ORIGINAL ARTICLE

Triple-Target Treatment Versus Low-Frequency Electrostimulation for Anal Incontinence

A Randomized, Controlled Trial

Thilo Schwandner*, Claudia Hemmelmann*, Tankred Heimerl, Walter Kierer, Gerd Kolbert, Reinhard Vonthein, Rolf Weinel, Markus Hirschburger, Andreas Ziegler, and Winfried Padberg

SUMMARY

Background: In the nonsurgical treatment of anal incontinence, the combination of amplitude-modulated medium-frequency stimulation and electromyographic biofeedback (EMG-BF), known as triple-target treatment (3T), is superior to EMG-BF alone. The aim of this trial is to compare 3T with the standard treatment, low-frequency stimulation (LFS).

Methods: 80 patients with anal incontinence of Grade I or higher who presented to physicians or centers specialized in coloproctology were enrolled in this multicenter randomized trial with blinded observer. The trial had an open parallel-group design. Randomization was performed centrally by telephone. The primary endpoint was the Cleveland Clinic Score (CCS) after self-training at home with either 3T or LFS in two 20-minute sessions per day for 6 months. The secondary endpoints included the proportion of patients regaining continence, and the patients' quality of life (QoL). On completion of the trial as planned, the results were evaluated with an intention-to-treat analysis. Study registration: DRKS00000138 (<http://register.germanctr.de>).

Results: 39 patients were randomized to 3T, and 41 to LFS. After 6 months of treatment, the CCS (mean $\pm$ standard deviation) was 3.1 ± 4.2 in the 3T group and 9.6 ± 3.9 in the LFS group. The median improvement in the CCS at 6 months compared to baseline was 7 points greater in the 3T group than in the LFS group (95% CI: 5–9, $p < 0.001$). Anal continence was regained by 54% of the 3T patients, but none of the LFS patients (95% CI for the difference: 37.18% – 69.91%, $p < 0.001$). QoL scores were higher in all dimensions in the 3T group than in the LFS group. No major adverse effects occurred in either group.

Conclusion: 3T is superior to LFS in the treatment of anal incontinence. The available evidence suggests that the success of 3T is based on the combined effect of biofeedback and medium-frequency stimulation. LFS of the type applied in this trial has no effect. 3T should be used in routine clinical practice instead of LFS.

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Anal incontinence remains a major clinical challenge because it markedly impairs patients' quality of life and because the available treatments to date have not been adequately effective. Currently, the treatment of anal incontinence generally begins with the elimination of individual factors that promote incontinence (1), involving, for example, bowel habits and food and fluid intake. Liquid stools are made more regular with solidifying fiber supplements or medications, while excess pressure on the bladder and bowel is avoided through changes in the patient's everyday behavior. If these measures do not succeed in cases of chronic anal incontinence, the recommended next step usually consists of nonsurgical methods such as pelvic floor exercises, biofeedback (EMG-BF), and electrical stimulation (2), with the purpose of bolstering the strength and coordination of the sphincter muscles. Surgery is the first line of treatment for acute sphincter injuries (2).

In Germany, the Medical Aids Directory (*Hilfsmittelverzeichnis, HMV*) regulates the ordering of biofeedback and electrical stimulation and its reimbursement by the statutory health insurance companies (3). Reimbursability is predicated on the demonstration of efficacy and cost-effectiveness; level I evidence is usually required for the reimbursement of active medical products. Although the categories of EMG-BF and low-frequency electrical stimulation (LFS) have been included in the HMV as prescribable and reimbursable interventions for a number of years, their efficacy has never been adequately demonstrated. In multiple systematic reviews (4–6), it has been found that the flawed methods of the available clinical trials made it impossible to arrive at any definitive judgment about efficacy (7). Poor compliance also affects the effectiveness of LFS (8).

In view of the lack of evidence for the standard methods then in use and the availability of an alternative treatment for anal incontinence, namely, amplitude-modulated medium-frequency stimulation (AM-MF), an investigator-initiated, multicenter study group was founded in 2006. Its goal was to investigate the efficiency of the three treatment components EMG-BF, LFS, and AM-MF in a series of randomized

Klinik für Allgemein-, Viszeral-, Thorax- und Transplantationschirurgie, Fachbereich Medizin, Justus-Liebig-Universität Gießen: Dr. med. Schwandner, Heimerl, Dr. med. Hirschburger, Univ.-Prof. Dr. med. Padberg

Institut für Medizinische Biometrie und Statistik, Universität zu Lübeck, Universitätsklinikum Schleswig-Holstein, Campus Lübeck: Dr. rer. hum. biol. Hemmelmann, Dr. rer. pol. Vonthein, Univ.-Prof. Dr. rer. nat. Ziegler

Zentrum für Klinische Studien Lübeck, Universität zu Lübeck: Dr. rer. nat. hum. biol. Hemmelmann, Dr. rer. pol. Vonthein, Univ.-Prof. Dr. rer. nat. Ziegler

Enddarmzentrum Hessen-Mitte, Pohlheim: Dr. med. Kierer

Koloproktologische Praxis, Marburg: Priv.-Doz. Dr. med. Weinel

End- und Dickdarmzentrum Hannover: Dr. med. Kolbert

* Equal contribution

BOX

Important differences between AM-MF and LFS:

LFS: Left: low-frequency sine-wave stimulation (100 Hz, 50 mV). Every negative half-wave (below) induces a nerve action potential (upper curve). Right: All fibers in a sufficiently intense applied field are activated at the same time: the all-or-nothing principle.

AM-MF: Left: medium-frequency sine-wave stimulation (3000 Hz, 500 mV). An action potential is induced only by the summation of multiple negative half-waves. An induction mosaic results that more closely resembles natural, asynchronous recruitment (right).

The mechanism of action of EMG-biofeedback:

The goal of training in patients with fecal incontinence is to strengthen the pelvic floor and sphincter muscles selectively without activating muscles that raise the intra-abdominal pressure. The natural functions maintaining continence generally operate unconsciously; therefore, most patients have trouble finding the right muscles to activate. The sphincter muscles and the pelvic floor generate electrical potentials in the microvolt range both in movement and at rest. These potentials are measured by the biofeedback device, so that muscle contractions can be transduced into an auditory or visual channel.

The mechanism of action of EMG-triggered electrical stimulation:

The goal of EMG-triggered stimulation is to gain neural control over the pelvic floor and sphincter muscles by exploiting neuroplasticity in afferent-efferent loops. The proprioceptive organs within hypoactive muscles send only weak proprioceptive feedback to the brain. As a result, the cortical representation of these muscles deteriorates, and a catabolic spiral (vicious circle) ensues. EMG-triggered stimulation can convert the vicious circle to a virtuous one: The patient contracts the pelvic floor and sphincter muscles with maximal effort. The device measures the strength of contraction that has been achieved and accordingly sets a threshold strength above which it will stimulate the muscle to strengthen the contraction. If, for example, the patient can generate a potential of 10 microvolts with maximal effort, the stimulation is set to be turned on whenever a potential of 8 microvolts is reached.

The result is that the brain receives a stronger proprioceptive signal, without being able to detect that it has been artificially generated. Strong contraction leads to greater central activation and probably also has decentral effects as well.

controlled trials and to determine the clinical value of a new combination called triple-target treatment (3T). An overview of these different techniques is provided in the *Box*.

The concept of 3T is based on the finding that cortical activation differs in healthy and incontinent persons (9). In incontinent persons, the brain sends “corrupt” motor programs to the organs of continence, receives abnormally weak sensory feedback in return, and, as a result, is in a permanently stressed state. Coordination training with the aid of EMG-BF strengthens activity in the premotor cortex and the submotor area, while simultaneously lessening sensory and emotional activity in the rostral portion of the cingulate gyrus. This effect provides a theoretical basis for the use of EMG-BF and EMG-triggered stimulation as components of 3T.

A central hypothesis of the 3T concept is that treating the sphincter muscles alone is not enough. Healthy persons, while in resting state, can generate a roughly 90° angulation of the anal canal toward the pubic bone by contracting the puborectal sling; this anorectal angle is an important static factor for continence. Strengthening the tensile force of the puborectalis muscle (10) to aid in the generation of this angle and thereby close off the anal canal is one of the main therapeutic aims of 3T.

It is not possible, however, to strengthen all of the muscles involved in anal continence with exercises alone. The internal anal sphincter consists of smooth muscles and is not amenable to voluntary exercises; furthermore, it is difficult to actively reach the slow-twitch type I fibres (11, 12). It thus makes sense to use electrical stimulation on the smooth and slow muscular components.

Low-frequency stimulation, as used in most studies of anal incontinence, can be very painful when applied to the pelvic floor (13–15). Natural muscle fiber recruitment begins with the slow fibers and reaches the rapid ones last, but the activation of muscle fibers by low-frequency stimulation proceeds in the opposite sequence (16). Thus, the slow fibers are activated only at the end, and only with intense stimulation. As the pelvic floor is a densely innervated area, the therapeutic window for electrical stimulation in it is narrow; as a result, many patients cannot tolerate the intense stimulation needed to activate the slow muscle fibers (8, 17).

Stimulation with alternating current at medium frequency (MF > 1000 Hz) does not have this disadvantage, because its biological effect is based on a different principle than the all-or-nothing effect of low-frequency stimulation (18). Any individual impulse is too weak to depolarize nerve cell membranes; instead, the effect arises through asynchronous summation, and therefore fewer nociceptive neurons are excited, and the penetration is deeper. Patients can tolerate much more intense currents with this technique than with LFS, leading to strong contractions of the sphincter muscles and the pelvic floor (12, 14, 17).

In 3T, medium-frequency stimulation is also delivered with EMG triggering, which has found other

FIGURE

Flowchart of the 3T-FILES trial

useful applications in neurology for the recovery of motor capabilities (19). EMG-triggered stimulation uses weak anal EMG signals as the trigger for electrical induction of muscle contraction. This strengthens proprioceptive feedback and thereby enhances both central and decentral rehabilitative processes.

In summary, the 3T concept comprises the following components:

- Goal 1: Perineal and puborectal stimulation of the inaccessible smooth fibers and poorly accessible tonic fibers with AM-MF.
- Goal 2: Performance-coupled training of phasic voluntary muscle with EMG-biofeedback.
- Goal 3: Central and decentral neuroplastic training with EMG-triggered stimulation.

The first trial comparing 3T to EMG-BF alone (12, 20) was completed in 2008. Twice as many patients became continent with 3T as with EMG-BF alone (50% vs. 25%). Thus, the additional application of medium-frequency stimulation in the 3T group led to continence in an additional 25% of patients. Many of these patients had sphincter injuries; EMG-BF alone was only moderately effective in such cases (20).

We now report the findings of a further trial, which is the first randomized controlled trial comparing 3T to LFS.

Methods

The supplementary material (*eSupplement, eBox*) contains a detailed description of the methods of this trial, as well as further items that we report in accordance with the CONSORT 2010 recommendations (21).

Briefly stated, patients in the 3T group were treated with the Contrain® multifunction trainer (Procon GmbH, Hamburg, Germany), while patients in the comparison (LFS) group were treated with the EMS H5 4000 digital device. The two devices were fitted with electrodes of identical type, with longitudinal transmission, in order to make the mode of application of the two treatments as similar as possible. The patients were followed up at monthly intervals and informed that the devices stored data relating to their training. The number of exercises per day, and the performance in each exercise, were detected and recorded by the Contrain device, while the H5 device recorded the stimulation time.

3T consisted of AM-MF stimulation combined with EMG-BF; a detailed description of the treatment protocol is found in reference (12). Patients were instructed to train at home for 20 minutes every morning with an alternating combination and for another 20 minutes every evening with EMG-triggered stimulation.

In the LFS group, the usual settings for LFS in anal incontinence were used (14). The LFS patients, like the

TABLE 1

Characteristics of the patients in each treatment group at trial baseline

	3T			LFS			p ^{*1}
	n	Mean	SD	n	Mean	SD	
Age (years)	39	62.34	11.81	41	63.53	9.64	0.6372
Body-mass index (kg/m ²)	38	27.38	5.17	40	26.20	4.18	0.4625
Duration of incontinence (months)	39	24.77	30.40	41	26.68	21.60	0.1716
Resting pressure	35	33.14	7.02	36	31.64	8.96	0.9862
Squeezing pressure	35	52.60	11.93	36	49.61	12.18	0.2237
Number of deliveries	31	2.10	1.08	34	1.94	1.07	0.5084
	n	%		n	%		p ^{*2}
Grade I incontinence	4	10.3		5	12.2		1.0000
Grade II incontinence	33	84.6		33	80.5		
Grade III incontinence	2	5.1		3	7.3		
	n	%		n	%		p ^{*3}
Sphincter damage	8	20.5		6	14.6		0.5640
Damaged anal sensibility	2	5.1		2	4.9		1.0000
Descent of perineum	5	12.8		5	12.2		1.0000
Rectocele	22	56.4		24	58.4		1.0000
Hysterectomy	14	35.9		20	48.8		0.2667
Urinary incontinence	8	20.5		15	36.6		0.1413
Rectal mucosal prolapse	25	64.1		30	73.2		0.4713
Fistula surgery	5	12.8		5	12.2		1.0000
Hemorrhoidectomy	6	15.4		4	9.8		0.5133
Diabetes mellitus	4	10.2		2	4.9		0.4261
Psyllium	4	10.3		7	17.1		0.5196
Loperamide	1	2.6		3	7.3		0.6158

3T, triple-target treatment; LFS, low-frequency stimulation; n, number of patients; SD, standard deviation; p^{*1}, p-value by exact two-sided U test; p^{*2}, p-value by exact two-sided Cochran-Armitage trend test; p^{*3}, p-value by Fisher's two-sided exact test.

3T patients, were encouraged to participate actively in their stimulation. To avoid biasing the results of the trial through differences between the two groups in the duration of training and time of day at which it was performed, the LFS patients were instructed to train for 20 minutes every morning and every evening, like their counterparts in the 3T group.

Patients were included in the trial if they were at least 18 years old, had anal incontinence of grade I or higher of any cause, and had not obtained satisfactory relief from an initial phase of intervention consisting of regulation of bowel habits, behavior changes, and pelvic floor exercises. Patients were excluded if they had overflow incontinence, grade III⁰ rectal prolapse, or chronic inflammatory bowel disease of any kind; if

they were emotionally or intellectually unable to carry out the required training without help; if they were pregnant or thought they might be pregnant; and if they did not give their consent in writing to participation in the study.

In distinction to the 3T-AI trial (12), the patients were not recruited on the same day they were informed about the trial, but had one to two weeks to think about it before being recruited.

The goal of the trial was to show a difference, if present, between the results of 3T and those of LFS in the treatment of anal incontinence after six months of treatment.

The primary endpoint was the Cleveland Clinic Incontinence Score (CCS) in its validated German version (22) after six months of treatment in comparison to baseline. Possible CCS scores range from 0 (continent) to 20 (totally incontinent). Treatment was begun on the day of randomization. The secondary endpoints are described in detail in the supplementary material (*eBox*). Patients filled out questionnaires themselves at baseline as well as three and six months after randomization.

Randomization, blinding, sample size calculation, and statistical analysis are described in detail in the supplementary material.

The Universitätsklinikum Giessen-Marburg, Campus Giessen, was the sponsor of the trial. The trial was financially supported by Procon GmbH.

Results

Details of the clinical trial

As planned, 80 patients were included in the trial, out of a total of 109 patients who were screened for eligibility. The trial began on 25 May 2009 and ended as planned on 10 November 2010, after the last recruited patient had been followed up for six months. The patients were randomized to receive either 3T or LFS (*Figure*). The baseline characteristics of each group of trial participants are given in *Table 1* and in the part of *Table 2* that concerns baseline characteristics. The groups were comparable with respect to the balancing variables used at the time of randomization. 65 (81%) of the patients were female. At baseline, 9 (11%) had grade I incontinence, 66 (83%) grade II, and 5 (6%) grade III. About 18% had endosonographically diagnosed sphincter damage; the location and extent were similar. 36% were incontinent of both urine and stool.

Primary endpoint

In the intention-to-treat analysis, the reduction of CCS from baseline to six months after the start of treatment was significantly larger in the 3T group than in the LFS group ($p = 9.8 \times 10^{-10}$) (*Table 2*). The median improvement in CCS over baseline at six months in the 3T group was 7 points (95% confidence interval, 5.5–9; $p = 5.8 \times 10^{-11}$), while the LFS group had no significant change in CCS over baseline at six months (median, worsening by one point; 95% CI, 0–2; $p = 0.0645$). Per-protocol analysis yielded similar findings (*eTable*).

TABLE 2

Mean and standard deviation (SD) of the continuous primary and secondary endpoints in the two treatment groups

Endpoint	Follow-up	3T vs. LFS		3T				LFS			
		Median diff.	p ^{*1}	Mean	SD	Median diff	p ^{*2}	Mean	SD	Median diff	p ^{*2}
	time (months)	(95% CI)				(95% CI)				(95% CI)	
Primary endpoint											
CCS	Baseline	1 (-1 – 3)	0.3390	9.9	4.1			9.1	3.6		
	3	-3 (-5 – -1)	0.0018	6.2	4.2	-4 (-5.5 – -3)	1.57×10 ⁻⁷	9.3	4.0	0 (-1.5 – 2)	0.8069
	6	-7 (-9 – -5)	9.8×10 ⁻¹⁰	3.1	4.2	-7 (-9 – -5.5)	5.8×10 ⁻¹¹	9.6	3.9	1 (0 – 2)	0.0645
Secondary endpoints											
Vaizey	Baseline	0 (-1 – 2)	0.5751	12.3	4.2			12.0	3.5		
	3	-5 (-8 – -3)	1.9×10 ⁻⁵	7.5	5.3	-5.5 (-7 – -4.5)	5.6×10 ⁻⁸	12.4	3.7	0.5 (-1 – 2.5)	0.5652
	6	-10 (-12 – -8)	6.4×10 ⁻¹²	3.8	5.0	-8.3 (-11 – -7.5)	5.8×10 ⁻¹¹	12.6	3.5	1 (0 – 2)	0.0965
Lifestyle	Baseline	0.1 (-0.3 – 0.4)	0.5958	3.0	0.8			3.0	0.8		
	3	0.6 (0.2 – 0.9)	0.0001	3.6	0.5	0.8 (0.6 – 1.0)	7.5×10 ⁻⁹	2.9	1.0	0 (-0.3 – 0.3)	0.9426
	6	0.7 (0.4 – 1)	1.1×10 ⁻⁸	3.8	0.4	1 (0.75 – 1.3)	2.4×10 ⁻⁷	2.9	1.0	0 (-0.3 – 0.2)	0.9351
Behavior	Baseline	0.1 (-0.3 – 0.4)	0.6680	2.2	0.9			2.2	0.9		
	3	1.2 (0.8 – 1.6)	1.0×10 ⁻⁷	3.3	0.8	1.1 (0.8 – 1.4)	1.2×10 ⁻¹⁰	2.1	0.9	0 (-0.2 – 0.2)	0.5124
	6	1.6 (1.1 – 2)	2.5×10 ⁻¹⁰	3.6	0.7	1.4 (1 – 1.7)	3.3×10 ⁻¹⁰	2.2	1.0	0 (-0.2 – 0.2)	0.9776
Depression	Baseline	0.2 (-0.1 – 0.5)	0.3383	3.4	0.9			3.2	0.9		
	3	0.4 (0.1 – 0.8)	0.0029	3.9	0.5	0.5 (0.2 – 0.9)	3.3×10 ⁻⁵	3.2	1.0	0 (-0.2 – 0.3)	0.7536
	6	0.5 (0.2 – 0.9)	0.0003	4.0	0.4	0.6 (0.4 – 1)	2.4×10 ⁻⁵	3.2	1.0	0.1 (-0.1 – 0.3)	0.4420
Embarrassment	Baseline	0.3 (0 – 0.7)	0.2563	2.8	0.9			2.6	0.9		
	3	0.7 (0.3 – 1.3)	0.0002	3.5	0.7	1 (0.7 – 1.3)	1.9×10 ⁻⁵	2.8	0.9	0.2 (-0.1 – 0.8)	0.2004
	6	1 (0 – 1.7)	0.0001	3.7	0.7	1.2 (1 – 1.5)	2.1×10 ⁻⁵	2.9	1.0	0.7 (0.2 – 1)	0.0030
ICIQ-SF	Baseline	-1 (-4 – 2)	0.4431	8.0	2.9			9.2	3.6		
	3	-4 (-7 – -1)	0.0103	5.1	2.4	-4.5 (-)	0.0625	9.2	3.7	-0.5 (-)	1.0000
	6	-5 (-8 – -3)	0.0012	4.0	2.8	-6 (-7 – -1)	0.0313	9.4	3.3	0.5 (-)	0.9375
Pressure at rest	Baseline	0 (-1.6 – 2)	0.9597	33.1	6.6			31.7	8.4		
	3	1 (-1 – 2)	0.4657	33.8	6.6	1.5 (1 – 4)	0.0301	31.6	9.0	1 (-10 – 2)	0.4063
	6	2 (0 – 3.6)	0.1059	35.4	6.0	2.5 (2 – 3.5)	1.5×10 ⁻⁶	32.3	8.9	1.5 (1 – 2.3)	0.0071
Pressure on bearing down	Baseline	1 (-0.1 – 4)	0.2284	52.4	10.4			49.8	11.4		
	3	2 (0 – 5)	0.0482	53.5	11.0	1.5 (1 – 2.5)	0.0007	49.6	12.0	1 (-7 – 1.5)	0.4648
	6	3.9 (1 – 6)	0.0140	55.6	9.9	3 (2.5 – 5.5)	1.6×10 ⁻⁶	49.8	13.1	1 (0 – 2)	0.0610

3T, triple target treatment; LFS, low-frequency stimulation; CCS, Cleveland Clinic Score, from 0 (continent) to 20 (incontinent); adapted Vaizey Score, from 0 (continent) to 24 (incontinent); Urinary incontinence: ICIQ-SF, International Consultation on Incontinence Questionnaire Short Form, from 0 (continent) to 16 (incontinent); Median diff, median difference; SD, standard deviation; 95% CI, exact 95% Hodges-Lehmann confidence interval; p¹, exact two-sided U test; p², exact two-sided Wilcoxon rank-sum test; n, absolute frequency in each treatment group.

There were 39 patients in the 3T group and 41 in the LFS group. ICIQ-SF scores were available for comparison in 8 patients in the 3T group and 13 in the LFS group.

Secondary endpoints

The results for the primary endpoint were confirmed by the results for the secondary endpoints (Table 2). The 3T and LFS groups differed in the change of CCS from baseline to 3 months after the start of treatment, just as they did in the change from baseline to 6 months. Significantly better results were obtained with 3T than with LFS in the adapted Vaizey score, in every dimension

of the quality of life, in urinary incontinence, and in manometry (Table 2).

The results of treatment were significantly better with 3T than with LFS in the entire patient group, as shown in Table 3 ($p = 3.4 \times 10^{-12}$). At the end of treatment, 53.85% of the 3T patients but none of the LFS patients were continent (95% CI for absolute risk reduction, 37.18%–69.91%; $p = 1.01 \times 10^{-6}$).

TABLE 3

Results at last follow-up

Results	3T		LFS	
	n	%	n	%
Continent	21	53.8	0	0.0
Grade of continence improved	11	28.2	2	4.9
Frequency of incontinence improved	1	2.6	0	0.0
No improvement	4	10.3	34	82.9
Dropped out of trial	2	5.1	5	12.2
Overall	39	100.0	41	100.0

3T, triple-target treatment; LFS, low-frequency stimulation.
 $p = 1.3 \times 10^{-13}$ by two-sided exact Cochran-Armitage trend test.
 For change by 1 unit or more, odds ratio = 0.1880
 (exact 95% confidence interval, 0.0839 – 0.3470).

Incontinence did not improve or became worse in only 10% of the 3T patients, compared to 82.9% of the LFS patients (odds ratio for a 1-point change, 0.1880; 95% CI, 0.0839–0.3470; $p = 1.3 \times 10^{-13}$).

No side effects were reported in the 3T group. In the LFS group, about half of the patients complained of pain during stimulation. Some reported a feeling of pressure that persisted for hours after training. Some patients could be motivated to use a high enough current intensity to induce motor activity during their training, but 22% of the LFS patients could not tolerate such intensities and therefore stimulated at levels below the motor threshold (roughly 20 mA).

Discussion

This randomized trial confirms our earlier results showing the superiority of 3T over EMG-BF alone. The difference is even greater in the present trial, because many patients became totally asymptomatic with 3T, while many patients who had LFS experienced no benefit whatsoever. The ineffectiveness of LFS is particularly striking in view of its current monopoly position in the German Medical Aids Directory. Other randomized trials have also shown it to be ineffective (14, 23).

While planning this trial, we hypothesized that LFS would not work because LFS at intensities high enough to induce muscle contraction would be intolerably painful (14). The trial results partly bear out this hypothesis: 22% of patients stimulated themselves at levels below the motor threshold. Other patients, however, were able to get used to higher intensities. The average current intensity at the end of treatment was 45.6 mA (SD, 14.27 mA). Nonetheless, even the patients who tolerated stimulation above the motor threshold did not obtain any functional improvement from it.

Our current hypothesis to explain the difference in efficacy of LFS and AM-MF is that the depth to which

the stimulation penetrates is the most important determinant of its effect: the levator plate, and especially the puborectalis muscle, should be entirely under the influence of the stimulation. This hypothesis is derived from the two patient groups' differing perceptions of passive contractions: both groups had the identical type of rectal electrode (to prevent bias related to differences in transmission), yet the LFS patients felt nothing more than sphincteric contractions, even at intensities above 40 mA, which some patients described as very unpleasant. In contrast, most 3T patients reported an "elevator feeling" that came about only with strong contractions of the puborectal sling, during which the pelvic floor visibly rose. The maximum tolerated intensity was markedly higher in medium-frequency stimulation than in LFS; the mean difference between the two was 127 mA (SD 34 mA) at the beginning of stimulation and 253 mA (SD 95 mA) at the end.

A further component of 3T, namely, EMG-triggered stimulation with a computer-generated sliding trigger threshold, may well make a large contribution to its success. The strong mental concentration that the device demands of the patient during this exercise probably leads to better central motor presence and control (24) than does traditional EMG-BF without electrical stimulation. In the usual alternating combination of stimulation and biofeedback, the patient repeats a four-component cycle consisting of contraction, relaxation, stimulation, and relaxation). Experience reveals, however, that only well-rested patients are able to keep concentrating on this sequence. In contrast, in EMG-triggered stimulation, stimulation is given, as it were, only as a reward for correct contraction, while the program oversees the patient's performance: contraction, stimulation, relaxation. The EMG-triggered program may be more effective than the alternating training regime. As soon as the trigger program is switched on, the device's EMG recordings often show an increase of 50% or more, leading us in turn to ask why alternating EMG-BF is ever used at all. As a didactic matter, however, many patients can only understand the trigger program once they have experienced the alternating program.

Although the duration of follow-up in this trial (six months) is three months shorter than in the 3T-AI trial, the 3T patients achieved essentially the same good results in this trial as in the earlier one. This should not be misunderstood as implying that six months of stimulation suffice for an optimal result. The apparently more rapid improvement is, in part, due to a statistical effect arising from the different mode of recruitment in the two studies. The additional one to two weeks that we gave prospective participants in the present trial to make up their minds about participation led to a better selection of motivated patients, and higher compliance in the present trial also undoubtedly accounts for some of the observed difference in results. Empirical experience outside the setting of the 3T trials reveals that the good result lasts three to four years in about half of all

KEY CLINICAL MESSAGES

- The most common cause of anal incontinence is weakness of muscle groups in the pelvic floor.
- Targeted training is used to enhance the responsiveness of the sphincter muscles.
- It is impossible for anatomical reasons to train all components of the organ of continence with physical exercises alone. The effectiveness of EMG-biofeedback for training of the phasic voluntary musculature is significantly enhanced by the addition of medium-frequency electrical stimulation (AM-MF) of the inaccessible smooth muscle and poorly accessible tonic fibers.
- In the 3T trials, 50% of patients regained continence with a combination of EMG-biofeedback and AM-MF, while only 25% did with EMG-biofeedback alone. AM-MF is markedly superior to low-frequency stimulation (LFS), which has been the customary treatment until now.
- In the present trial, no patient treated with LFS became continent. Three randomized therapeutic trials have now demonstrated that LFS lacks functional efficacy.

patients, and that a second treatment is often requested after that. 10% to 15% of patients seem to benefit more from permanent treatment; in others, the results deteriorate as the patient grows older. For harder evidence in these matters, further controlled trials are needed.

It is a limitation of this trial that, for technical reasons, the two devices we tested cannot be applied in blinded fashion, and the trial could therefore be performed only with blinding of the investigators doing the follow-up evaluation. A further aspect is that the control group was tested with LFS alone, not in combination with biofeedback. If we had compared 3T with a combination of EMG-BF and LFS, rather than with LFS alone, we would have expected to obtain the same results as the 3T-AI trial, because the inefficacy of LFS has already been demonstrated (14, 23). We would have needed four times as many patients to conduct such a trial but would not have gained any further useful knowledge from it.

Taken together with the 3T-AI trial, this trial shows that 3T is superior to both EMG-BF and LFS. It also shows that LFS fails to relieve anal incontinence. 3T, not LFS, should be the routinely used clinical treatment, and this evidence-based judgment should be reflected by a corresponding change in the German Medical Aids Directory.

Trial registration

<http://register.germanctr.de>, DRKS-ID: DRKS00000138

Trial protocol

The entire trial protocol as submitted to the Ethics Committee is available from the corresponding author on request.

Conflict of interest statement

The trial was supported by Procon GmbH, Hamburg.

Thilo Schwandner accepted support from the Procon company in the setting of this trial. The company's financial support extended to the provision of the electrical stimulation devices that were used in the trial.

Walter Kierer and Thilo Schwandner received reimbursement from Procon GmbH of travel expenses and fees for a course on the subject of constipation.

Thilo Schwandner has a "flying doctor" contract with the Ethicon company for STARR and TRANSTARR operations (constipation). The Department of General, Visceral, Thoracic, and Transplantation Surgery of the University of Giessen receives fees for the training of visiting physicians in the area of coloproctology at the Giessener Klinik.

Thilo Schwandner receives honoraria for lectures in coloproctology from the Ethicon company and for lectures on fistula surgery from the Cook company. He has also received financial support for research from the Cook company.

The remaining authors state that they have no conflicts of interest.

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Corresponding author

Univ.-Prof. Dr. rer. nat. Andreas Ziegler
 Institut für Medizinische Biometrie und Statistik
 Universität zu Lübeck
 Universitätsklinikum Schleswig-Holstein, Campus Lübeck
 Maria-Goeppert-Str. 1
 23562 Lübeck, Germany
 ziegler@imbs.uni-luebeck.de

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ORIGINAL ARTICLE

Triple-Target Treatment Versus Low-Frequency Electrostimulation for Anal Incontinence

A Randomized, Controlled Trial

Thilo Schwandner*, Claudia Hemmelmann*, Tankred Heimerl, Walter Kierer, Gerd Kolbert, Reinhard Vonthein, Rolf Weinel, Markus Hirschburger, Andreas Ziegler, and Winfried Padberg

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eSUPPLEMENT

Triple-Target Treatment Versus Low-Frequency Electrostimulation for Anal Incontinence

A Randomized, Controlled Trial

Thilo Schwandner*, Claudia Hemmelmann*, Tankred Heimerl, Walter Kierer, Gerd Kolbert, Reinhard Vonthein, Rolf Weinel, Markus Hirschburger, Andreas Ziegler, and Winfried Padberg

Methods

Interventions

The patients in the 3T group were treated with the Contrain[®] multifunction trainer (Procon GmbH, Hamburg, Germany), and the patients in the LFS group were treated with the EMS H5 4000 Digital device. The two devices were fitted with identical stimulating electrodes with longitudinal transmission in order to avoid any differences in the mode of application of stimulation. Stimulation in the LFS group was with biphasic impulses at 40 Hz with a pulse width of 260 microseconds. In the 3T group, medium-frequency impulses lasting 1 and 5 microseconds were grouped in biphasic impulse chains with a frequency of 40 Hz; thus, modulation was comparable in the two patient groups.

The patients were taught how to use the device with an electrode in the anus. They were seen afterward in monthly follow-up and were informed that the devices stored data relating to their training.

The 3T group: EMG-BF combined with electrical stimulation

3T consisted of AM-MF stimulation in combination with EMG-BF; a detailed description of the treatment protocol is found in (e1). The patients were instructed to train with an alternating combination at home each morning for 20 minutes. The exercises were performed in the standing position and involved repeating the cycle of electrical stimulation, relaxation, voluntary contraction, and relaxation. The patient's main task in the active training segments was to lift up the electrode in the rectum as in an elevator and then to keep it in this position by muscle contraction. This can only be done by raising the perineum and simultaneously contracting the puborectalis muscle. Merely contracting the sphincter does not generate a lifting effect.

The 3T patients were also instructed to carry out EMG-triggered stimulation for 20 minutes each evening. The patient must exert enough effort to exceed a computer-set dynamic threshold for contraction strength so that the electrical stimulation is turned on and summated muscle contraction arises. This, in turn, reinforces proprioceptive feedback to the brain, promoting the neuroplastic process (e2, e3). The control program adapts the visualized EMG range and the demanded strength of contraction (threshold value) to the patient's individual capabilities.

The training effect of 3T is shown in the *Figure* (e4).

The LFS group: low-frequency electrical stimulation

Low-frequency stimulation was provided for 5 seconds with pauses of 10 seconds in between. The ramp-up time for each stimulation was 1 second; these are the usual settings for LFS in the treatment of anal incontinence (e5). The LFS patients were encouraged to stimulate at intensities sufficient to induce muscle contraction and not simply to let the stimulation take its effect passively, but rather to contract the perceived muscle actively in addition to any contraction induced by the stimulation. These instructions were analogous to those given to the 3T patient. The LFS patients were instructed to train for 20 minutes each morning and each evening so that the timing and duration of training would be the same in the two patient groups.

Patients

Patients with incontinence of any cause of grade I or higher who were at least 18 years old were considered potential trial participants. All underwent an initial evaluation of their suitability for participation. Patients were excluded if they had overflow incontinence, grade III⁰ rectal prolapse, or chronic inflammatory bowel disease of any kind; if they were emotionally or intellectually unable to carry out the required training without help; if they were pregnant or thought they might be pregnant; and if they did not give their consent in writing to participation in the study. In distinction to the 3T-AI trial (12), the patients were not recruited on the same day they were informed about the trial, but had one to two weeks to think about it before

Klinik für Allgemein-, Viszeral-, Thorax- und Transplantationschirurgie, Fachbereich Medizin, Justus-Liebig-Universität Gießen: Dr. med. Schwandner, Heimerl, Dr. med. Hirschburger, Univ.-Prof. Dr. med. Padberg
Institut für Medizinische Biometrie und Statistik und Zentrum für Klinische Studien Lübeck, Universität zu Lübeck, Universitätsklinikum Schleswig-Holstein, Campus Lübeck: Dr. rer. hum. biol. Hemmelmann, Dr. rer. pol. Vonthein, Univ.-Prof. Dr. rer. nat. Ziegler
Enddarmzentrum Hessen-Mitte, Pohlheim: Dr. med. Kierer
Kolo-proktologische Praxis, Marburg: Priv.-Doz. Dr. med. Weinel
End- und Dickdarmzentrum Hannover: Dr. med. Kolbert
* Equal contribution

being recruited. Recruitment took place in multiple centers: the outpatient clinic of the department of general surgery at the Universitätsklinikum Giessen and the private practices of coloproctologists in Hanover, Marburg, and Pohlheim.

In each center, the trial was begun only after approval of the local ethics committee in addition to central trial registration. All of the local ethics committees found that the trial met their requirements.

Goal of the trial

The goal of the trial was to show a difference between 3T and LFS in the treatment of anal incontinence after six months of treatment.

Endpoints

The primary endpoint was the Cleveland Clinic Incontinence Score (CCS) in its validated German version (6) after six months of treatment in comparison to baseline. Possible CCS scores range from 0 (continent) to 20 (totally incontinent). Treatment was begun on the day of randomization. A window of ± 2 weeks around the precisely calculated date for each follow-up was considered acceptable.

The secondary endpoints included a comparison of the two treatment groups at 3 months and the changes in CCS scores from baseline to follow-up at 3 months among the patients in each group. The German adaptation of the St. Marks Incontinence Score (Vaizey Score) (e6) and the Fecal Incontinence Quality of Life Scale (FIQoL) (e7) were considered as well, and each dimension of the FIQoL was considered separately. The success of treatment was defined as before (e1):

- continence for an entire month up to the moment of follow-up,
- improvement in continence grade (incontinence of liquid or solid stool changed to incontinence of flatus, regardless of frequency),
- no change in continence grade (or change merely from solid to liquid stool or vice versa), but with a decrease of frequency by at least 2 CCS points,
- no change or worsening.

Continence grades were as defined by Parks (e8): grade I: incontinence of flatus, grade II: incontinence of liquid stool (with or without flatus), grade III: incontinence of solid stool (with or without flatus or liquid stool). The secondary endpoints are listed in the *eBox*.

Patients filled out questionnaires themselves at baseline as well as three and six months after randomization. The Contrain device stored information on the number of exercises performed each day and the performance achieved in each. The H5 device stored the stimulation times.

Randomization

Before randomization, all participating patients were registered for the baseline investigation. Randomization was performed centrally by telephone at the Center for Clinical Trials at the University of Lübeck after receipt of all registration documents to guarantee

the concealment of treatment allocations. 1:1 randomization was performed with RITA, Version 1.20 (e9). The self-adjusting design of Nordle and Brantmark (e10) was used with center and incontinence grade as column variables and gender as row variable.

Blinding

This was an open multicenter trial with a parallel-group design and blinded observers, i.e., questionnaires were administered to patients only by persons who did not know which treatment group they belonged to. Persons not otherwise involved in the trial recorded all secondary end points.

Statistical techniques

The following hierarchical tests were used, with a global significance level of 5%:

- Comparison of 3T and LFS with the exact two-sided U-Test with respect to the change in CCS scores from baseline to the follow-up at 6 months.
- Within the 3T group, comparison of the CCS scores at baseline and at 6 months after randomization with the exact two-sided Wilcoxon rank-sum test. Hodges-Lehmann point estimators and exact 95% Hodges-Lehmann confidence intervals were calculated.

An identical analysis was performed for each of the secondary endpoints; adapted Vaizey Score, FIQoL (separately for each dimension), urinary incontinence, body-mass index (BMI; kg/m^2), and manometry. The use of stool-regulating medications was analyzed by Fisher's exact two-sided test. The exact two-sided Cochran-Armitage trend test was used to assess differences in unsuccessful treatment and Park's continence grade (e8). Absolute and relative risks, odds ratios (ORs), and exact two-sided confidence intervals were used to assess effect strengths (e11).

Subgroup analyses were performed similarly. Any endpoint that could not be determined at the time of follow-up was considered to be the same as at the last available observation. Missing data from the baseline investigation (nine manometric values, one value of FIQoL, and one BMI) were replaced by averaging. The intention-to-treat (ITT) analysis was supplemented by per-protocol (PP) analyses that included only patients who received treatment for at least three months and came to at least one of the planned follow-ups. All other analyses were descriptive. All statistical analyses were performed with the aid of SAS Version 9.2.

The potential effect of the study center was analyzed with a mixed linear model in which the center was a random variable.

No interim evaluations were performed, and the trial methods and endpoints were not changed after the initiation of the trial.

On the basis of the results of our first trial (e1), we expected *a priori* a mean CCS difference of 3.4 points between the two patient groups and a standard deviation of 5.2 points in each group. Using a two-sided U test, we determined that, on the assumption of a normal

distribution, 80 patients would need to be randomized in a 1:1 proportion to detect the expected difference with a probability of 80% at the 5% significance level.

Corresponding author

Univ.-Prof. Dr. rer. nat. Andreas Ziegler
Institut für Medizinische Biometrie und Statistik
Universitätsklinikum Schleswig-Holstein
Campus Lübeck
Maria-Goeppert-Str. 1, 23562 Lübeck, Germany
ziegler@imbs.uni-luebeck.de

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eBOX

Secondary endpoints

- Comparison of treatment groups (change from baseline investigation to follow-up at 6 months) and
- Changes from baseline investigation to follow-up at 3 and 6 months in the following measures:
 - a) Validated new St. Marks Incontinence Score (Vaizey Score) (e12) in its adapted German version (e6); values ranging from 0 (continent) to 24 (totally incontinent),
 - b) Fecal Incontinence Quality of Life Scale (FIQoL) (e7) (separate consideration of each dimension),
 - c) Urinary incontinence, rated according to the International Consultation on Incontinence Questionnaire Short Form (ICIQ-SF) (e13),
 - d) Assessment of results (e1):
 - Continent for an entire month up to the moment of follow-up,
 - Improvement in continence grade (incontinence of liquid or solid stool changed to incontinence of flatus, regardless of frequency),
 - No change in continence grade (or change merely from solid to liquid stool or vice versa), but with a decrease of frequency by at least 2 CCS points,
 - No change or worsening,
 - e) Continence grade (e8): grade I: incontinence of flatus, grade II: incontinence of liquid stool (with or without flatus), grade III: incontinence of solid stool (with or without flatus or liquid stool),
 - f) Achievement of individual therapeutic goals. This relates to the changes in everyday life that the individual patients designate as being among the three main consequences of their disease. The patients rate the changes occurring during therapy according to the customary grading system used in school in Germany (1 = very good, 6 = unsatisfactory),
 - g) Systematic stool diary according to Vaizey (e14),
 - h) Stool frequency,
 - i) Use of medications to regulate stool,
 - j) Manometry (mmHg),
 - k) Subgroups with and without sphincter injury,
 - l) Subgroups with and without neuropathy,
 - m) Stratification by center.

eTABLE

Mean and standard deviation (SD) of the continuous primary and secondary endpoints in each treatment group (per-protocol population)

Endpoint	Follow-up time (months)	3T vs. LFS					3T					LFS	
		Median diff. (95% CI)	p ^{*1}	n	Mean	SD	Median diff (95% CI)	p ^{*2}	n	Mean	SD	Median diff (95% CI)	p ^{*2}
Primary endpoint													
CCS	Baseline	1 (-1 – 3)	0.3390	39	9.95	4.10			41	9.10	3.62		
	3	-3 (-5 – -1)	0.0022	37	6.00	3.97	-4 (-5.5 – -3)	1.57×10 ⁻⁷	36	9.17	4.07	0 (-1.5 – 2)	0.8069
	6	-7 (-10 – -5)	4.9×10 ⁻¹⁰	36	2.58	3.74	-7.5 (-9 – -6)	2.9×10 ⁻¹¹	35	9.60	3.98	1 (0 – 2)	0.0645
Secondary endpoints													
Vaizey	Baseline	0 (-1 – 2)	0.5751	39	12.30	4.20			41	12.00	3.50		
	3	-5 (-8 – -3)	3.4105	37	7.27	5.18	-5.5 (-7 – -4.5)	5.6×10 ⁻⁸	36	12.25	3.83	0.5 (-1 – 2.5)	0.5652
	6	-10 (-12 – -8)	1.3×10 ⁻¹¹	36	3.43	4.60	-9.5 (-11 – -8)	1.2×10 ⁻¹⁰	35	12.57	3.60	1 (0 – 2)	0.0965
Lifestyle	Baseline	0.1 (-0.3 – 0.4)	0.5958	39	3.04	0.77			41	2.95	0.81		
	3	0.5 (0.1 – 0.8)	0.0004	37	3.66	0.49	0.8 (0.6 – 1.0)	7.5×10 ⁻⁹	36	3.00	0.96	0 (-0.3 – 0.3)	0.9426
	6	0.7 (0.3 – 1.1)	7.1×10 ⁻⁸	36	3.84	0.40	1.1 (0.8 – 1.3)	3.8×10 ⁻⁷	35	2.97	0.98	0 (-0.25 – 0.23)	0.9351
Behavior	Baseline	0.1 (-0.3 – 0.4)	0.6680	39	2.25	0.90			41	2.15	0.85		
	3	1.16 (0.8 – 1.7)	2.85×10 ⁻⁷	37	3.34	0.77	1.1 (0.8 – 1.4)	1.2×10 ⁻¹⁰	36	2.20	0.95	-0.1 (-0.3 – 0.2)	0.5124
	6	1.44 (0.9 – 1.9)	2.8×10 ⁻⁹	36	3.65	0.62	1.5 (1.2 – 1.8)	7.6×10 ⁻¹⁰	35	2.27	1.02	0 (-0.22 – 0.19)	0.9776
Depression	Baseline	0.2 (-0.1 – 0.6)	0.2986	39	3.37	0.86			41	3.15	0.93		
	3	0.33 (0 – 0.71)	0.0182	37	3.85	0.51	0.5 (0.2 – 0.9)	3.3×10 ⁻⁵	36	3.27	1.01	0.02 (-0.2 – 0.3)	0.7536
	6	0.33 (0.1 – 0.9)	0.0035	36	3.99	0.38	0.7 (0.4 – 1.0)	2.7×10 ⁻⁵	35	3.29	1.03	0.06 (-0.2 – 0.4)	0.5789
Embarrassment	Baseline	0.33 (0 – 0.67)	0.2412	39	2.84	0.89			41	2.63	0.90		
	3	1 (0.33 – 1.67)	0.0001	37	3.58	0.65	1 (0.67 – 1.33)	1.97×10 ⁻⁵	36	2.75	0.92	0.33 (0 – 0.83)	0.1491
	6	1 (0 – 1.67)	3.3×10 ⁻⁵	36	3.77	0.59	1.33 (1 – 1.67)	2.84×10 ⁻⁵	35	2.86	0.98	0.67 (0.17 – 1)	0.0030
ICIQ-SF	Baseline	-1 (-4 – 2)	0.4431	8	8.00	2.93			13	9.23	3.63		
	3	-4 (-8 – -1)	0.0132	7	4.71	2.29	-4.5 (–)	0.0625	12	8.83	3.64	-0.5 (–)	1.0000
	6	-5 (-9 – -3)	0.0013	7	3.43	2.51	-6 (-7 – -1)	0.0313	12	9.08	3.20	0.5 (–)	0.9375
Resting pressure	Baseline	0 (-1.62 – 2)	0.9597	39	33.06	6.64			41	31.73	8.39		
	3	1 (-1 – 5)	0.2826	37	34.62	5.58	1.5 (1 – 4)	0.0301	36	29.65	11.04	1 (-10 – 2)	0.4063
	6	2 (0 – 4)	0.0531	36	35.76	6.46	2.5 (2 – 3.5)	1.48×10 ⁻⁶	35	31.52	10.02	1.5 (1 – 2.31)	0.0110
Squeezing pressure	Baseline	1 (-0.08 – 4)	0.2284	39	52.44	10.44			41	49.79	11.40		
	3	4 (0 – 9)	0.0243	37	56.10	8.78	1.5 (1 – 2.5)	0.0007	36	47.83	14.04	1 (-7 – 1.5)	0.4648
	6	4 (1 – 8)	0.0041	36	56.82	10.06	3 (2.5 – 5.5)	1.61×10 ⁻⁶	35	48.81	14.85	1.5 (-0.5 – 2.5)	0.0719

3T, triple target treatment; LFS, low-frequency stimulation; CCS, Cleveland Clinic Score, from 0 (continent) to 20 (incontinent); adapted Vaizey Score, from 0 (continent) to 24 (incontinent); ICIQ-SF, International Consultation on Incontinence Questionnaire Short Form, from 0 (continent) to 16 (incontinent); Median diff, median difference; SD, standard deviation; 95% CI, exact 95% Hodges-Lehmann confidence interval; p^{*1}, exact two-sided U test; p^{*2}, exact two-sided Wilcoxon rank-sum test; n, absolute frequency in each treatment group.