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Guidelines

Transcutaneous Electrical Nerve Stimulation for Treating Neurogenic Lower Urinary Tract Dysfunction: A Systematic Review

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Abstract

Context: Transcutaneous electrical nerve stimulation (TENS) is a promising therapy for non-neurogenic lower urinary tract dysfunction and might also be a valuable option in patients with an underlying neurological disorder.
Objective: We systematically reviewed all available evidence on the efficacy and safety of TENS for treating neurogenic lower urinary tract dysfunction.
Evidence acquisition: The review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement.
Evidence synthesis: After screening 1943 articles, 22 studies (two randomised controlled trials, 14 prospective cohort studies, five retrospective case series, and one case report) enrolling 450 patients were included. Eleven studies reported on acute TENS and 11 on chronic TENS. In acute TENS and chronic TENS, the mean increase of maximum cystometric capacity ranged from 69 ml to 163 ml and from 4 ml to 156 ml, the mean change of bladder volume at first detrusor overactivity from a decrease of 13 ml to an increase of 175 ml and from an increase of 10 ml to 120 ml, a mean decrease of maximum detrusor pressure at first detrusor overactivity from 18 cmH_20 to 72 cmH_20 and 8 cmH_20, and a mean decrease of maximum storage detrusor pressure from 20 cmH_20 to 58 cmH_2O and from 3 cmH_20 to 8 cmH_2O, respectively. In chronic TENS, a mean decrease in the number of voids and leakages per 24 h ranged from 1 to 3 and from 0 to 4, a mean increase of maximum flow rate from 2 ml/s to 7 ml/s, and a mean change of postvoid residual from an increase of 26 ml to a decrease of 85 ml. No TENS-related serious adverse events have been reported. Risk of bias and confounding was high in most studies.

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Conclusions: Although preliminary data suggest TENS might be effective and safe for treating neurogenic lower urinary tract dysfunction, the evidence base is poor and more reliable data from well-designed randomised controlled trials are needed to make definitive conclusions.
Patient summary: Early data suggest that transcutaneous electrical nerve stimulation might be effective and safe for treating neurogenic lower urinary tract dysfunction, but more reliable evidence is required.

1. Introduction

Lower urinary tract dysfunction is common in neurological patients resulting in symptoms that have a pronounced effect on quality of life [1]. The site and nature of the neurological lesion determines the pattern of dysfunction [1,2]. The high prevalence of neurogenic lower urinary tract dysfunction (NLUTD) is reflected by the wide distribution of neural control in health and depends on the underlying neurological disorder, for instance reaching about 25% in patients with Alzheimer's disease and approaching 100% in those suffering from multiple sclerosis at an advanced stage [1,2]. NLUTD substantially impairs quality of life and lower urinary tract function becomes one of the most relevant aspects in daily life of the neuro-urological patient [1,3]. Optimal treatment of storage and/or voiding symptoms is a main challenge in this population, especially because conventional treatments often fail.

In 1974, Sundin et al [4] showed for the first time that electrical pudendal stimulation resulted in the inhibition of bladder contraction in cats. This technique was improved, extended to different stimulation sites, and is now used as transcutaneous electrical nerve stimulation (TENS) for the treatment of various urological dysfunctions. Electrical stimulation is applied continuously or is event driven. TENS is reported to be a potent and safe treatment option, both in patients suffering from chronic pelvic pain [5,6] and non-neurogenic overactive bladder syndrome [7,8]. Positive treatment effects might also be expected in patients with an underlying neurological disorder. We therefore performed a systematic review to assess and appraise all available evidence on the efficacy and safety of TENS for treating NLUTD.

2. Evidence acquisition

2.1. Data sources and searches

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement [9]. The protocol for the review is available on PROSPERO (CRD42014008678) (http://www.crd.york.ac.uk/PROSPERO). We systematically searched Embase, Medline, Cochrane Central Register of Controlled Trials, and Health Technology Assessment Database (from January 1, 1946 to January 23, 2015). No language or date restrictions were applied. We additionally searched the reference list of all included studies and any relevant review articles. The search strategies are available in the Supplementary data.

2.2. Study selection

We aimed to include all original studies that reported efficacy and/or safety data on TENS for treating NLUTD, including randomised controlled trials (RCTs), comparative non-RCTs, and single-arm cohort studies. Nonoriginal articles, studies not published as full-text, those including children only, and those not discriminating between non-neurological and neurological patients were excluded. Only outcomes, which were reported in more than three studies, were included in the analyses. There was no language restriction. All identified abstracts were imported into a bibliography management software (EndNote X5 [M.P.S.] or X7 [T.G., T.M.K.]; Thomson Reuters, PA, USA) and sorted according to inclusion and exclusion folders by drag and drop. Abstracts of all identified studies were independently reviewed by two authors (T.G. and M.P.S.). Studies reporting on TENS (defined as any transcutaneous electrical nerve stimulation) for treating NLUTD (defined as any type of lower urinary tract dysfunction caused by a neurological disorder) were reviewed in full text.

2.3. Data extraction and risk of bias assessment

The variables assessed included year of publication, study type, number of patients, sex and age, underlying neurological disorder, duration of neurological disorder, acute (ie, stimulation during urodynamic investigation only) and chronic (ie, daily upon weekly stimulation during 3–102 wk before neuro-urological re-assessment), stimulation site (clitoral/penile, vaginal/rectal, sacral dermatome, or suprapubic), stimulation frequencies, pulse widths, stimulation signs (perception threshold and/or toes' plantar flexion) and durations, TENS effects on urodynamic parameters and bladder diary variables, and any adverse events. Data from eligible reports were extracted (by treatment group in comparative studies) in duplicate (T.G. and M.P.S.) and discrepancies were resolved by a third reviewer (T.M.K.).

The Cochrane Risk of Bias Assessment tool was used for RCTs [10]. This included the assessment of sequence generation, allocation concealment, blinding of participants, therapists, and outcome assessors, completeness of outcome data, selective outcome reporting, and other potential sources of bias (Supplementary Fig. 1 and 2).

Risk of bias in noncomparative studies cannot be assessed with the approach described above. Therefore, concern was extended in noncomparative studies to address external validity by assessing whether study participants were selected consecutively or were representative of a wider patient population and whether specified

confounding factors were reported. A list of the three most important potential confounders for efficacy and safety outcomes was developed with clinical content experts (European Association of Urology Neuro-Urology guidelines panel). For each study, we asked whether each prognostic confounder was considered and whether, if necessary, the confounder was controlled for in analysis. The potential confounding factors are underlying neurological disorder (eg, multiple sclerosis, Parkinson's disease, etc), sex, and type of therapy (acute or chronic TENS). Attrition bias and selective outcome reporting were also assessed. This is also a pragmatic approach informed by methodological literature [10].

2.4. Data synthesis

Effect estimates of TENS were calculated as the difference (d) between study completion X1 and baseline X0, that is, 6–12 wk after baseline. For each study the variance at time point x was calculated, using the standard deviation $(SD)_x$ and group size n, as: $VAR = SD_x^2/n$. The correlation coefficient was assumed to be 0.5, being a conservative value that leads to the highest variance. Thus, the variance of d (VAR_d) was: $VAR_{X0} + VAR_{X1} - 2^*0.5^*\sqrt{(VAR_{X0} * VAR_{X1})}$ and the corresponding $SD_d = \sqrt{n} * VAR_d$. In case of missing SD_x these were imputed taking the largest of reported SD_x. Pooling of data via meta-analysis was planned for RCTs but it was not possible since outcome measures of the different studies varied widely and only two RCTs were available. In non-RCTs, no data pooling was planned due to different study designs and the expected clinical and methodological heterogeneity of included studies. However, forest plots were generated in order to provide a visual representation of results to show the direction and magnitude of effects. This was performed using the metan command of the Stata statistics software package (Stata 14.0 statistics software package; StataCorp 2015. Stata Statistical Software: Release 14. College Station, TX, USA).

Risk of bias summary and graphs (Supplementary Fig. 1 and 2) were generated using Cochrane RevMan software (RevMan v 5.3; Informatics and Knowledge Management Department, London, UK).

3. Evidence synthesis

3.1. Search results

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the literature search and results is shown in Figure 1. After screening 1943 abstracts, 22 studies were included in a narrative synthesis [11] (Tables 1–4; Fig. 2A–H): two RCTs [12,13], 14 prospective cohort studies [14–27], five retrospective case series [28–32], and one case report [33].

3.2. Study and patient characteristics

Overall, the 22 included studies enrolled a total of 450 patients: 203 women (45%), 234 men (52%), and in 13 patients (3%) sex was not reported. The mean age of

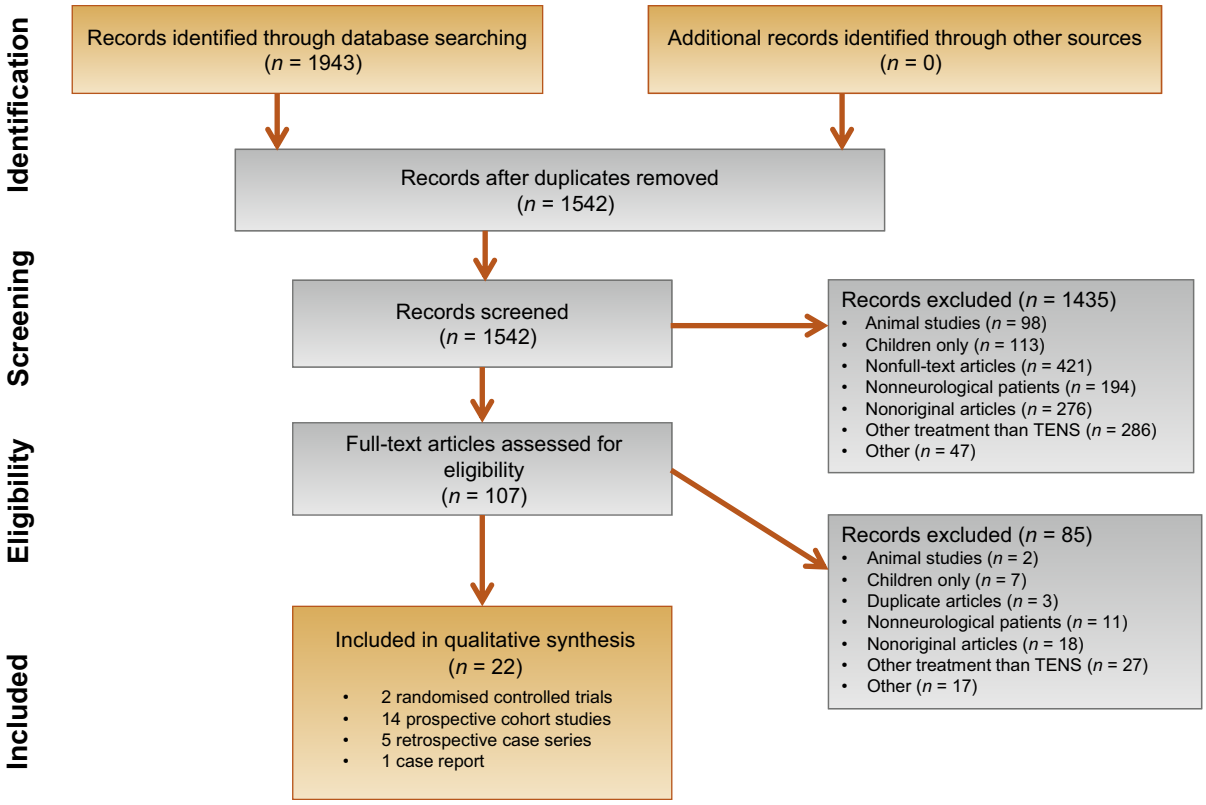

Fig. 1 – Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram.
TENS = transcutaneous electrical nerve stimulation.

Table 1 – Characteristics of included studies

	Study	Total patients (female/male)	Type of therapy	Site of stimulation	Stimulation frequencies	Pulse width	Stimulation amplitude/ pulse current	Stimulation duration	Test duration in d	Mean age in yr	Neurological disorder	Mean duration of neurological disorder in yr	No. of adverse events	Outcomes measured
RCTs	Guo et al 2014 [12]	Con 29 (8/21)	Chronic	None	Con	Con	Con	Con	60	65	CVA 29	NR	0	MCC, MSD, MFR, L24
		Exp 32 (11/21)		Sacral	75 Hz	200 μs	16 mA	30 min/d	60	68	CVA 32	NR	0	
	McClurg et al 2008 [13]	Con 37 (26/11)	Chronic	Placebo vaginal/rectal (+EMG biofeedback)	Con	Con	Con	Con	63	52	MS 37	11	0	MFR, L24, PVR
		Exp 37 (31/6)		vaginal/rectal (+EMG biofeedback)	10Hz	450 μs	NR	30 min/d	63	47	MS 37	10.2	0	
Non-RCTs	Dalmose et al 2003 [14]	10 (4/6)	Acute	Clitoral/penile	20 Hz	200 μs	2 × bulbocavernosus reflex threshold	<2 h	1	39	cSCI 8, iSCI 2	9.4	NR	MCC, BDO, MDO
	Fjorback et al 2006 [28]	10 (4/6)	Acute	Clitoral/penile	20 Hz	200 μs	1.5 × bulbocavernosus reflex threshold	<2 h	1	45	MS 10	NR	0	MSD
	Fjorback et al 2007 [29]	11 (3/8)	Acute	Clitoral/penile	20 Hz	200 μs	Maximal tolerable level	<2 h	1	NR	MS 11	NR	NR	BDO
	Hansen et al 2005 [30]	13 (NR)	Acute	Clitoral/penile	20 Hz	200 μs	2 × bulbocavernosus reflex threshold	<2 h	1	NR	SCI 13	NR	1	MCC, MSD
	Horvath et al 2010 [31]	9 (2/7)	Acute	Clitoral/penile	10/15 Hz	200 μs	2 × pudendo-anal reflex threshold	<2 h	1	56	cSCI 6, iSCI 3	24	0	MCC
	Lee et al 2002 [33]	1 (0/1)	Chronic	Penile	25 Hz	250 μs	2 × pudendo-anal reflex threshold	<2 h	21	33	iSCI 1	9	0	MCC, L24
	Lee et al 2003 [15]	8 (0/8)	Acute	Penile	25 Hz	250 μs	2 × pudendo-anal reflex threshold	<2 h	1	36	cSCI 3, iSCI 5	3.6	0	MDO
	Lee et al 2011 [16]	40 (4/36)	Acute	Clitoral/penile	25 Hz	250 μs	2 × pudendo-anal reflex threshold	<2 h	1	44	cSCI 23, iSCI 17	8.2	NR	BDO
	Lee et al 2012 [32]	6 (0/6)	Chronic	Penile	25 Hz	250 μs	2 × pudendo-anal reflex threshold	1–3 ×/d	28	45	cSCI 3, iSCI 3	6.4	NR	MCC, BDO
	Opisso et al 2008 [18]	17 (4/13)	Acute	Clitoral/penile	20 Hz	200 μs	1.5 × bulbocavernosus reflex threshold	<2 h	1	49	MS 1, CVA 1, cSCI 6, iSCI 4 others 5	NR	NR	MCC, MSS
	Opisso et al 2011 [19]	12 (4/8)	Acute	Clitoral/penile	20 Hz	200 μs	1.5 × clitoral/penile urethral reflex threshold	<2 h	1	36	MS 1, cSCI 5, iSCI 5, others 1	5	NR	MCC, MSD
	Opisso et al 2013 [17]	11 (5/6)	Acute	Clitoral/penile	20 Hz	200 μs	1.5 × clitoral/penile urethral reflex threshold	<2 h	5	39	MS 2, iSCI 5, others 4	8	0	MCC, MSD
	Pannek et al 2010 [20]	21 (16/5)	Chronic	Vaginal/rectal	8 Hz	400 μs	NR	40 min/d	84	48	MS 10, PD 3, HD 6, iSCI 2	NR	0	V24
	Previnaire et al 1995 [21]	10 (1/9)	Acute	Clitoral/penile	5 Hz	500 μs	2 × bulbocavernosus reflex threshold	<2 h	1	31	cSCI 10	2	NR	MCC
	Previnaire et al 1998 [22]	5 (1/4)	Chronic	Clitoral/penile	5 Hz	500 μs	Maximal tolerable level	20 min/d	28	42	cSCI 5	1	0	MCC
	Primus et al 1996 [23]	30 (30/0)	Chronic	Clitoral	20 Hz	1500 μs	Maximal tolerable level	20 min/d	84	58	MS 30	10	0	MCC
	Radzieszewski et al 2009 [25]	22 (4/18)	Chronic	Suprapubic/sacral	50 Hz	200 μs	20 mA	15 min/d	60	32	SCI 22	NR	0	MCC, MFR, PVR
	Radzieszewski et al 2013 [24]	28 (6/22)	Chronic	Suprapubic/sacral	50 Hz	200 μs	20 mA	15 min/d	712	33	cSCI 5, iSCI 23	0.7	NR	MCC, MFR, PVR
	Skeil et al 2001 [26]	44 (33/11)	Chronic	Sacral	20 Hz	200 μs	Comfortable sensation	180 min/d	42	51	MS 10, PD 2, CVA 13, HD 3, SCI 5, others 11	15	0	MCC, BDO, MSD, MDO, L24, V24, PVR
	Yokozuka et al 2004 [27]	7 (6/1)	Chronic	Sacral	20 Hz	300 μs	Maximal tolerable level	30 min/d	30	64	MS 1, CVA 3, SCI 1, others 2	NR	0	MCC, L24, V24

Acute = stimulation during urodynamic investigation only; BDO = bladder volume at first detrusor overactivity; Chronic = daily upon weekly stimulation during 3–102 wk before neuro-urological re-assessment; Con = control intervention; cSCI = complete spinal cord injury; CVA = cerebrovascular accident; EMG = electromyography; Exp = experimental intervention; HD = herniated disk; iSCI = incomplete spinal cord injury; L24 = leakages per 24 h; MCC = maximum cystometric capacity; MDO = maximum detrusor pressure at first detrusor overactivity; MFR = maximum flow rate; MS = multiple sclerosis; MSD = maximum storage detrusor pressure; NR = not reported; PD = Parkinson's disease; PVR = postvoid residual; RCTs = randomised controlled trials; SCI = spinal cord injury not otherwise specified; V24 = voids per 24 h.

Table 2 – Treatment outcomes of randomised controlled studies

Study	Intervention	No. of patients	Maximum cystometric capacity in ml				Maximum storage detrusor pressure in cmH_2O				Leakages per 24 h				Maximum flow rate in ml/s				Postvoid residual in ml			
			BL	UT	Difference	*p* value	BL	UT	Difference	*p* value	BL	UT	Difference	*p* value	BL	UT	Difference	*p* value	BL	UT	Difference	*p* value
Guo et al [12]	Con	29	185	195	10		59	62	3		4.18	3.86	−0.32		7.1	7.4	0.3					
	Exp	32	178	218	40	<0.05[a]	57	49	−8	<0.05[a]	4.02	1.61	−2.41	<0.05[a]	7.3	10.8	3.5	<0.05[a]				
McClurg et al [13]	Con	37									2.1	1.1	−1	<0.001[b]	15	17	2	NS[b]	69	56	−13	<0.005[a]
	Exp	37									2.1	0.3	−1.8	<0.001[b]	13	20	7	<0.005[b]	74	38	−36	

BL = baseline; Con = control intervention; Exp = experimental intervention; NS = not significant; UT = under treatment.
[a] *p* value comparing control group with experimental group under treatment.
[b] *p* value comparing difference between baseline and under treatment in the same group.

patients was 46 yr. Patients suffered from multiple sclerosis ($n = 150$), incomplete spinal cord injury ($n = 70$), complete spinal cord injury ($n = 79$), spinal cord injury not otherwise specified ($n = 36$), cerebrovascular accident ($n = 78$), herniated disk ($n = 9$), Parkinson's disease ($n = 5$), and others ($n = 23$). Eleven (all non-RCTs) studies reported on acute and 11 (two RCTs, nine non-RCTs) on chronic TENS, 15 on clitoral/penile, two on vaginal/rectal, three on sacral, and two on suprapubic stimulation (Table 1).

3.3. *Efficacy of TENS*

Treatment outcomes of RCTs and non-RCTs are shown in Tables 2–4. In acute and chronic TENS, the mean increase of maximum cystometric capacity (Fig. 2A) ranged from 69 ml to 163 ml and from 4 ml to 156 ml, respectively. The mean change of bladder volume at first detrusor overactivity (Fig. 2B) ranged from a decrease of 13 ml to an increase of 175 ml and from an increase of 10 ml to 120 ml, respectively. In acute and chronic TENS, the mean decrease of maximum detrusor pressure at first detrusor overactivity (Fig. 2C) ranged from 18 cmH_20 to 72 cmH_20 and 8 cmH_20, respectively, and the mean decrease of maximum storage detrusor pressure (Fig. 2D) ranged from 20 cmH_20 to 58 cmH_2O and from 3 cmH_20 to 8 cmH_2O, respectively. In chronic TENS, the mean decrease in the number of voids per 24 h (Fig. 2E) and in the number of leakages per 24 h (Fig. 2F) ranged from 1 to 3 and from 0 to 4, respectively. The mean increase of maximum flow rate (Fig. 2G) ranged from 2 ml/s to 7 ml/s and the mean change of postvoid residual (Fig. 2H) ranged from an increase of 26 ml to a decrease of 85 ml.

3.4. *Safety of TENS*

One patient did not tolerate stimulation and therefore therapy had to be stopped [30]. No other adverse events have been reported (Table 1).

3.5. *Risk of bias and confounding*

The risk of bias and confounding was relevant in both RCTs and non-RCTs (Supplementary Fig. 1 and 2). In particular, a high risk of selective outcome reporting bias was found.

4. Discussion

4.1. *Principal findings*

The positive impact on urodynamic (maximum cystometric capacity, maximum detrusor pressure at first detrusor overactivity, maximum storage detrusor pressure, and maximum flow rate) and bladder diary (voids per 24 h, leakages per 24 h) parameters as well as the favourable adverse event profile, indicate that TENS might be effective and safe for treating NLUTD. This is underlined by the statistically significant differences between the treatment and control group in the RCT by Guo et al [12] for these outcomes. Although our findings are promising,

Table 3 – Treatment outcomes of nonrandomised controlled studies

Study	No. of patients	Maximum cystometric capacity in ml				Bladder volume at first detrusor overactivity in ml				Maximum detrusor pressure at first detrusor overactivity in cmH_2O				Maximum storage detrusor pressure in cmH_2O			
		BL	UT	Difference	*p* value	BL	UT	Difference	*p* value	BL	UT	Difference	*p* value	BL	UT	Difference	*p* value
Dalmose et al [14]	10	210	349	139	0.016	170	157	−13	0.54	51	33	−18	0.045				
Fjorback et al [28]	10													85	27	−58	NR
Fjorback et al [29]	11					170	247	77	NR								
Hansen et al [30]	13	322	480	158	NR									72	28	−44	NR
Horvath et al [31]	9	149	223	74	<0.05												
Lee et al [33]	1	205	353	148	NR												
Lee et al [15]	8									83.6	11.6	−72	<0.01				
Lee et al [16]	40					99	274	175	<0.01								
Lee et al [32]	6	204	360	156	NR	45	166	121	NR								
Opisso et al [19]	12	161	296	135	0.002									93	45	−48	0.002
Opisso et al [18]	17	186	255	69	0.003									73	34	−39	0.001
Opisso et al [17]	11	156	248	92	0.003									91	71	−20	NS
Pannek et al [20]	21																
Previnaire et al [21]	10	156	318	163	<0.01												
Previnaire et al [22]	5	153	157	4	NS												
Primus et al [23]	30	336	389	53	<0.0001												
Radziszewski et al [24]	28	237	339	102	<0.005												
Radziszewski et al [25]	22	252	374	122	<0.005												
Skeil et al [26]	44	197	211	14	NS	123	134	10	NS	40.4	32.4	−8	NS	51	48.2	−2.8	NS
Yokozuka et al [27]	7	202	264	62	NR												

BL = baseline; NR = not reported; NS = not significant; UT = under treatment.

Table 4 – Treatment outcomes of nonrandomised controlled studies

Study	No. of patients	Voids per 24 h				Leakages per 24 h				Maximum flow rate in ml/s				Postvoid residual in ml			
		BL	UT	Difference	*p* value	BL	UT	Difference	*p* value	BL	UT	Difference	*p* value	BL	UT	Difference	*p* value
Lee et al [33]	1					5	1	–4	NR								
Pannek et al [20]	21	6.5	4.1	–2.4	NR												
Radziszewski et al [24]	28									7.4	11	3.6	<0.005	193	116	77	<0.005
Radziszewski et al [25]	22									6.3	11.4	5.1	<0.005	191	106	–85	<0.005
Skeil et al [26]	44	12.6	11.2	–1.4	NS	1.8	1.6	–0.2	NR					134	160	26	0.02
Yokozuka et al [27]	6	8.9	6.1	–2.8	NR	2.4	1.6	–0.8	NR								

BL = baseline; NR = not reported; NS = not significant; UT = under treatment.

the inaccuracy of the evidence appears to be high with some controversial findings. Most of the studies are small and underpowered, especially to allow for subgroup analyses (for instance comparison of different stimulation sites, stimulation parameters and duration, different neurological disorders, and different urodynamic patterns). In addition, there is significant risk of bias and confounding.

4.2. *Findings in the context of existing evidence*

In recent years, neuromodulation therapies using electrical stimulation of peripheral nerves such as the sacral nerve roots, tibial nerve, pudendal nerve, and dorsal genital nerves have become more and more popular in the urological community. Clitoral and penile electrodes are used stimulating the dorsal clitoral nerve and dorsal penile nerve in women and men, respectively. Electrodes are also placed into the vagina and rectum resulting in a stimulation of the pudendal nerve and the inferior rectal nerve. Although the stimulation sites are different and the exact mechanism of action remains to be elucidated, the modulation of spinal cord-mediated reflexes through interneurons and brain networks by peripheral afferents seem to be involved [33]. Indeed, dorsal clitoral nerve stimulation during bladder filling in healthy women reduced the activation of certain cortical areas suggesting a neuromodulation effect on supraspinal centres relevant for lower urinary tract control [34]. However, there is a complete lack of literature about the mechanism of action of TENS for treating NLUTD so appropriately designed studies are highly warranted.

Previous systematic reviews showed beneficial effects of sacral neuromodulation [35] and tibial nerve stimulation [36] for treating NLUTD, but the quality of evidence is still low. In a recent RCT, it was found that TENS is as effective as oxybutynin for the treatment of overactive bladder in children [37]. However, no similar comparative study is available assessing the effect of TENS for treating adult patients with an underlying neurological disorder.

4.3. *Implications for research*

Although the findings of our systematic review are promising, plausibility has to be added through appropriately designed RCTs, especially to assess the reproducibility of results for different underlying neurological disorders and stimulation parameters. RCTs investigating treatment effects in different neurological disorders using urodynamics, bladder diary, validated disease- and condition-specific questionnaires, as well as cost-effectiveness data are needed to generate high-level evidence allowing appropriate conclusions for daily clinical practice. Importantly, there are no treatment standards for TENS and no guidelines for therapeutic regimes and these need to be developed through further studies. Moreover, individual adjustment of stimulation parameters by analogy with sacral neuromodulation might improve outcomes and warrants additional investigations.

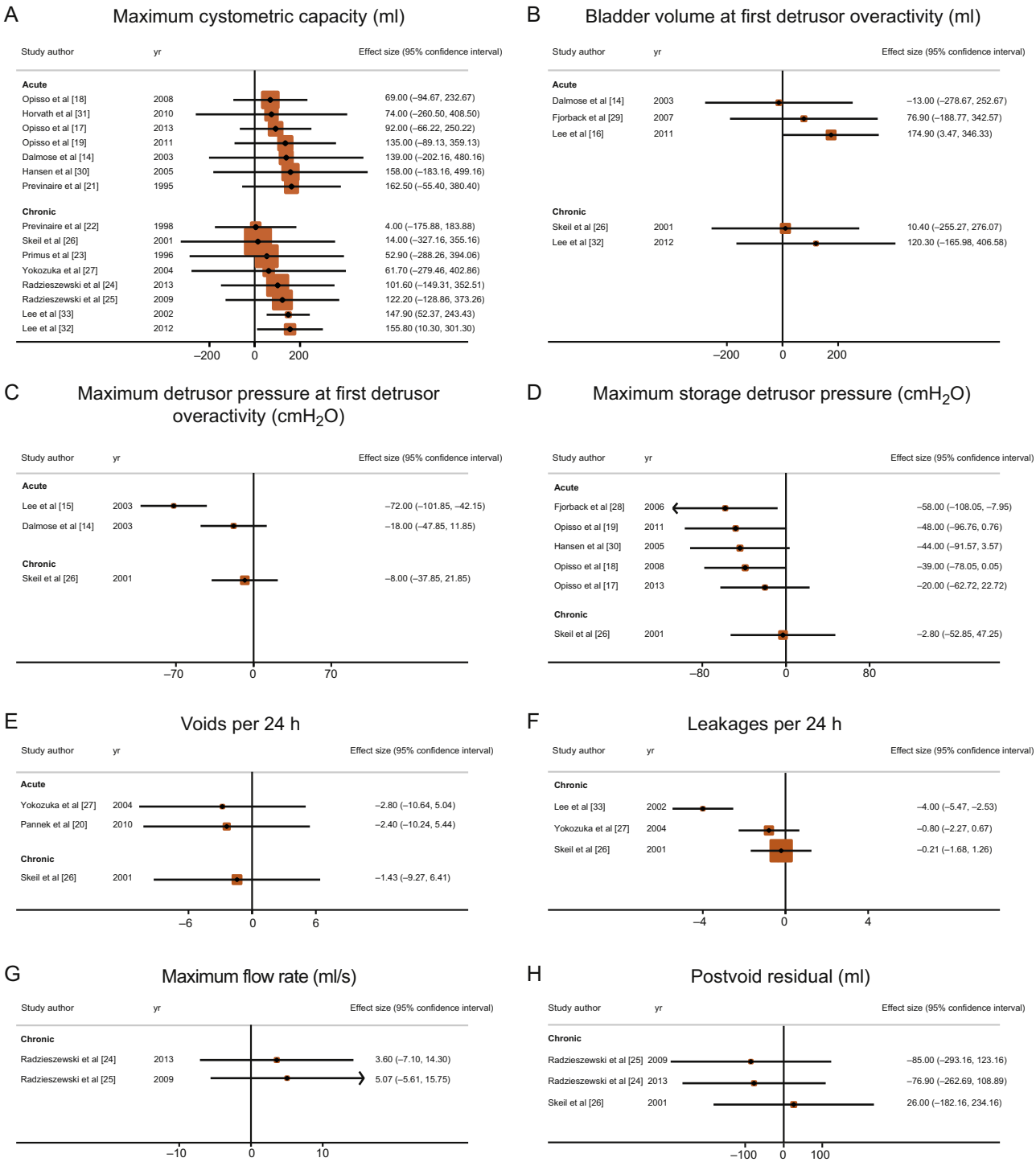

Fig. 2 – Effects of transcutaneous electrical nerve stimulation on (A) maximum cystometric capacity in ml; (B) bladder volume at first detrusor overactivity in ml; (C) maximum detrusor pressure at first detrusor overactivity in cmH2O; (D) maximum storage detrusor pressure in cmH2O; (E) number of voids per 24 h; (F) number of leakages per 24 h; (G) maximum flow rate in ml/s, (H) postvoid residual in ml (mean values with 95% confidence intervals). Positive values indicate an increase, negative values a decrease.

4.4. Implications for practice

NLUTD is not a homogenous entity and can result from a wide range of neurological disorders [1]. Thus, the treatment goal of TENS varies between different neurological disorders and includes achieving urinary continence, improving quality of life, preventing urinary tract infection, and protecting the upper urinary tract (renal function). This highlights the importance of prospective studies to investigate disease-specific TENS outcomes.

The benefits of TENS are that it is noninvasive, associated with few adverse events, and easy to self-apply at home by

the patient. Moreover, repeated magnetic resonance imaging is not compromised due to the absence of a metallic implant and in some patients additional beneficial effects on sexual and bowel dysfunction may occur.

4.5. Limitations of this study

This report is the first systematic review assessing and appraising all available evidence of TENS for treating NLUTD and several limitations need to be addressed. Included studies are mostly cohort studies with a before-and-after treatment design and besides the two RCTs no study had a comparator. This is a major issue, as a placebo effect might be relevant but could not be assessed appropriately. Primary outcomes and methodology varied widely and in about one quarter of results SDs for baseline and follow-up measurements were missing and had to be imputed. As the estimate of the covariance was not reported we thus assumed it to be 0.5. We therefore make attentive to cautious interpreting of the summary figures reported. However, since we aimed to summarise existing evidence, we consider our approach to be acceptable. The included studies reported either on acute or chronic TENS, but not on both, and various clinically relevant outcome parameters were not consistently investigated such as subjective versus objective stimulation effects, duration of TENS effects, impact on comorbidities such as neurogenic sexual and bowel dysfunction as well as spasticity, and patient adherence to TENS. Moreover, studies were small and outcomes varied widely. Thus, scarcity of data did not allow for subgroup analyses (for instance comparison of different stimulation sites, stimulation parameters and duration, different neurological disorders, and different urodynamic patterns). Finally, the risk of bias and confounding was substantial (in both RCTs and non-RCTs) and more reliable evidence is urgently required. Despite these limitations, TENS seems to become a valuable treatment option before more invasive therapies (which mostly lack high-level evidence data) are considered.

5. Conclusions

Preliminary evidence indicates that TENS is an effective and safe treatment option for patients with NLUTD. However, quality of evidence was low, especially due to a lack of well-designed, appropriately sampled, and powered RCTs. This systematic review demonstrated the potential of TENS for treating NLUTD and identified the need for more reliable data in order to make definitive conclusions.

Author contributions: Thomas M. Kessler had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Gross, Schneider, Kessler.
Acquisition of data: Gross, Schneider, Kessler.
Analysis and interpretation of data: Gross, Schneider, Bachmann, Kessler.
Drafting of the manuscript: Gross, Schneider, Kessler.
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Statistical analysis: Gross, Schneider, Bachmann, Kessler.
Obtaining funding: Gross, Schneider, Bachmann, Blok, Groen, 't Hoen, Castro-Diaz, Padilla Fernandez, Del Popolo, Musco, Hamid, Ecclestone, Karsenty, Phé, Pannek, Kessler.
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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.eururo.2016.01.010.

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