increased the visual and auditory signals and gave patients feedback on their performance when contracting the external anal sphincter and the pelvic floor muscles. The physiotherapists conducted telephone follow-ups with 4 weeks interval to motivate and stimulate the patients to exercise regularly at home. The biofeedback session was repeated if the patient was uncertain how to do the training. The patients received a customized program of 1–6 biofeedback sessions during 4–6 months including an individual program for home training.

Medical treatment (B)

One single senior gastroenterologist performed the medical treatment. Patients had first a 1-h visit. During the first visit the medical history was obtained and the gastrointestinal symptom diary was evaluated together with the patient. The treatment consisted of loperamide in combination with stool-bulking agents. Patients started with a standardized dose of 2 mg loperamide once daily in combination with stool-bulking agents (stericulia or isphagula husk). Approximately every second week, the

gastroenterologist had contact with the patients, either by phone or during a short visit during which the doses were individualized and finely titrated with the aim to reduce urgency but without causing constipation. The median number of visits was 1 (1, 2) and the median number of telephone contacts was 2 (1, 4). The dose data were collected by the gastroenterologist from patients recall during the follow-ups. The final dose of loperamide was given as a median dose of 1 mg (0.5, 1) and the final dose of stool-bulking agent was given as a median dose of 2 g (0, 8).

Statistical analyses and sample size calculation

Sample size calculations estimated that 40 patients would be required in each group to detect a 3 unit difference between groups as significant given an initial number of FI events of 6 per two weeks (standard deviation (SD) 10) ($\alpha = 0.05$, $\beta = 0.20$). Statmate 1 (GraphPad Software) was used for the sample size calculation.

Data were expressed in median, 25^{th} and 75^{th} percentile, range, mean, SD, number, and percentages. Comparisons between groups were calculated with the Mann–Whitney U-test. For comparison of findings before and after treatment, the Wilcoxon signed-rank test was used. $p \leq 0.05$ (two-tailed) was considered as significant. The statistical package SPSS version 21 (IBM group) was used.

Ethical permission

Ethical permission for the study was approved by the Ethics Committee, Faculty of Health Sciences, Linköping, Sweden (Dnr 02–220). The patients received oral information and gave their written informed consent before enrolling the study. All

patients provided signed informed consent prior to the start of the study. This trial is registered with http://clinicaltrials.gov, number NCT02165475**.**

RESULTS

The median age of the 57 patients who completed the study was 58 (27–78) years. The median duration of FI symptoms was 5 (1–22) years. On average they had median 2 (1–5) vaginal deliveries. The 3–D EAUS examination revealed a complete rupture of both the EAS and the IAS in 9 (17%) of the patients. Intact sphincters were seen in 11 (21%) of the patients (Table I). The women had in median 3 (range 5) biofeedback sessions. The number of leakages was not related to the number of biofeedback sessions with physiotherapist ($p = 0.43$) or age ($p = 0.10$).

At the start of the study, before treatment, the patients had median 22 (3–94) bowel movements during the recorded 2-weeks. Eight patients (14%) had 21 or more bowel movements per week. No significant differences were found at the baseline between the two treatment groups regarding number of parities, age, symptoms, bowel habits, anorectal physiology variables, or the frequency of sphincter injuries.

Outcome assessment by symptom diary

From start to completion of the study patients demonstrated a significant decrease of loose stool ($p = 0.02$) and urgency ($p = 0.001$). Moreover the numbers of leakages without forewarning ($p = 0.04$) decreased significantly as well as the numbers of passive leakages ($p = 0.05$) (Table II).

Altogether, the patients recorded 610 FI episodes during 2 weeks on the pre-treatment diary. They had a median of six FI episodes during the two recorded weeks. There was no significant decrease of FI episodes after single treatment with biofeedback or

medical treatment (Table III). However, the number of FI episodes decreased significantly after the combination treatment. On the post-treatment diary, 37% recorded no FI leakages. The median number of FI episodes decreased to 2.5 ($p < 0.0001$) (Table II). There was no significant difference between the two treatment groups at any time-point.

No significant difference ($p = 0.62$) could be detected when comparing women with no sphincter ($n = 11$) defect to women with sphincter defect ($n = 41$) regarding the number of leakages after the combination treatment. Further subgroup analysis regarding sphincter injuries was not meaningful due to low number of patients.

Outcome assessment by anorectal physiology

Rectal sensitivity increased significantly, both for the first sensation and the maximum tolerable rectal pressure from 20 to 10 cm H_2O and from 50 to 40 cm H_2O, respectively ($p < 0.01$) (Table II). However, there were no significant changes regarding the rectal volume. The anal squeeze pressure was not significantly higher (>0.05) after any of the single treatments or the combination treatment. However, the anal resting area pressure was significantly lower after the combination treatment compared to the baseline (Table II). There was no significant difference between the two treatment groups at any time-point (Table IV).

DISCUSSION

This study has shown that the combination of medical treatment and biofeedback therapy is effective in reducing the number of FI episodes. Almost 80% had a sphincter defect. Despite the presence of such a significant injury, 37% of the women reported no leakage episodes on the post-treatment diary. The decrease in leakages was associated with a decrease in number of leakages without forewarning, a decrease in number of stools with urgency, a decrease in number of loose stool consistency, and an increase in rectal sensory thresholds, both for maximum tolerable rectal pressure and first sensation.

The use of constipating agents in the treatment of FI is a common clinical strategy but loperamide studies have focused on FI patients with chronic diarrhea [19,20]. According to a recent Cochrane review, low-dose loperamide (starting at 2–4 mg) titrated to the patient's symptoms is considered to be effective in patients with FI [10]. Read et al [19] found that 4 mg loperamide twice daily reduced urgency and FI, increased anal canal resting pressure, and improved the ability to retain saline infused into the rectum in FI patients with chronic diarrhea. In contrast to earlier studies [19,20] the present study included FI patients who were heterogeneous in terms of stool consistency and lower doses of loperamide were used. One aim of the medical treatment was to reduce the urgency without causing constipation. Thus, the dose of loperamide was carefully titrated and the additional treatment with stool-bulking agents enabled us to use loperamide in patients with normal stool consistency without increasing the proportion of hard stools. The decrease in number of loose stools was first seen in the group, which started with medical treatment. A decreased resting pressure, which was

associated with an improvement in leakage episodes, may be due to successful patient relaxation between stools, an indirect sign of greater confidence to avoid leakage.

The sensory function of the rectum is an independent factor for the preservation of fecal continence [21]. The biofeedback in the present study focused on behavioural components and improving muscle function rather than focusing on sensory retraining. However, we were still able to demonstrate lowered thresholds for first sensation and urgency. One can argue that this may be due to the behavioral component, i.e. the women gained better control of their muscles, which made them rely more on their muscles and therefore being able to tolerate a greater rectal pressure. This was first seen in the group that started with biofeedback therapy. Interestingly, it has earlier been demonstrated by Buser et al [22] that conscious rectal sensation correlates with an internal sphincter relaxation. In their study, anorectal retraining techniques resulted in correction of sensory delay, elimination of FI, and improved sensory threshold in 10 of 13 patients [22].

We also evaluated the two therapy options separately but we could not show any difference between the two groups at any point. There is no standardization in the literature of biofeedback therapy. Different training programs, instrumentation, adjunctive strategies, patient samples, outcome measures, and follow-up periods have been used and the limited number of studies together with methodological considerations do not allow a definitive assessment of the role of biofeedback therapy for FI [23]. The treatment duration and number of biofeedback sessions were variable in the present study and this lack of standardization must be acknowledged as a limitation

of this study. The study is also somewhat underpowered for detecting differences between the two treatment options.

The strengths in the present study are (1) the standardization of the treatment protocols, both medical and biofeedback, (2) the use of a prospective bowel function diary, and (3) anorectal physiology. Symptom assessment is important for monitoring the response to therapeutic interventions. With questionnaires, subjects have to summarize a changing pattern of bowel symptoms over an extended time period. It has been shown that reports of medically unrelated symptoms from people increase with time [24] and that the agreement between bowel habits reported by diary, and questionnaire is low [25]. Hence, the symptom diary, which was used in the present study, is therefore considered the superior method [26,27]. Fifty-seven patients completed the symptom diary at the last follow-up. However, 11–19% declined to repeat the anorectal measurements, which is not uncommon in studies including anorectal physiology.

In conclusion, the present study demonstrated clearly that a combination therapy with a standardized biofeedback- and medical treatment protocol is effective in reducing leakages in patients with FI. This symptom relief is associated with improved rectal sensation, decreased urgency, and normalized stool consistency.

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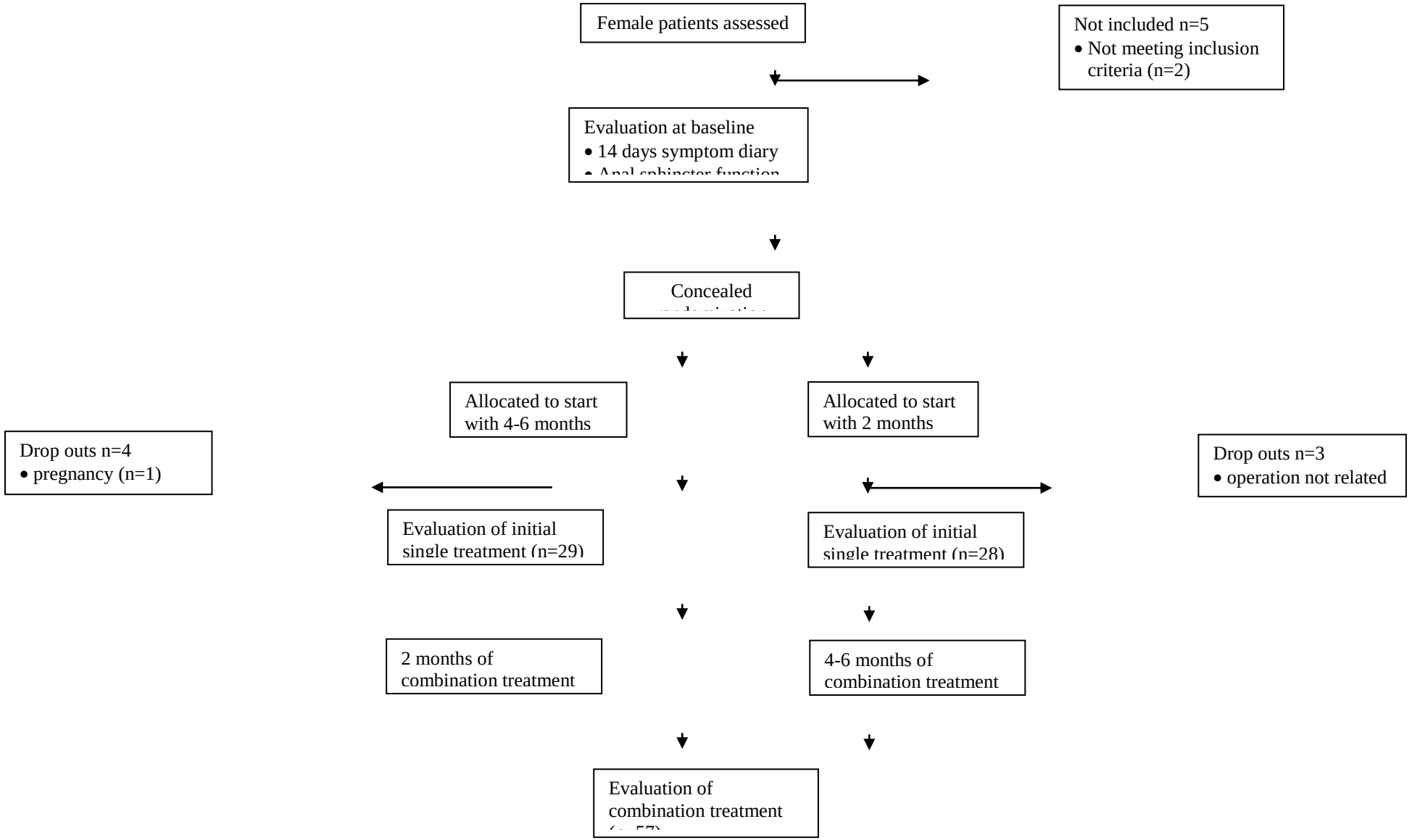
Female patients assessed
Not included n=5
• Not meeting inclusion criteria (n=2)
Evaluation at baseline
• 14 days symptom diary
Concealed
Allocated to start with 4-6 months
Allocated to start with 2 months
Drop outs n=4
• pregnancy (n=1)
Drop outs n=3
• operation not related
Evaluation of initial single treatment (n=29)
Evaluation of initial single treatment (n=28)
2 months of combination treatment
4-6 months of combination treatment
Evaluation of combination treatment

Figure 1.

FIGURE LEGENDS

Figure 1. Schematic flow of the study.

Table I. Descriptive characteristic at baseline including the results of the three-dimensional endoanal ultrasonography of the 57 patients who completed the study.

Variable	All patients (*n* = 57)	Group treated with biofeedback – medical treatment[#] (*n* = 29)	Group treated with medical treatment – biofeedback[# #] (*n* = 28)
Age in years, median (25^{th}, 75^{th} percentile)	58 (42, 67)	62 (46, 68)	57 (41, 67)
No. of parity, median (25^{th}, 75^{th} percentile)	2 (1, 3)	2 (1, 3)	2 (2, 3)
Years with FI symptoms, median (25^{th}, 75^{th} percentile)	5 (2, 10)	4 (2, 7)	5 (2, 12)
Endoanal ultrasonography	(*n* = 52)	(*n* = 26)	(*n* = 26)
Complete rupture of EAS, *n* (%)	15 (29)	10 (38)	5 (19)
Partial rupture of EAS, *n* (%)	25 (48)	10 (38)	15 (58)
Intact EAS, *n* (%)	12 (23)	6 (23)	6 (23)
Complete rupture of IAS, *n* (%)	11 (21)	5 (19)	6 (23)
Partial rupture of IAS, *n* (%)	14 (27)	6 (23)	8 (31)
Intact IAS, *n* (%)	27 (52)	15 (58)	12 (46)

FI = fecal incontinence, EAS = external anal sphincter, IAS = internal anal sphincter.

[#] Patients who were allocated to biofeedback therapy first and then had medical treatment added.

[##] Patients who were allocated to medical treatment first and then had biofeedback therapy added.

Table II. Symptoms, bowel habits of patients and anorectal physiology at baseline and after the combination treatment, i.e. medical treatment in combination with biofeedback therapy. The symptoms and bowel habits have been reported on a 2-week diary.

Variable Median (25^{th}, 75^{th} percentile)	Baseline	After combination treatment	*p*-value
Symptom and bowel habits recorded during a 2-week period	*n* = 57	*n* = 57	
Leakage episodes (*n*)	6 (2, 16)	3 (0, 5)	<0.0001
Leakage without forewarning (*n*)	4 (1, 14)	3 (2, 7)	0.04
Did not feel the leakage coming (*n*)	4 (1, 13)	3 (1, 5)	0.05
Number of days with gas leakage	12 (6, 14)	9 (3, 14)	0.14
Stool frequency	22 (15, 30)	20 (14, 29)	0.25
Numbers of normal stool consistency	12 (6, 15)	13 (8, 17)	0.11
Numbers of loose stool consistency	6 (1, 12)	4 (0, 9)	0.02
Numbers of hard stool	1 (0, 3)	0 (0, 2)	0.25

consistency			
Stools with urgency	11 (4, 18)	6 (2, 11)	0.001
Anorectal physiology			
Maximum anal squeeze pressure (mmHg)	54 (41, 72)	59 (45, 71)	0.33
Anal squeeze area pressure (mmHg)	151 (116, 186)	155 (120, 201)	0.51
Maximum anal resting pressure (mmHg)	33 (22, 48)	28 (21, 40)	0.06
Anal resting area pressure (mmHg)	91 (66, 120)	81 (66, 115)	0.04
	n = 55	*n* = 46	
Rectal pressure at first sensation (cm H_2O)	20 (10, 20)	10 (10, 20)	0.01
Rectal pressure at first sensation of urgency (cm H_2O)	20 (20, 30)	20 (20, 30)	0.30
Rectal pressure at maximal tolerable (cm H_2O)	50 (40, 60)	40 (40, 50)	<0.001

Comparisons are performed with Wilcoxon signed-rank test.

$p < 0.05$

Table III. Bowel habits of patients after single treatment with either biofeedback or medical treatment and after combination treatment, i.e. both medical and biofeedback treatment.

									Within-group comparisons	
	Baseline		After single treatment (i.e. biofeedback or medical treatment)			After combination treatment (i.e. both medical and biofeedback treatment)			Group treated with biofeedback first	Group treated with medical treatment first
Variable, median (25th, 75th percentile)	Group treated with biofeedback therapy first (n = 29)	Group treated with medical treatment first (n = 29)	Group treated with biofeedback therapy first (n = 28)	Group treated with medical treatment first (n = 28)	p-value	Group treated with biofeedback therapy first (n = 29)	Group treated with medical treatment first (n = 28)	p-value	p-value	p-value

Leakage episodes (*n*)	6 (2, 17)	6 (1, 16)	5 (2, 14)	7 (0, 17)	0.80	1 (0, 6)	3 (0, 5)	0.42	0.31^{A-B} $<0.01^{B-C}$ $<0.001^{A-C}$	0.27^{A-B} 0.02^{B-C} 0.02^{A-C}
Leakage without forewarning (*n*)	4 (1, 14)	4 (1, 16)	5 (0, 11)	6 (2, 17)	0.35	3 (1, 8)	4 (3, 5)	0.23	0.65^{A-B} 0.01^{B-C} 0.07^{A-C}	0.73^{A-B} 0.03^{B-C} 0.26^{A-C}
Did not feel the leakage coming (*n*)	5 (1,13)	3 (1, 16)	4 (0, 8)	5 (2, 15)	0.31	2 (1, 5)	4 (2, 5)	0.09	0.17^{A-B} 0.05^{B-C} 0.02^{A-C}	0.57^{A-B} 0.15^{B-C} 0.45^{A-C}
Days with gas leakage (*n*)	9 (5, 14)	14 (7, 14)	10 (1, 13)	13 (7, 14)	0.06	8 (1, 13)	9 (6, 14)	0.16	0.53^{A-B} 0.13^{B-C} 0.16^{A-C}	0.76^{A-B} 0.11^{B-C} 0.52^{A-C}
Number of stools	19 (14, 28)	26 (16, 33)	21 (14, 29)	21 (16, 29)	0.58	18 (13, 28)	22 (16, 29)	0.16	0.62^{A-B} 0.51^{B-C}	0.17^{A-B} 0.36^{B-C}

									0.88^{A-C}	0.30^{A-C}
Number of	12 (6, 14)	13 (7, 15)	12 (7, 17)	12 (7, 18)	0.97	13 (7, 17)	14 (8, 18)	0.70	0.14^{A-B}	0.26^{A-B}
normal stool									0.95^{B-C}	0.56^{B-C}
consistency									0.05^{A-C}	0.48^{A-C}
Number of	6 (1, 11)	8 (1, 15)	4 (0, 9)	4 (0, 9)	0.41	4 (0, 9)	5 (0, 10)	0.93	0.29^{A-B}	0.04^{A-B}
loose stool									0.52^{B-C}	0.96^{B-C}
consistency									0.36^{A-C}	0.03^{A-C}
Number of	1 (0, 4)	0 (0, 3)	1 (0, 3)	1 (0, 3)	0.38	0 (0, 2)	0 (0, 2)	0.95	0.12^{A-B}	0.88^{A-B}
hard stool									0.42^{B-C}	0.86^{B-C}
consistency									0.06^{A-C}	1.00^{A-C}
Stools with	6 (3,17)	13 (4, 21)	9 (3,19)	9 (5, 18)	1.00	6 (1, 11)	6 (2, 12)	0.88	0.69^{A-B}	0.08^{A-B}
urgency (*n*)									0.48^{B-C}	0.19^{B-C}
									0.19^{A-C}	$<0.01^{A-C}$

Between-group comparisons are performed with Mann–Whitney U-test and within-group comparisons with Wilcoxon signed-rank test. $p < 0.05$.

Within-group comparisons: A-B = comparisons between baseline and single treatment, i.e. either biofeedback or medical treatment; B-C = comparisons between single treatment, i.e. either biofeedback or medical treatment and combination treatment, i.e. biofeedback and medical treatment; A-C = comparisons between baseline and combination treatment, i.e. biofeedback and medical treatment.

Table IV. Anorectal physiology after single treatment with either biofeedback or medical treatment and after combination treatment, i.e. both medical and biofeedback treatment.

									Within-group comparisons	
	Baseline		After single treatment (i.e. biofeedback or medical treatment)			After combination treatment (i.e. both medical and biofeedback treatment)			Group treated with biofeedback first	Group treated with medical treatment first
Variable, median (25th, 75th percentile)	Group treated with biofeedback therapy first (n = 29)	Group treated with medical treatment first (n = 28)	Group treated with biofeedback therapy first (n = 29)	Group treated with medical treatment first (n = 28)	p-value	Group treated with biofeedback therapy first (n = 29)	Group treated with medical treatment first (n = 28)	p-value	p-value	p-value
Maximum anal squeeze	55 (39, 80)	54 (44, 69)	52 (37, 77)	51 (41, 67)	0.88	66 (34, 73)	55 (50, 64)	0.55	0.86^{A-B} 0.54^{B-C}	0.19^{A-B} 0.10^{B-C}

pressure (mmHg)									0.31^{A-C}	0.77^{A-C}
Anal squeeze area pressure (mmHg)	155 (121, 224)	146 (113, 171)	140 (113, 228)	145 (122, 174)	0.78	166 (116, 213)	150 (120, 190)	0.43	0.43^{A-B} 0.53^{B-C} 0.69^{A-C}	0.81^{A-B} 0.89^{A-B} 0.79^{A-C}
Maximum anal resting pressure (mmHg)	32 (22, 52)	35 (22, 43)	29 (20, 41)	35 (21, 39)	0.80	24 (18, 40)	35 (23, 46)	0.22	0.06^{A-B} 0.26^{B-C} 0.04^{A-C}	0.08^{A-B} 0.15^{B-C} 0.77^{A-C}
Anal resting area pressure (mmHg)	85 (70, 132)	94 (59, 117)	86 (65, 119)	89 (69, 108)	0.99	75 (66, 103)	86 (66, 116)	0.53	0.26^{A-B} 0.12^{B-C} 0.03^{A-C}	0.27^{A-B} 0.43^{B-C} 0.66^{A-C}
Rectal pressure at first sensation (cm H_2O)	20 (10, 20)	10 (10, 20)	N.A	N.A.	N.A.	10 (10, 20)	10 (10, 20)	0.90	0.03^{A-C}	0.17^{A-C}

Rectal pressure at first sensation of urgency (cm H_2O)	30 (20, 30)	20 (20, 30)	N.A	N.A	N.A	20 (20, 30)	20 (20, 30)	0.70	0.50^{A-C}	0.45^{A-C}
Rectal pressure at maximal tolerable (cm H_2O)	50 (40, 60)	50 (40, 60)	N.A	N.A	N.A	40 (40, 60)	40 (40, 50)	0.13	0.13^{A-C}	$<0.01^{A-C}$

N.A. Not applicable, i.e. manovolumetry was only performed at the inclusion and the final visit, i.e. after both groups had been treated with biofeedback and medical treatment.

Between-group comparisons are performed with Mann-Whitney U–test and within-group comparisons with Wilcoxon signed-rank test. $p < 0.05$.

Within-group comparisons: A-B = comparisons between baseline and single treatment, i.e. either biofeedback or medical treatment; B-C = comparisons between single treatment, i.e. either biofeedback or medical treatment and combination treatment, i.e. biofeedback and medical treatment; A-C = comparisons between baseline and combination treatment, i.e. biofeedback and medical treatment.