TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION: “WHAT IS THE EVIDENCE?”

Julie ROMBAUT

Promotor: Prof. Dr. P. Hoebeke
Co-promotor: Dr. L.A. Groen

Dissertation presented in the 2nd Master year in the programme of

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Date

11-4-2014

Rombaut Julie

Dr. L.A. Groen
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A warm appreciation is given to my parents and Jeroen, for their unceasing encouragement and support.

As well my sense of gratitude to all, who directly or indirectly, have lent their helping hand in this project.

Julie Rombaut
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ABSTRACT

Purpose

The aim of this dissertation is to critically analyze the evidence around the use of TENS in children with non-neurogenic bladder dysfunction. We attempt to make an overall conclusion about the efficacy of TENS treatment. We try to find out, how the population respond to TENS, if there is enough evidence and if all studies are homogenous concerning the used materials and methods with an affirmative outcome.

Materials and methods

Ten articles were selected through an electronic search of following databases: Web of Science, MEDLINE, Cochrane library and Pubmed. Following inclusion criteria were used: children between 0-18 years, English language, treatment with TENS and published in the last 10 years. Following limits were obtained: no congenital abnormalities or neurological diseases. For the meta-analysis only the articles that used the ICCS criteria concerning initial success were selected. A random effects meta-analysis was conducted.

Results

There is a big lack of level I evidence studies and a standardized protocol. Population groups differed, TENS application was diverse, and study procedure and outcome parameters used were irregular between studies. Despite that, the results are promising. An overall of 70% of the patients shows a 50-100% decrease in symptoms. This decrease is especially seen for incontinence and urge, for bladder capacity the results are less coherent. Only 21% of the overall patients showed a full response. This result cannot be generalized due to the big heterogeneity between the studies, as observed through our meta-analysis.
Conclusion

Transcutaneous electrical nerve stimulation is a non-invasive, easy to apply device with rare side-effects that showed promising results. It was more effective than sham in randomized controlled trials treating OAB. It deserves further research and a place in second-line treatment options.
SAMENVATTING

Doel

Het doel van deze thesis is het kritisch analyseren van de indicaties die bestaan voor het gebruik van TENS bij kinderen met een niet-neurogene blaasprobleem. We proberen een algemene conclusie te trekken aangaande de effectiviteit van een behandeling met TENS. In welke mate heeft de populatie baat bij TENS, bestaat er voldoende bewijskracht en zijn alle studies consistent betreffende de gebruikte materialen en methoden. Daarnaast onderzoeken we of alle studies eensgezind zijn.

Materialen en methoden


Resultaten

Er is een tekort aan studies met voldoende bewijskracht (level I) die berusten op gestandaardiseerde richtlijnen. De gekozen populaties verschillen, het gebruik van TENS gebeurde op verschillende manieren, en de studieprocedure en gekozen uitkomst parameters varieerden. Desondanks zijn de resultaten veelbelovend. Globaal 70% van de populatie zal initieel een daling in de symptomen vertonen tussen 50-100%. Deze resultaten zijn overtuigend wat betreft de symptomen incontinentie en drang, voor de blaascapaciteit zijn de resultaten niet eensgezind. Slechts 21% van de populatie zou sympoomvrij zijn na de behandeling. De statistische heterogeniteit tussen die studies is echter te groot om deze resultaten uit de meta-analyse te generaliseren.
Conclusie

Elektrische transcutane zenuwstimulatie is een niet-invasieve behandeling, gebruiksvriendelijk en zelden leidend tot bijwerkingen. De resultaten zijn positief. Het verdient een plaats tussen de behandelingsopties in 2de lijn maar verder onderzoek is aangewezen.
TRANSCUTANEOUS ELECTRICAL NERVE STIMULATION: "WHAT IS THE EVIDENCE?"

Introduction

Urinary incontinence is physiological up to the 5th year of life. Children develop stable bladder control in the 3rd to 6th year, initially during the day and later also during the night. (1) Nocturnal enuresis is still present in 10% of the 7 years olds, 3% of 12 and 1% of the 18 years olds. During the day 2-9% of the children are affected. (2) In the USA daytime wetting is estimated to affect 5-7 million children aged 6 years or older. (3)

Overactive bladder (OAB) is the most common voiding dysfunction in children occurring with a peak incidence between ages 5 to 7. (4) The impact of wetting in children can affect their life emotionally and behaviorally but also socially and can be a burden for the family. (5) A spontaneous remission rate of 15% per year is observed. (6) As we can see that only one third of those affected seek out specialized help, we can presume that every family sees this condition different, has other expectations of their children or even think of incontinence as a taboo. Nevertheless it is important to treat these children as it can have a potential impact in their future life. (7)

Non-neurogenic lower urinary tract disorders are common problems in pediatric urology. They are often challenging to treat and have a significant adverse affect on the quality of life. (8) Most children benefit by general lifestyle advice, behavioral modifications and conservative therapy such as bladder training, teaching abdominal/pelvic floor muscle interaction and relaxation exercises, biofeedback and drugs. Nevertheless, at least 20% of children with non-neurogenic lower urinary tract disorders are refractory to these treatments. (9)
OAB, according to the ICCS terminology, is the condition afflicting patients experiencing urgency symptoms whereas detrusor overactivity is the observation during cystometry of involuntary detrusor contractions during the filling phase. (1) There is mounting evidence that OAB is a sensory problem, and whether it’s origin is located in the central nervous system or at the bladder level is a matter for debate. (10) Symptoms include urinary urgency, frequency, nocturnia and may include urge incontinence.

Normal bladder function requires a complex interaction between autonomic (OS and PS nerves) and somatic (pudendal nerves) pathways at lumbosacral spinal level, where the effect of neuromodulation takes place. (11) The neural pathways that control lower urinary tract function are organized as simple on-off switching circuits that maintain a reciprocal relationship between the urinary bladder and the urethral outlet. (11) Transcutaneous stimulation has proven an effect in modulating bladder innervation and restoring the coordination of sacral reflexes. (4)

The bladder function in childhood is a dynamic entity. In the fetus, before the nervous system has matured, urine is presumably eliminated from the bladder by non-neural mechanisms. Primitive reflex pathways, organized in the spinal cord, regulate voiding at later stages of development. (11) Babies’ bladders fill to a set point, then automatically contract and empty. The nervous system matures as children grow. The brain begins to get messages from the bladder and sends messages to the bladder to keep it from automatically emptying until children can reach the toilet at a socially accepted time. (12) Bladder capacity increases, natural body alarms become activated, an overactive bladder settles down, production of ADH becomes normal and the response to the body’s signal that it is time to void improves (12). Reflex voiding is thus brought under the modulating influence of higher brain centers, where we can see an inhibitory perineal-to-bladder reflex and the adult form of reflex voiding. (11)
Amplification, coordination and timing are three functions needed for a normal micturition. (13) The storage and periodic elimination of urine depends on the coordinated activity of smooth and striated muscles in the two functional units of the lower urinary tract, i.e. a reservoir (bladder) and an outlet consisting of the bladder neck, the urethra and the urethral sphincter. (11) The coordination is mediated by a complex neural control system, located in the brain, the spinal cord and the peripheral ganglia. (11) Normal micturition control involves the periaqueductal gray and the pontine micturition center. (14) Maturational delay probably lies in reticulospinal pathways or in the inhibitory center within the cerebral cortex. (10)

The bladder has only two modes of operation: storage and elimination. It remains in a “turned off“ mode for most of the time. When desire to urinate occurs, the bladder “turns on” in an “all-or-none” manner to eliminate urine. (15) Voluntary control of the bladder and urethra, developed during maturation, has two important aspects. In both, namely registration of bladder filling sensation and manipulation of the firing of the voiding reflex, plays the periaqueductal gray (PAG) a crucial role. (11) The PAG receives and passes ascending bladder signals to higher brain centers and receives projections from higher brain centers. It also controls the primary input to the pontine micturition center (PMC). Higher brain centers can repress the excitatory signal to the PMC during bladder filling and thus prevent voiding or incontinence. (11)

Bladder contraction is initiated during the micturition amplification stage where afferent activity, originated from pelvic visceral organs and somatic afferent pathways by way of the pudendal nerves from the perineal muscle and skin, stimulates efferent excitatory input to the bladder. This positive feedback system is critical for sending signals of bladder fullness to the brain and to initiate micturition reflex. (15)
Transcutaneous electrical nerve stimulation (TENS) activates the somatic afferents of the pudendal nerves through peripheral nerve fibers. This excitation is said to result in a spinal and supraspinal inhibition which leads to an inhibition of the reflex bladder hyperactivity. Activation of somatic afferent pathways inhibit the processing of visceral afferent signals. (15) This neuromodulation acts centrally, with more involvement of the brain than the peripheral organs. (16) The success lies in the common visceral and somatic sensory innervation pathways in the central nervous system. (17) It is also reported that it has a positive effect on the pelvic floor through motor neuron excitation resulting in a contraction thus enhancing the striated urethral sphincter tone. (18) This reorganization of spinal reflexes and regulation of cortical activity results in a restored balance and coordination of the reflex pathways. (19) This evidence gives an indication but we should keep in mind that the exact mechanisms remain unknown. (16)

Nowadays transcutaneous surface electrodes have been applied over the sacral spinal outflow, related dermatomes, and the peroneal and tibial regions. It is applied during intermittent treatment sessions at home or at the clinic. Parameters used for stimulation include frequency, amplitude and pulse width. To modulate detrusor overactivity and to attain sufficient urethral relaxation, stimulation at 5-10Hz is efficacious. (20) Intensity is managed by the child to achieve the highest but tolerable rate. The pulse width, or duration, generally used to inhibit the bladder, is between 0.2 and 0.5ms.

According to the ICCS, TENS can be a reasonable alternative, when side effects of drugs become intolerable or when conventional primary urotherapy does not achieve satisfactory results. Should parents opt for non-pharmacological treatment, electrical stimulation can be proposed as a primary treatment for OAB. (16)

The aim of this dissertation is to critically analyze the evidence around the use of TENS in children with bladder dysfunction. TENS is a non-invasive treatment, free of side effects, easily adapted to home and can be used without the need of pharmacology.
All valuable reasons for children and their parents to consider TENS. But are all present studies of a great value and can we make an overall conclusion about the efficacy of TENS? Is TENS just a good alternative or also a good first-line treatment? And is there a need or even way to set up randomized controlled trials that are more homogenous concerning the used materials, methods and results in the future?
Method

The articles were obtained through the use of several databases. The electronic search included Web of Science, MEDLINE, Cochrane library and Pubmed. For the background study we used various types of studies whereas only original articles were selected for our literature study. Bibliographies of reviews were screened as to find the original articles that were relevant. Following inclusion criteria were used: children between 0-18 years, English language, treatment with TENS and published in the last 10 years. Following limits were obtained: no congenital abnormalities or neurological diseases.

The terms used in the above databases were: electrical stimulation, electrical nerve stimulation, bladder dysfunction, OAB, neuromodulation, non-neurogenic bladder dysfunction, lower urinary tract disorders, nocturnal enuresis, incontinence, children, refractory. These terms were used in different combinations and with the use of Boolean operators.

Original articles out of reviews were looked at and dependent on the abstract and evidence they were selected. All the consensus papers of the ICCS were used to have a good understanding of the correct terminology and the standards there are nowadays.

Meta-analysis

Concerning the meta-analysis we made a more thorough selection. We started off with the ten articles selected for our literature study and screened on an outcome parameter based on initial success that is standardized according to the ICCS criteria.

According to the ICCS, treatment outcomes defining initial success are as followed: Nonresponse is defined as a 0% to 49% decrease, partial response is defined as a 50% to 89% decrease, response is defined as a 90% or greater decrease and full response is defined as a 100% decrease or less than 1 symptom occurrence monthly. (1)
Only these articles were selected that stated to use these criteria. The results were statistically analyzed with the use of R-package “meta”. A random effects meta-analysis of single proportions to calculate an overall proportion was conducted. Exact binomial confidence intervals were calculated for individual study results. The method used to estimate the between-study variance tau was the “DerSimonian-Laird” estimator.

The results are presented in a forest-plot. The forest-plot provides the summary data entered for each study. For the individuals studies a 95% confidence interval and the proportion is showed. Were this procedure to be repeated on multiple samples, the calculated confidence interval (which would differ for each sample) would encompass the true population parameter 95% of the time. The model used to perform the meta-analysis is the random effects model, which holds into account that there is variability in-between the studies and within the individual studies. In addition, it provides the weight for each study, the overall effect estimate, and the statistical significance of the analysis. The area of each square is proportional to the study’s weight in the meta-analysis. A test for heterogeneity examines the null hypothesis that all studies are evaluating the same effect. The quantity, which we call I-squared, describes the percentage of total variation across studies that is due to heterogeneity rather than chance. I-squared lies between 0% and 100%. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. (21)
Results

Study design

As the study design give us an idea about the level of evidence, it is important to screen the ten remaining articles on this aspect to be able to describe the strength of the results. Randomized controlled trials have a level I evidence, and should thus be seen as the studies with the most “strength”. When no control group is used, they normally fall in a level IV evidence.

Hoebek et al. (22) and Bower et al. (23) were the first ones to do a study around TENS in children. Both mention in their title “pilot study”. This type of study is, a small scale inductive study, planned in order to give an idea about the usefulness, time, cost, effect size and other variables in an effort to improve the study design upon large-scaled projects. Hoebek et al. didn’t state the study type, however he writes that “prospective studies are needed”, which makes us believe that it wasn’t a prospective trial. (22) Bower et al. on the other hand specifically states a prospective study. (23) Either way in both studies, no control group is used. Both have thus a level 4 evidence.

When we look at the other studies, four were prospective studies (24-27) without control group (level IV evidence), one retrospective (28) without control group (level IV evidence) and three (29-31) were randomized controlled trials (level I evidence).

Lordelo et al. performed a prospective, single-blind, sham-controlled study with 37 children older than 4 years whom presented with OAB. (31) Sham group patients who did not have complete remission continued with PSTENS. We can call this a cross-over trial, as the sham group became part of the active treatment group. Hagstroem et al. published a double-blind randomized control trial of 27 patients. (30) De Oliveira et al. randomized a total of 45 children with primary monosymptomatic enuresis without the use of sham. (29)
Study population

The study population tells us something more about the impact an article can have. It gives us also an indication for which problems TENS is used nowadays and who these authors see as possible candidates for treatment with TENS. Do they use strict inclusion or exclusion criteria, so that a positive result is certain but that extrapolation to our real-life patient population would not be relevant or are these kids carefully chosen to make sure that at the end we have proper indications of whom benefit and whom not?

Hoebeke et al.-2001

The study population consisted of 41 children, 15 girls with mean age 10.2 years and 26 boys with mean age 10.7 years. All children had urodynamically proved detrusor hyperactivity and suffered daytime wetting and urge. They were resistant to standard urotherapy and anticholinergic treatment. Anticholinergics were continued during neurostimulation in those who had partial effect and were stopped where it had no effect or delivered significant side effects. (22)

Bower et al.-2001

Twenty eligible children were included with a mean age of 7.5 years (range from 5 to 12). Inclusion criteria were children with urinary urgency or urge incontinence, either stabilized on long-term pharmacotherapy or either never used medication, and older than 5 years. Children were excluded when following symptoms or causes were present: organic and structural causes of incontinence, urinary tract infections, dyssnergic voiding on uroflowmetry or a post-void volume greater than 20ml. Fifteen girls and two boys completed the protocol requirements for data collection, 3 withdrew from study due to illness. (23)
Prospectively, a population of 36 children with a mean age of 7 years was examined. Seventeen were between 3 and 5 years. The children were assigned to two groups:

- **Group 1:** children with urge syndrome treated with superficial parasympathetic electrical stimulation.
- **Group 2:** children with voiding dysfunction treated with biofeedback.

Exclusion criteria were: children aged < 3 years, children who had not yet been toilet trained, children with urgency or UI secondary to anatomical anomalies and children with neurological disorders. The urge syndrome was defined as the presence of an uninterrupted flow, no vesical-sphincter dyscoordination at EMG and no high post-void residual (PVR). Dysfunctional voiding was defined as vesicoperineal dyscoordination at EMG during voiding, or the presence of a high PVR. (24)

Following symptoms were present (24):

- **Group 1:** 19 children (17 girls and 2 boys) with urge syndrome.
  - Symptoms of urgency were present in all nineteen.
  - Urge urinary incontinence was demonstrated in 16 children.
  - Episodes of urinary incontinence per month: nine children had daily episodes, two more than 10, four between 3-10 and one occasionally.
  - Nocturnal enuresis was present in 11 children.
  - A history of UTI was found in 11.
  - A disturbance of fecal elimination was seen in 12 children.
  - Two children were previously treated unsuccessfully with oxybutynin.

- **Group 2:** 17 children (16 girls, one boy) with voiding dysfunction
  - Symptoms of urgency were present in all seventeen.
  - Fifteen had urge urinary incontinence.
  - Eight had daily episodes of UI per month, two more than 10 episodes, three between 3-10 and two less than 3 episodes.
  - Nocturnal enuresis was present in 10 children, all with associated daily UI.
A history of UTI was found in 14 children.

- A disturbance of fecal elimination was seen in 10 children.
- Ten children were previously treated unsuccessfully with medication.

**Maim-Buatsi et al.- 2007**

A retrospective chart review of eighteen children (13 girls and 5 boys) with a mean age of 9.4 years (range 5-14) was done. They were treated with TENS from 2003 to 2005 for non-neurogenic OAB. These children had persistent symptoms of OAB despite treatment with anticholinergics and behavioral therapy. All of these children previously used anticholinergics during 1.3 ± 0.8 years. Fifteen had incontinence with an average of 3.2 daytime accidents and of these, seven had also nocturnal enuresis. Three had only symptoms of urgency/frequency. (28)

**Hagstroem et al.- 2009**

They conducted a double-blind randomized controlled trial using sham. A total of 27 children with refractory daytime urinary urge incontinence were randomized. Ten boys and 15 girls with a mean age of 8.6±1.6 years were included according to following criteria: aged between 5-14 years, daytime urinary incontinence at least 2 days per week, urgency, normal urinalysis, unremarkable urinary tract ultrasound and normal physical examination. Incontinence had to be refractory to a minimum of 12 months urotherapy, which consisted of disorder demystification, improvement in the child perception of bladder function and structure, proper toilet posture, normalization of fluid intake and timer assisted scheduled voiding. Pharmacotherapy with anticholinergics for at least 3 months had to be undertaken. Children were excluded when they suffered ongoing fecal problems, had previously tried electrostimulation or drew a suspicion of LUT obstruction, which was the case in 2 children. (30)
**Lordelo et al. - 2009**

A long-term follow-up prospectively studied 36 girls and 13 boys with an average age of 10.2 years (range 5-17) with OAB symptoms. They all underwent TENS with a minimum follow up of 6 months. OAB was defined by “the presence of urgency with or without urge incontinence, an associated bell shaped curve, post void residual urine less than 10% of expected bladder capacity on US, and more than 3 voids daily recorded in the voiding diary.” All children with a neurological disorder, children with anatomical anomalies of the lower urinary tract or children with a follow up of less than 6 months were excluded. All presented with symptoms of urgency and holding maneuvers to avoid urinary loss. Daytime incontinence existed in 43 (88%), and UTI was present in 35 (77%). (27)

**Lordelo et al. - 2010**

They included 19 children with non-monosymptomatic nocturnal enuresis (NMNE), 6 boys and 13 girls with a mean age of 9 years (range 5-17 years). Following inclusion criteria were applied: a history of 5 years or more of at least one episode of nocturnal enuresis per week, symptoms of OAB (urgency with or without urge incontinence), uroflowmetry with a bell-shaped curve, post void residual urine less than 10% of EBC and more than 3 voids per day recorded in the voiding diary. The exclusion criteria were any sign or symptom of neurological disorder or anatomical alteration of the LUT such as PUV, ureterocele or ectopic ureter. One month before beginning TENS, all patient underwent urotherapy. Only patients who did not show improvement of OAB symptoms and maintained NE at least once a week underwent TCPSE. (26)

**Lordelo et al. - 2010**

A randomized controlled trial studied 25 girls and 12 boys with symptoms of OAB. The average age was 7.5 years (range 5-10 years). Female gender was predominant in both groups. Inclusion criteria were: OAB, no PVR urine and bell-shaped curve on uroflowmetry. (31)
Patients with lower urinary tract symptoms secondary to anatomical anomaly or with a neurogenic bladder were excluded. Just as children with a nonresident status or inability to comply with treatment requirements. (31)

All children underwent urotherapy (booklet) and no medication was given before or during treatment. The children were randomized and assigned to either the test group (n=21) or the sham group (n=16). The majority of patients had daytime incontinence and enuresis (n=30), used holding maneuvers to prevent voiding (n=27) and had a history of UTI (n=24). There were no statistical differences in both groups. The 16 children in the sham group underwent active treatment afterwards, where 14 finished all session. In that way they became part of the test group. (31)

Barroso et al.- 2013

They prospectively studied 59 children with OAB without dysfunctional voiding. The population consisted of two groups, one with 22 children who underwent posterior tibial nerve stimulation and the other with 37 children who were treated with TENS, which of the latter will be our focus. Inclusion criteria consisted of: presence of voiding urgency with or without daytime incontinence, bell shaped curve and low PVR volume. If neurological abnormalities, anatomical abnormalities of lower urinary tract or signs of dysfunctional voiding, such as an abnormal uroflowmetry curve and PVR greater than 10% of expected bladder capacity (EBC) or greater than 20ml, were present the children were excluded. None of the children used anticholinergics before or during the study. All patients underwent standard urotherapy.(25)

The group who underwent parasacral TENS (n=37) had a mean age of 7.5 years and consisted of more females (n=25) than males (n=12). Diurnal incontinence was present in 30 (81%), urgency in 33 (89%) and enuresis in 34 (92%) children. (25)
De Oliveira et al.- 2013

The prospective randomized clinical trial included 45 children older than 6 years with primary mono-symptomatic enuresis. Exclusion criteria employed were: age younger than 6 years, presence of NMNE or secondary enuresis, history of treatment for enuresis within 6 months before entering the study or presence of neurological, psychiatric or renal disease. Randomization was done in 2 groups. The control group consisted of 18 children (6 boys and 12 girls) with a mean age of 9.9 years (range 6 to 16). In the experimental group, 27 children (10 boys, 17 girls) were enrolled with a mean age of 9.8 years (range 6 to 14). The percentage of wet nights before treatment was 77% in the CG and 78.3% in the EG. The control group (CG) underwent behavioral therapy and the experimental group (EG) behavioral therapy with parasacral TENS. (29)

An overview can be found in table 1.
### Table 1: Study population

<table>
<thead>
<tr>
<th>References</th>
<th>Level of evidence</th>
<th>Active treatment (n)</th>
<th>Mean age (years)</th>
<th>Type LUTD</th>
<th>Refractory treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoebeke et al.(^{(22)})</td>
<td>Level IV</td>
<td>41</td>
<td>10.5</td>
<td>Detrusor overactivity</td>
<td>All patients</td>
</tr>
<tr>
<td>Bower et al.(^{(23)})</td>
<td>Level IV</td>
<td>17</td>
<td>7.5</td>
<td>OAB and Urge incontinence</td>
<td>refractory symptoms</td>
</tr>
<tr>
<td>Barroso et al.(^{(24)})</td>
<td>Level IV</td>
<td>25</td>
<td>7</td>
<td>Group 1 (TENS); OAB +- urge incontinence</td>
<td>11% of the patients</td>
</tr>
<tr>
<td>Maim-Buatsi et al.(^{(28)})</td>
<td>Level IV</td>
<td>18</td>
<td>9.5</td>
<td>OAB +- Urge incontinence</td>
<td>All patients</td>
</tr>
<tr>
<td>Hagstroem et al.(^{(30)})</td>
<td>Level I</td>
<td>25</td>
<td>8.6</td>
<td>Urge incontinence</td>
<td>All patients</td>
</tr>
<tr>
<td>Lordelo et al.(^{(27)})</td>
<td>Level IV</td>
<td>49</td>
<td>10.2</td>
<td>OAB+- Urge incontinence</td>
<td>Not stated</td>
</tr>
<tr>
<td>Lordelo et al.(^{(26)})</td>
<td>Level IV</td>
<td>19</td>
<td>9</td>
<td>Non-monsoymptomatic Nocturnal Enuresis</td>
<td>All patients</td>
</tr>
<tr>
<td>Lordelo et al.(^{(31)})</td>
<td>Level I</td>
<td>37 *</td>
<td>7.5</td>
<td>OAB+- Urge incontinence</td>
<td>Not stated</td>
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<tr>
<td>Barroso et al.(^{(25)})</td>
<td>Level IV</td>
<td>37</td>
<td>7.5</td>
<td>OAB +- Urge incontinence</td>
<td>None of the patients</td>
</tr>
<tr>
<td>De Oliveira et al.(^{(29)})</td>
<td>Level I</td>
<td>27</td>
<td>9.8</td>
<td>Primary monosymptomatic enuresis</td>
<td>None of the patients</td>
</tr>
</tbody>
</table>

\(^*\) test group + sham who underwent active treatment

\(^**\) On prophylactic antibiotics
Transcutaneous electrical nerve stimulation can be used in several manners by means of a different setting and/or time, a different frequency, intensity or pulse width. The most important reason that the application of TENS is used differently between the studies should be, to find the best and most compliant treatment. Cause only when TENS is applied correctly, on the given times and with the right stimulus that we can evaluate its effectiveness. Can we attribute this heterogeneity to our reasonable way of thinking or are there other factors that play an important roll?

At home or in the office

TENS was administered in 6 studies at the office (24-27, 29, 31) and in 4 studies at home TENS was instructed (22, 23, 28, 30). In all studies the two electrodes were placed bilaterally on each side of the S2-S3 region.

Electrical parameters

Frequency - Hoebeke et al used a low 2Hz frequency. (22) A frequency of 10Hz was used in seven studies. (23, 24, 26, 27, 29-31) In one study a current stimulation at a frequency of 20Hz was used. (25) In one study the frequency was not stated. (28)

Intensity - In nine studies, the intensity was increased to a maximum that could be tolerated by the child. Barroso et al. observed a mean intensity of 22mA, Maim-Buatsi et al. had an adjustable amplitude up to 60mA and the maximum intensity in the study of Hagstroem et al. was 40mA. The mean intensity reached in their active group was 37.7mA. In one study the intensity was not stated. (22)

Pulse width - The pulse width varied from 150 microseconds to 700 microseconds. Five studies used a pulse width of 700µsec (25-27, 29, 31), one group 200µsec (30), one 150µsec (22), and in three this was not stated. (23, 24, 28)
**Application duration of the device and the full treatment time-span**

Hoebeke et al. applied the TENS device for 2 hours daily. If the child responded after a 1 month trial period, treatment was continued for 6 months. (22) Bower et al. applied the device 1 hour twice daily, in the morning before going to school and after coming back from school. Treatment duration varied among the children with a minimum of 1 month. Five children had treatment for one month, nine for 2 months, two for 3 months and one for 5 months. (23) Barroso et al. administered TENS 3 times a week with 20 minutes sessions. The mean number of electrical stimulation sessions was 13 with a range from 4 to a maximum of 20 sessions. (24) We could see the same procedure in three other studies. (25-27) One group’s procedure consisted of 20 TENS sessions. Of the 21 children allocated in the test group, two dropped out earlier. Of the 16 children in the sham group, 14 finished all 20 sessions. (31) TENS was done for 20 minutes twice a day in another group. The mean length of TENS use was 8±7 months. (28) Hagstroem et al. performed TENS 2 hours daily during 4 weeks. The active and sham treated groups showed high compliance with the procedure with a median of 27 days of TENS sessions with a range from 25 to 28 and 23 to 28 days respectively. (30) De Oliveira et al. had TENS applied 3 times weekly on alternate days for a total of 10 sessions. (29)

<table>
<thead>
<tr>
<th>References</th>
<th>At home/Office</th>
<th>Av Treatment duration</th>
<th>Time scheme</th>
<th>Intensity (mA)</th>
<th>Pulses (μsec)</th>
<th>Frequency (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoebeke et al. (22)</td>
<td>Home</td>
<td>4wk (1-6mths)</td>
<td>2hrs/d</td>
<td>Not mentioned</td>
<td>150</td>
<td>2</td>
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<tr>
<td>Bower et al. (23)</td>
<td>Home</td>
<td>4wk (1-5mths)</td>
<td>1hr 2xd</td>
<td>Max tolerated</td>
<td>Not mentioned</td>
<td>10</td>
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<tr>
<td>Barroso et al. (24)</td>
<td>Office</td>
<td>4.4 wks (1.3-6.6)</td>
<td>3x20min/wk</td>
<td>Max tolerated</td>
<td>Not mentioned</td>
<td>10</td>
</tr>
<tr>
<td>Maim-Buatsi et al. (25)</td>
<td>Home</td>
<td>8±7mths</td>
<td>20 min 2/d</td>
<td>Max tolerated</td>
<td>Not mentioned</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Hagstroem et al. (30)</td>
<td>Home</td>
<td>4 wks</td>
<td>2hrs/d</td>
<td>Max tolerated</td>
<td>200</td>
<td>10</td>
</tr>
<tr>
<td>Lordelo et al. (27)</td>
<td>Office</td>
<td>not stated- max 6.6wks</td>
<td>3x20min/wk</td>
<td>Max tolerated</td>
<td>700</td>
<td>10</td>
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<tr>
<td>Lordelo et al. (26)</td>
<td>Office</td>
<td>6.6wks</td>
<td>3x20min/wk</td>
<td>Max tolerated</td>
<td>700</td>
<td>10</td>
</tr>
<tr>
<td>Lordelo et al. (31)</td>
<td>Office</td>
<td>up to a max 6.6 wks</td>
<td>3x20min/wk</td>
<td>Max tolerated</td>
<td>700</td>
<td>10</td>
</tr>
<tr>
<td>Barroso et al. (25)</td>
<td>Office</td>
<td>6.6 wks</td>
<td>3x20min/wk</td>
<td>Max tolerated</td>
<td>700</td>
<td>20</td>
</tr>
<tr>
<td>De Oliveira et al. (29)</td>
<td>Office</td>
<td>3.3 wks</td>
<td>3x20min/wk</td>
<td>Max tolerated</td>
<td>700</td>
<td>10</td>
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</tbody>
</table>
Study procedure

The set-up of the study can learn us more about how the child was treated from day 1 till the end. It can help us in reconstructing “the story” of the study. How was the child evaluated, how many times did it have to come back for treatment and was there a long or short follow-up.

Hoebeka et al.- 2001

Prior to the start, detrusor hyperactivity had to be proved using urodynamics with methods, definitions and units according to the ICCS standards. A one month trial to evaluate the effectiveness of TENS before continuing was done. If there was a positive response to treatment, treatment was continued for 6 months with an evaluation every 2 months. A year after therapy they observed whether the child was cured or relapsed. (22)

Bower et al.- 2001

Before the start of the study all the eligible children had to fill in data needed to meet the protocol requirements. Only these children who completed the data could proceed. The treatment interval was left open beyond one month for each child and progress was checked monthly at the clinic. The duration of treatment was 1 month in 5 cases, 2 months in 9, 3 months in 2 and 5 months in 1. At each clinical visit guided inquiry was made about the practicalities of using neuromodulation as home treatment. One month after cessation of TENS, a final set of follow-up data was requested. (23)

Barroso et al.- 2006

All children were treated first for 1 month with behavioral orientation. If the children were not cured by this procedure, they started with TENS and/or biofeedback treatment. Prior to treatment, evaluation by a noninvasive, urodynamic examination was done that comprised of: a voiding chart completed for > 3 days, uroflowmetry with EMG and a
kidney and bladder ultrasound with an estimate of the PVR. Also a urine sample of each was examined biochemically and cultured. Children came back for evaluation 1 month after the first treatment session and then at 3 months intervals. Mean number of sessions was 13.1 with a mean follow-up of 13.8 months. Before each session data was collected through the parents. Children had to fill in data before the start of the treatment, after the last session and then every 3 months afterwards. In association with treatment, behavioral training was given. (24)

*Maim-Buatsi et al.* 2007

Children with OAB, clinically diagnosed according to the definition of the ICCS, were included in this retrospective study. Anticholinergics were discontinued or continued.

- 10 continued concomitant with TENS use
- 8 discontinued due to lack of efficacy (4) or because of side-effects (4)

At baseline non-invasive uroflowmetry and PVR urine quantification were recorded. This was redone after treatment. Response to TENS was evaluated at each follow-up clinical visit, but they did not state when this follow-up clinical visit was scheduled. Clinical variables were evaluated as well. Mean length of TENS use was 8±7 months and the mean follow-up after starting TENS was 13±9 months. (28)

*Hagstroem et al.* 2009

This study included 27 children with refractory daytime urinary urge incontinence. Two weeks before hospitalization and throughout the study, these children had to stop taking anticholinergics. A week before the first visit, they had to complete the Dry Pie form during 7 days and record a 48-hour frequency-volume chart. They were admitted 3 days to pediatrics. On day 1, a suprapubic catheter was inserted and the children had to fill in an urgency VAS. On days 2 and 3, ambulatory 24-hour natural fill urodynamics and conventional VU were performed to rule out infravesical obstruction and document detrusor overactivity. Children proceeded to neuromodulation when detrusor overactivity was confirmed and no signs of LUT obstruction were present. TENS sessions were done
for four weeks at home and had to be documented. During week 4 they had to fill in Dry Pie forms again and record a 48-hour bladder diary including fluid intake. At the final consult, urgency VAS had to be filled in and children gave their subjective opinion on improvement. The ability to apply the TENS electrodes correctly was verified. (30)

Lordelo et al.- 2009

A Long-term study evaluated children with a minimum follow-up of 6 months. One month before TENS and during follow-up, behavioral training was recommended. Only patients who did not improve significant with this approach moved on to treatment. TENS was done for a maximum of 20 sessions. One month after the last treatment session, children were asked to come back for evaluation. Follow-up visits were scheduled at 3-months intervals during the first 2 years and 6-months intervals thenceforth. The mean follow up ranged from 6-80 months with an average of 35.3 months. (27)

Lordelo et al.- 2010

Nineteen children were included in this study. Initially they were evaluated through a protocol, which consisted of: a detailed, non-validated questionnaire, a 3-day voiding diary, a modification of the Toronto score, an abdominal plain film, a uroflowmetry and a kidney and bladder US with measurement of PVR urine. One month before TENS all patients underwent urotherapy and behavioral orientation for NE. Only patients who did not show improvement, underwent TENS. A maximum of 20 sessions were given. Follow-up appointments were scheduled 1, 3 and 6 months after treatment. After the first 6 months, the intervals prolonged to 6 months subsequently. (26)
Lordelo et al.- 2010

All patients had to keep a voiding diary for 3 days as an assessment tool. Evaluation of the PVR urine was done with the help of an ultrasound. All children underwent urotherapy. TENS was administered in the office for 20 sessions. Right after finishing treatment, patients were reassessed. Patients from the control group who did not improve, continued with 20 sessions of PSTENS. (31)

The outcome was evaluated with the use of 4 criteria, at baseline and at the end of treatment. Average treatment duration was 6.6 weeks. Mean follow-up was 16.2 months with a range from 3 to 29 months. (31)

Barroso et al.- 2013

All patients were prospectively evaluated through a structured questionnaire. All collected data, which consisted of demographic characteristics, symptoms, evaluation, treatment approach and outcome were entered in the database. None of the children used anticholinergics. A professional evaluated the patient before and after treatment. Before treatment children were evaluated by urinalysis, urine culture, uroflowmetry, kidney and bladder US with measurement of PVR and voiding. Before starting treatment, a history of urinary tract infection (UTI) was investigated. Parasacral TENS was done for 20 sessions. Treatment success was evaluated after the last session, for which parents were questioned and children could participate. All patients underwent urotherapy. (25)

De Oliveira et al.- 2013

This randomized prospective clinical trial evaluated children with proven primary monosymptomatic enuresis (MNE). At first a standardized clinical interview consisting of questions about general health status and urinary symptoms to understand the characteristics of the enuresis was done. Parents had to keep a voiding diary for their children as to evaluate frequency, bladder volumes and presence of urgency or
incontinence. In that way they were able to differentiate between mono- and non-monosymptomatic enuresis. Two weeks in advance to treatment a diary of wet nights with the episodes of enuresis was administered. This to have a starting point to evaluate the efficacy of treatment. Urinalysis was done to exclude UTI. The control group underwent behavioral therapy. The orientations were verbally reinforced at every clinical visit, two times a week for the first month and monthly for the next 6 months. The experimental group underwent behavioral therapy and TENS for a total of 10 sessions, 3 times weekly. (29)

After executing the 10 sessions the patients were followed and reassessed every 2 weeks for the first month and monthly during the next 6 months. No furtherance of behavioral orientations were done. A follow-up of 6 months happened. (29)

An overview can be found in table 3.
### Table 3: Study Procedure

<table>
<thead>
<tr>
<th>References</th>
<th>Pretreatment investigations</th>
<th>Data collection</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoebeke et al. (22)</td>
<td>Urodynamics</td>
<td>Evaluation of effectiveness after a one month trial. Afterwards every 2 months</td>
<td>1 year after therapy</td>
</tr>
<tr>
<td>Bower et al. (23)</td>
<td>Fill in data needed to meet protocol requirements</td>
<td>Progress reviewed monthly</td>
<td>1 month after cessation of therapy</td>
</tr>
<tr>
<td>Barroso et al. (24)</td>
<td>A non-invasive, urodynamic examination Urine sample</td>
<td>Parents: Before each session (3x/wk.) Children: Before start of treatment and after last session and then every 3 months</td>
<td>Evaluation 1 month after first treatment session, then at 3 months interval. Mean: 13.8 months</td>
</tr>
<tr>
<td>Maim-Buatsi et al. (28)</td>
<td>Non-invasive uroflowmetry PVR urine quantification</td>
<td>At each follow-up visit</td>
<td>13±9 months</td>
</tr>
<tr>
<td>Hagstroem et al. (30)</td>
<td>Invasive urodynamics Conventional VU</td>
<td>During week 4 and at final consult</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Lordelo et al. (27)</td>
<td>Behavioral training</td>
<td>One month after the last treatment session and at follow-up sessions.</td>
<td>A 3 month interval (first 2 years) 6 month interval thenceforth. Mean: 6-80 months with an average of 35.3.</td>
</tr>
<tr>
<td>Lordelo et al. (26)</td>
<td>Noninvasive urodynamic examination, abdominal plain film, uroflowmetry, kidney and bladder US with measurement of PVR urine</td>
<td>Not mentioned</td>
<td>1, 3 and 6 months after treatment. After first 6 months: 6 month interval</td>
</tr>
<tr>
<td>Lordelo et al. (31)</td>
<td>Voiding diary US; PVR urine</td>
<td>Reevaluation right after finishing treatment</td>
<td>Mean: 16.2 months (range 3-29)</td>
</tr>
<tr>
<td>Barroso et al. (25)</td>
<td>Urinalysis, urine culture, uroflowmetry, kidney and bladder US with PVR volume calculation.</td>
<td>After the last session</td>
<td>6.6 weeks</td>
</tr>
<tr>
<td>De Oliveira et al. (29)</td>
<td>Standardized clinical interview, voiding diary, diary of wet nights, urinalysis</td>
<td>After 10 sessions, every 2 weeks for the first month. Monthly during the next 6 months</td>
<td>6 months</td>
</tr>
</tbody>
</table>
Outcome parameters

The outcome parameters, defined by the authors, are the parameters that will be evaluating effectiveness of treatment. These are the parameters that will tell us if TENS is successful or not. What are for them the improvements that should occur? Are the definitions, used for the several outcome parameters, equal between the studies? Do they use standardized parameters? Are the outcome parameters used consistent and do they make it possible to come to an overall conclusion?

Hoebke et al.- 2001

This study defined response as less detrusor hyperactivity symptoms. Following outcome parameters were used: significant decrease in voiding frequency, increase in bladder capacity and decrease in incontinence frequency. These outcome parameters were calculated with the help of a voiding diary which had to be filled in 1 week before onset of therapy and 1 week before each follow-up visit. In this diary they had to record voiding frequency, bladder capacity, incontinence and urge. At each follow-up visit children were interviewed about their voiding symptoms. (22)

Bower et al.- 2001

They evaluated and compared pre- and post treatment and follow-up measures of urgency, incontinence and bladder storage. Following outcome parameters were used: (23)

1. Response to urgency: calculated with the help of visual analogue scale measuring, rescored at the end of each month.
2. Severity of incontinence: analyzed through change in documentation on Dry Pie, filled in each evening
3. Bladder storage: measured through data out of the frequency volume chart, through monthly 1-day chart reports.

*Barroso et al. - 2006*

They evaluated the effectiveness with following parameters. Success of treatment had to be filled in by the parents before each session with following options: “complete resolution”, “important”, “mild” or “no resolution”. A Visual analogue scale (VAS) was used where 0 represented no improvement and 10 no more symptoms. This number was then multiplied by ten to give a percentage. Children were evaluated by scoring their symptoms, with the help of the dysfunctional voiding scoring system (DVSS). (24)

*Maim-Buatsi et al. - 2007*

They evaluated the response to TENS retrospectively with data from each follow-up clinical visit and according to the ICCS criteria. A minimum of 50% decrease in frequency of daytime accidents was defined as “improved”, completely continent was defined as “dry”. The others were defined as “unchanged”. Secondary outcome parameters were average flow rate, maximal flow rate, PVR urine volume, bladder capacity and uroflow curve, calculated with the help of non-invasive uroflowmetry and PVR urine quantification at baseline and after a course of TENS treatments. (28)

Following clinical variables were taken into account: age, sex, frequency of accidents, duration, previous or concomitant anticholinergic use, daytime and nighttime wetting, and side effects of TENS unit. (28)

*Hagstroem et al. - 2009*

This study defined their outcome parameters clear and good. Primary and secondary outcomes were given.

The primary endpoint was response to treatment, as determined by comparing pre-intervention incontinence scores with scores during intervention week 4. (30)
Incontinence scores were calculated using Dry Pie records, filled in at baseline and during week 4. Response was defined as none, partial, response or complete daytime continence, according to ICCS criteria. (1)

Secondary end points were calculated with the help of 48-hour frequency-volume charts filled in during the week preceding hospitalization and during week 4.

The end points were: number of wet days per week, number of urgency incontinence episodes/day, voiding frequency, MVV and AVV in ml standardized for age, total daily fluid intake, fluid intake before 4pm and response to urgency with the help of VAS. Children gave their subjective opinion on the effect of TENS with the help of a multiple choice of “improved”, “unchanged”, or “worse” before revealing the type of TENS. (30)

Lordelo et al. - 2009

They evaluated the effectiveness with a questionnaire, filled in by the caregivers, according to the ICCS criteria concerning the presence of OAB symptoms. Initial outcome was then defined as: “nonresponse”, “partial response”, “significant response” or “full response”. The outcome was only based on daytime symptom resolution, persistence of nocturnal enuresis was not considered a failure. Parents rated symptom improvement qualitative and quantitative. Qualitative the parents had following options: “complete”, “significant”, “mild” or “no improvement.” Quantitative they had to rate the percentage of improvement on a scale of 0-100%. Long-term outcomes were defined as “relapse”, “continued success” or “complete success”. Of which the latter meant that there was no relapse after 2 years of treatment. (27)

Lordelo et al. - 2010

This study evaluated the effectiveness of TENS with a questionnaire according to the definition of ICCS. Caregivers could choose out: “non-response”, “partial response”, “response” or “full response” conforming the decrease in symptoms. (26)
**Lordelo et al.- 2010**

This study used 4 outcome parameters. (31)

1. Improvement of the child filled in by the parents, who had following options: “improved significantly”, “mildly” or “not at all”.
2. Improvement scored by the parents with the help of VAS 0-10 where 0 equals no improvement and 10 equals complete resolution of symptoms.
3. DVSS through the non-validated adapted Toronto score before and after treatment.
4. Number of voids daily, AVV and MVV before and after treatment evaluated with the help of a voiding diary.

**Barroso et al.- 2013**

This study evaluated treatment success with a DVSS and with a score of improvement through VAS. All data were filled in by the parents with the help of the children when possible. Parents were also verbally questioned about the resolution of urgency, diurnal incontinence and enuresis. (25)

**De Oliveira et al.- 2013**

This study evaluated the results according to the ICCS standardization. “No response”, “partial response”, “response” or “full response”, were an indication of the decrease in wet nights. The average rate of improvement was calculated with the formula of “improvement in %”= (100- (wet days after treatment/wet days before treatment)). (29)

An overview can be found in table 4.
<table>
<thead>
<tr>
<th>References</th>
<th>Voiding diary</th>
<th>Dry Pie</th>
<th>VAS</th>
<th>Frequency volume chart</th>
<th>DVSS</th>
<th>Improvement (qualitative or quantitative)</th>
<th>Treatment success (ICCS)</th>
<th>Non-invasive uroflowmetry</th>
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</thead>
<tbody>
<tr>
<td>Hoebeka et al.</td>
<td>x</td>
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<td>Bower et al.</td>
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<td>Maim-Buatsi et al.</td>
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<td>Hagstroem et al.</td>
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<td>De Oliveira et al.</td>
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</tbody>
</table>
Outcome results

The outcome results of the studies are our main focus. Did TENS prove his effect? In which circumstances? When was TENS not effective, could there be found a reason why? Had TENS a long-term effect? And are all the results from the different studies consistent so that we can make an overall conclusion about the effectiveness?

_Hoebeke et al._- 2001

**After one month trial therapy**
15 boys and 13 girls presented with an increase in bladder capacity, decrease in urge, decrease in incontinence and/or improved sensitivity. Thirteen children showed no response of which 9 boys lacked motivation and 4 didn’t show a clinical effect regardless of motivation. (22)

**After 6 months therapy**
A significant increase in bladder capacity, decrease in daily voiding frequency and decrease in incontinence periods per week were marked. (22)

**One year after therapy**
Twenty-one of 41 children were definitely cured (51.2%), 7 children relapsed. (22)

_Bower et al._- 2001

Three outcome parameters were evaluated.
About the response to urgency a significant decrease could be seen.
Concerning the severity of incontinence, 73.3% reported improvement in continence. Seven became dry, 4 were less incontinent and 4 showed no improvement. There was a significant difference between the number of dry days before and after treatment.
For the bladder storage results only 58.8% of the patients completed the frequency-volume chart. Eight reported significant increase in voided volumes at the end of treatment and the mean maximum storage increased from 141ml to 196ml. (23)
**Barroso et al. - 2006**

Two groups were evaluated. Patients of group one were treated with TENS and the second group of patients was treated with biofeedback training.

**Group one - TENS**

This group consisted of 19 children of whom twelve had a complete clinical improvement, six a significant and one showed a mild improvement. The VAS showed an improvement of 100% in 12 children, 90% in 5 children, 80% in 1 child and 30% in 1 as well. Of the six children who showed a significant response, three were completely resolved of their urgency symptoms but daily UI was sporadically present. The other three children’s daily UI resolved but after all they had episodes of urgency. (24)

**Group 2 - biofeedback**

This group comprised of 17 children of whom ten showed a complete improvement, two a significant and 5 a mild improvement. The VAS showed an improvement of 100% in 10 children, 90% in 1, 70% in 1, 50% in 1, 40% in 2, 20% in 1 and 10% in 1. The parents of 11 children were satisfied, 6 children had salvage therapy with electrical stimulation. Of these six, 4 improved by 100% and 2 by 90% and 40% respectively. Thus four showed complete resolution, one a significant and one a mild improvement. (24)

When we look at the 25 children who got TENS, 16 showed complete resolution (64%), 7 a significant response (28%) and two a mild improvement (8%).

**Maim-Buatsi et al. - 2007**

Fifteen patients were evaluated with incontinence and 3 with only urgency/frequency. Of the 15 patients with incontinence: 2 became dry, 9 were significantly improved and 4 reported no improvement. Marked urinary frequency was seen in 12 of which 8 had significant subjective improvement. Of the 7 patients with nocturnal enuresis, one became dry and 6 showed no improvement.
Two children stopped treatment early with no improvement. In one this was due to discomfort, the other quit treatment due to a sensation of decreased stimulus to void. Overall there were 14 out of 18 children compliant with the therapy. (28)

No prognostic factors showed a significant difference between the group that improved with TENS and the group that did not. On the uroflowmetry/PVR data, no significant change in peak or average uroflow, bladder capacity, or PVR urine volume before and after TENS use was seen. A parabolic post-TENS curve showed a statistically significant correlation with patients who became dry or improved. (28)

Overall the study concluded with a 73% improvement rate at 13 months follow-up. (28)

Hagstroem et al.- 2009

Active TENS group
This group consisted of 13 children of which 8 (62%) showed a partial response, 5 (38%) showed no response and none showed a significant or full response. Ten children (77%) reported a subjective effect after treatment. This group showed a significant decrease in incontinence scores, wet days per week, number of daily urge incontinence episodes and improved response to urgency. All of these were not seen in the sham treated group. (30)

No differences were seen between responders and non-responders concerning the number of completed TENS sessions or stimulation in intensity. Also no differences were seen between the secondary end points of responders versus non-responders. (30)

SHAM group
This group consisted of 12 children of whom one showed a partial response and one full. Five children (42%) reported an improvement after treatment (not significant).
Active group vs. SHAM group
The differences between the 2 groups were only found in the number of pretreatment wet days per week. The change in scores of the pre-intervention and post-intervention endpoint parameters were calculated. The scores of wet days per week and incontinence episodes per day were higher in the active group than in the sham treated group. Although it did not gain statistical significance, they observed a tendency toward a more marked decrease in incontinence scores in the active group. Bladder reservoir function did not change in both groups. (30)

Lordelo et al. - 2009
Reported an initial and long-term success of treatment with TENS. (27)
Initial success (27)
When we looked at all symptoms together a full response was seen in 36 (77%), response or partial response was seen in 3 (6%) and no response in 8 (17%) children.
A total of 49 children presented with symptoms of urgency. Full response for urgency was reported in 37 (79%), response or partial response in 3 (6%) and no response in 7 (15%).
Incontinence was present in 43 children. After TENS, 31 (76%) children showed a full response, 2 (5%) reported response or partial response and 8 (20%) showed persistent symptoms.
Parents reported a percentage of symptom improvement. 25 parents reported a 100% improvement, 6 a 90 to 99%, 2 a 80 to 89%, 3 a 50-59% and 1 less than 50% improvement. Data were missing for 12 patients.

LT success (27)
Of the 49 children who presented with urgency, 41 (84%) showed continued success and 8 relapsed (3 had persistent symptoms, 5 improved only after anticholinergics)
Daytime incontinence had a continued success in 32 of the 43 children (74%). Eleven children relapsed of which 3 showed significant improvement, 4 had persistent symptoms and 4 resolute after anticholinergics.

When we look at all the symptoms presented, 38 showed continued success (74%) and 11 patients relapsed (22%).

Thirty-five children presented with UTI before TENS. Thirty-three (94%) showed continued success and two relapsed (6%).

Before treatment nocturnal enuresis was present in 32 children. Of these, 24 (75%) had resolution of symptoms, 8 (25%) persisted.

A total of 30 patients could be followed 2 years or more where complete success could be reported in 22 (73%) while 8 (27%) showed relapses. After a full response, 3 patients (10%) had symptoms reappear soon after the procedure.

Lordelo et al. - 2010.

This study evaluated a population of 19 children with NMNE. When we look at nocturnal enuresis 8 (42%) resolved completely, 4 (21%) showed a partial response, 6 (32%) showed no change, and 1(5%) had increased intensity. The Toronto score of following pretreatment variables: UTI, urge incontinence, frequency, voiding difficulty, nocturnia and constipation, could not predict failure. A 100% resolution of daytime symptoms was seen in 13 patients of which 7 also showed complete resolution of NE. Seven patients did not described a full response but one of them on the other hand did resolve of the nocturnal enuresis. (26)

Lordelo et al. - 2010

This randomized controlled trial included 21 patients in the test group and 16 in the sham group.
Improvement quantitative and qualitative (31)
A complete improvement in 61.9% (13) and a significant improvement in 38.1% (8) was documented in the test group. In the sham group none showed complete resolution and 31.3% reported significant improvement. The VAS scores of the test group were between 5 and 10 of which 13 patients gave the highest score. The sham group reported a score between 1 and 9 of which 10 gave a score below five.

The sham group underwent PSTENS afterwards. Fourteen children underwent all 20 sessions, one child stopped at session 18 with a 100% improvement. Another child was not compliant and abandoned treatment at session 14 with a 70% improvement. Overall, a 100% improvement was seen in 13 (81.25%) and a significant improvement in three (18.75%)

Dysfunctional voiding scoring system - Modified Toronto score (31)
Statistically they could note a difference in the DVVS scores before and after treatment with a greater significant reduce in the test group.

Voiding diary (31)
Mean voided volumes and average voided volumes increased significant in the test group, this was not a statistical significant difference in the control group.
A significant decrease in the number of voids daily was seen when compared with the test group.

Final results (31)
Full response in 26 (70%) and partial response in 11 (30%) patients. Six children had persistent incontinence right after treatment. Recurrence after a mean follow up of 16.2 months was seen in 4 (10%). Four presented with UTI, for which one was operated, one improved significant but postponed voiding, in one OAB and UTI recurred after a period
of complete improvement in symptoms and one presented with UTI at session 15 and disappeared for follow-up.

*Barroso et al- 2013*

As the focus of our study lies on TENS, we only evaluate these subjective outcomes. The VAS reflected the improvement as seen by the parents. A full response was present in 70% of the parasacral TENS group. A significant decrease in DVSS scores after treatment in both groups could be observed. Only 12% had persistent urgency symptoms, 20% persistent diurnal incontinence and in contrast with these results, a greater part, 59% of the patients still had nocturnal enuresis. (25)

*De Oliveira et al.- 2013*

This study noticed a decrease in wet nights in both groups. Improvement in wet nights was 37.3% in the control group and 61.8% in the experimental group. In the EG 15% showed a response to treatment, 56% a partial response, and 30% showed no response. In the control group these percentages were 6%, 33% and 61% respectively. None of the patients showed a full response. (29)

An overview can be found in table 5.
### Table 5: Significant outcome results

<table>
<thead>
<tr>
<th>References</th>
<th>Bladder capacity</th>
<th>Urge</th>
<th>Incontinence</th>
<th>Nocturnal enuresis</th>
<th>Initial Success</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoebeke et al. (22)</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td>After 1 month: 68%</td>
</tr>
<tr>
<td>Bower et al. (23)</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td>Improvement: 73.3%</td>
</tr>
<tr>
<td>Barroso et al. (24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maim-Buatsi et al. (28)</td>
<td>Unchanged</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td>Complete improvement: 64.4%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No significant</td>
<td>Significant: 28%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>change</td>
<td>Mild: 8%</td>
</tr>
<tr>
<td>Hagstroem et al. (30)</td>
<td>Unchanged</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td>Partial response: 62%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No response: 38%</td>
</tr>
<tr>
<td>Lordelo et al. (27)</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td>Full response: 77%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Partial response or response: 6%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No response: 17%</td>
</tr>
<tr>
<td>Lordelo et al. (26)</td>
<td></td>
<td>↓</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lordelo et al. (31)</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td>NE:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Complete resolution: 42%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Partial: 21%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- No change: 32%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>- Increased urgency: 5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Daytime symptoms: 68% showed a 100% resolution</td>
</tr>
<tr>
<td>Barrosso et al. (25)</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td></td>
<td>Full response 70%</td>
</tr>
<tr>
<td>De Oliveira et al. (29)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Response: 15%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Partial response: 56%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No response: 30%</td>
</tr>
</tbody>
</table>
Meta-analysis

A meta-analysis was undertaken with 5 studies that all used the same standardized outcome parameter according to the ICCS criteria. Initial success is defined as a complete response when a 100% reduction of the symptoms can be seen, a partial response as a 50-99% reduction is marked and no-response when less than 50% reduction in symptoms is observed. (32) Events belonging to the criteria are set out against the total events.

The first meta-analysis was done to see which children benefited from TENS application, with a partial response or full response.(Fig 1) When we look at the results of this meta-analysis, we can see a quite consistent outcome. There is no heterogeneity (I-squared=0%) observed across the studies so that we can generalize the individual results to an overall conclusion. The overall measure of effect shows that 70% of the patients that underwent TENS show a partial or full response, with a rather narrow confidence interval of 61%-77%.

As for a full response (Fig 2), the heterogeneity across the studies is high (I-square=87.2%). The evidence cannot be described as consistent. This reduces the recommendations about treatment if our aim for the treatment of TENS would be a full response. Only 21% of the overall patients show a full response with a wide confidence interval. None of the patients showed a full response in two studies in contrast with one study where a full response in 73% of the patients could be seen. This heterogeneity has to be found due to the heterogeneity in the studies rather than chance. In the discussion we try to find what can be the cause of this. Is it due to the study population, the study design or rather the study procedure? And as with this result, we have to make a critical analysis of what our goal is when we treat children with TENS and what the patients can expect of their treatment.
Figure 1: Full and Partial Response to TENS

![Figure 1: Full and Partial Response to TENS](image1)

Figure 2: Full Response to TENS

![Figure 2: Full Response to TENS](image2)
Discussion

Study design

Only 3 studies (29-31) conducted a randomized controlled trial of which two used sham. With the use of sham, patients do not know whether they get the treatment or they don’t, which reduces bias when it comes to results delivered by them. Hagstroem et al. was the only one to start a double-blind randomized controlled trial and thus when we discuss the results it is important to keep in mind that his study, even without the knowledge of used criteria, has the highest level of evidence. Bias in this study is reduced to a minimum, as the investigators as well as the patients were blinded. Nevertheless we should recognize that sham might result in a placebo effect which makes it difficult to estimate the real effect of TENS.

Most of the studies were prospective without control group and so without the ability to compare the results. The outcome can therefore be a result of a single TENS effect but also a result of a range of other variables or prognostic factors. These variables should be taken into account. In prospective studies bias, such as loss of individuals to follow-up, should be avoided. Prospective studies usually have fewer possible sources of bias and confounding than retrospective studies.

Study population

When we look at the study populations used (table 1), a big heterogeneity should keep us from drawing too big assumptions. When it comes to defining the type of lower urinary tract disorder, the differences are there especially for OAB and dysfunctional voiding. Not every study used the definitions there are nowadays described by the ICCS. Some of the studies pre-dated the ICCS criteria, others did not use it. Above that, we have populations with OAB, OAB with detrusor hyperactivity, OAB without dysfunctional voiding, NMNE, MNE,… On one hand it gives us a good view for which indications
TENS can be used but on the other hand this makes it hard for comparing keeping in mind that studies for TENS in children are already sparse.

The way how the study population is defined is not always very detailed. A lot of children included were refractory to treatment but what does refractory mean, for which treatments and for how long were they refractory. We can assume that this factor can have an influence on the outcome. Patients refractory to other treatments are probably harder to cure than the same group of patients that present with the same dysfunction but not with such a history. In two studies (25, 29) none of the patients included had treatment before, this can result in more positive outcome results than in the others. Two studies did not state whether patients already had treatment or not. (27, 31) Severity of incontinence is another aspect that is poorly described. Incontinence episodes however did not seem to have a statistically significant influence on responding or not responding to TENS. (30)

Concerning the exclusion criteria, all studies excluded children with anatomical and neurological anomalies. Other exclusion criteria are mainly chosen to prevent outcome bias, for example the maturation of the child’s bladder, history of treatment or other problems related with LUTD.

Mean age ranges from 7 to 10.5 years. We have to be careful with the results of Barrosso et al. (24) Of the 36 children examined, 17 children (47%) were between 3 and 5. The ICCS terminology however states that urge is only applicable when bladder control is attained or children are above 5. He does exclude children who haven’t been toilet trained but this doesn’t mean that these children already attained bladder control at that certain age. This can influence his outcomes positively as these children can attain bladder control through natural maturation.
Nocturnal enuresis was concomitant present in eight out of ten studies, of which in two it specifically includes children with this pathology. In the two other studies it is not stated whether the child also suffers from enuresis.(22, 23) The presence of children with UTI, a common concomitant disease present in children with lower urinary tract disorder, is more shattered. In some studies UTI was present, others excluded this and some put the children with proven UTI on prophylactic antibiotics before the start of, and during the study. It is hard to tell whether these children should or shouldn’t be excluded. Children who are not excluded might lean closer to the real-life population that is eligible for TENS. Above that there might be a chance that TENS also has a positive effect on (recurrent) urinary tract infections. As this was proven in the study of Barrosso et al.(24) On the other hand excluding patients that suffer from UTI makes the study population more homogenous as it can have an influence on the outcome results and should thus be seen as a prognostic factor. Patients presenting with UTI might be harder to treat than patients in the study group who didn’t present with UTI. Two studies examined this difference through comparing the response group with the non-responders. A statistical difference could not be found concerning UTI. (26, 30) Inclusion of UTI as a pre-treatment variable and comparing if there is a difference between non-responders and responders, is of an added value.

The studies obtained do strive, to my opinion, to find patient groups that will benefit from TENS. In these studies they still explore the possibilities with different study populations, which can be justified as there aren’t many studies available about this topic. Nevertheless the aim of this exploration should be to find the right indications where TENS can be used so that in the future all these studies will lead to clear standardized guidelines for the use of TENS.
Application of TENS

As we could see out of the table, there isn’t an accepted standard on how to use TENS. The time scheme, frequency used and pulses vary. The maximum frequency used is 20 Hz as a frequency of more than 20Hz may be hazardous because it excites the neuromotor system, which increases pelvic floor muscle tension. What we can see is that the time scheme with at-home TENS is done daily whether TENS done in the office is 3 times a week. This probably as to make it attainable for the patients. If we make a comparison between both, they both have their advantages and disadvantages as seen in the table below.

<table>
<thead>
<tr>
<th>TENS AT HOME</th>
<th>TENS IN THE OFFICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>3x a week</td>
</tr>
<tr>
<td>Free to choose when to apply TENS</td>
<td>On appointment</td>
</tr>
<tr>
<td>Familiar surrounding</td>
<td>Clinical setting</td>
</tr>
<tr>
<td>No transfer</td>
<td>Transfer to hospital</td>
</tr>
<tr>
<td>Compliance cannot be checked</td>
<td>Good eye on compliance</td>
</tr>
<tr>
<td>TENS application done right?</td>
<td>TENS applied correctly</td>
</tr>
</tbody>
</table>

In the end it is hard to tell which surrounding is preferred. It probably depends on what the patients and their parents see as the easiest way. Some of them will prefer to stay at home and should take the responsibility to apply TENS each day in a correct way. Others will perhaps be more compliant if they are forced to come to the hospital. For these people, who don’t feel so secure to take the responsibility, in the office TENS will be the right choice. When we look at studies to investigate the effectiveness of TENS, we might prefer TENS in the office as we will be able to evaluate with a greater certainty the compliance of the patient and the correct application so that our results are not biased when it comes to these factors. But the results between the studies who’ve done TENS at
home and these done in the office don’t differ that much. And the differences are likely
due to other variables then application, duration and scheme. Leaving the option open to
the patients and their parents will lead to patient empowerment and shared decision
making which are both good for better compliance.

**Study procedure**

The study procedure is not always described in a comprehensive and structured way.
Pretreatment investigations include non-invasive or invasive urodynamics, ultrasound,
abdominal plain film, clinical interview, voiding diary, uroflowmetry, urinalysis, etc.
Some investigations are needed to confirm the diagnosis, others will be part of the
evaluation as objective parameters.

Flow measurement is a cornerstone of the diagnosis in children after toilet training. As
toilet training normally proceeds TENS treatment, this examination should be done.
Dysfunctional voiding is observed through uroflow measurements. Urodynamic studies
investigate the filling and emptying phase of bladder function and are necessary to affirm
that children present with detrusor overactivity. Hoebeke et al. proved detrusor
overactivity in a correct way according to ICCS criteria.

Data collection is done before and after treatment and depending on the study procedure
also during treatment and follow-up period. Data collection evaluates the effectiveness of
our study. Of course the differences between the pretreatment outcome parameters versus
the post-treatment outcome parameters are very important. But regular data collection
gives you the chance to verify if the patient is responding to TENS, still compliant to
treatment and to repeat the treatment protocols. It gives the patient the opportunity to
discuss problems they are having. More frequent visits to the therapist may also permit
greater action of the placebo effect, which may increase the effectiveness of the method.
Regular checking to see if the voiding diary is filled in correctly can be especially of a
value for these children who are treated at home. However the more data collection, the
more dedication there is needed from the patient. In the study of Bower et al. only 58.8% completed the frequency volume chart. This might be due to the inconvenience of collecting volumes and charting or due to a lack of motivation if symptoms were unchanged following treatment. (23)

In some the progress was reviewed monthly, in others at each follow-up visit and in the RCT of Hagstroem et al. the progress was evaluated right after a treatment period of 4 weeks. For compliance, regular follow-up appointments are important, for initial response, the follow-up has to be scheduled right after treatment and to see if treatment has a long-term effect, and to conclude complete success a follow-up of two years is needed. There are studies with data concerning the initial effect of TENS treatment, other studies conducted a long-term follow-up and in some studies it was vaguely described how long the follow-up took place. (see table 3)

Urotherapy is in almost all studies given concomitant with TENS therapy. In three studies it is not stated and in one study all patients had to be refractory to a minimum of 12 months urotherapy. They however do not state whether these guidelines were reinforced and had to be continued. Nevertheless the importance of urotherapy is proven and as it is a non-interventional approach, children can only benefit from this. Because in the contemporary setting, urotherapy will be a part of the treatment, it seems only normal to include this when evaluating therapy with TENS.

Concerning medication Hoebeke et al. and Maim-Buatsi et al. let their study group choose to either stop or continue with medication. This should be taken into account. In one study it was not stated and in seven studies no medication was taken.

As seen out of the table, a protocol would be of great benefit. The study procedures differ in so many ways. To be able to compare results, the set up should be similar, which is not the case here.
When it comes to evaluating the effectiveness of TENS, outcome parameters should be carefully chosen. The ICCS advises researchers who study children with daytime continence to assess and document 4 parameters namely incontinence, voiding frequency, voided volumes and fluid intake. All these parameters can be extracted out of a voiding diary if following data are included: a 48-hour documentation of voiding with timing and volume, 14 days documentation of daytime incontinence episodes and a minimum 48-hours documentation of fluid intake volume, timing and type.

When we look at the table (see table 4), the outcome parameters used are somehow similar. The parameters described in a voiding diary can include the outcomes that we extract out of Dry Pie forms, VAS scores and frequency volume charts. As for improvement scores, it is a subjective though important factor. Subjective relieve doesn’t always mean objective positive results but still what patients and parents believe to be an improvement might be of a more important value. Not every patient needs an objective 100% success rate, some will be happy with lower percentages. Improvement rated by the parent or child gives us more information about how the patient experiences the treatment success. Nevertheless it can also overestimate the effects of TENS. That’s why when studies incorporate subjective outcomes, it might be a good idea to have a long-term follow up, just as Lordelo et al. did with his RCT. People’s opinions vary from the moment and changes that occur. If the child for example went from 8 times wetting his pants to three, this will be seen for the parents as a significant improvement. Nevertheless if the child does not improve in the coming months and it stays incontinent, parents will readjust their opinion and will rate differently.

Treatment success is a standardized outcome according to ICCS criteria. As we made a meta-analysis of this outcome parameter, this will be further discussed below.
When we look at the studies conducted, Hagstroem et al. level I evidence study might be the one that covered the most objective parameters. The drawback is the short-term follow up. Some studies only used subjective parameters. Lordelo et al. long-term study is one of them. They counter this bias by saying that the satisfaction of the parents and patients are more important in their opinion than the lack of objective parameters such as urodynamics. (27) Barrosso et al. results are also only based on subjective data, and so prone to error because the impression of the parents about the outcome can vary at any given moment according to their beliefs, as we already discussed above. (25) Two other studies rated as well the success rate subjectively by improvement of symptoms. (24, 31) Overall when we discuss the results, it will be important to make a difference between the results that are objective and those who are subjective.

**Outcome results**

The outcome results in all studies are positive regarding to TENS treatment. In some studies a greater overall success is seen than in others but they all come to the same conclusion. TENS is a non-invasive and easy to apply device without side-effects which should be considered as therapy when children are refractory to first-line treatment. As a lot of studies state, compliance is a very important factor. The importance is great to make people aware of the daily or three times weekly appliance. We don’t see a big difference between the outcomes of patients treated at home or in the office. It is a matter of preference according to the advantages they both have, outlined above.

We can see an overall significant decrease in incontinence and urge. Except for the study of Barrosso et al. the following remark is needed. The table that is given shows us the results of both biofeedback and TENS treatment. These numbers concerning continence, urgency, nocturnal enuresis and UTI outline a significant decrease but it makes it rather impossible to estimate the effect TENS had as the results aren’t outlined separately. (24)
For bladder capacity the results are not coherent. Two studies don’t see any change in bladder capacity \(28, 30\) whereas three state an increase\(22, 23, 31\) These differences might be confounded as two studies used anticholinergics\(22, 28\) A more accurate result should be found in those studies that used invasive urodynamics. \(22, 30\) When we combine both factors Hagstroem et al. had the best circumstances and he could not note a significant change in bladder capacity. \(30\)

As for nocturnal enuresis, we do see a decrease in some studies but not as outspoken as the incontinence. Enuresis depends on 3 factors namely polyuria, nocturnal bladder overactivity and arousal and sleep mechanisms. It can thus be caused by extrinsic factors which tend to respond good on behavioral therapy but also by intrinsic factor on which TENS would possibly have a positive effect. Still confirmation is needed as in all studies that examined nocturnal enuresis, a marked population still showed no improvement. In the study of De Oliveira et al. where only children with mono-symptomatic enuresis were included, none of them showed complete resolution\(29\) In the study of Barrosso et al. 59\% of the patients had persistent enuresis. In the study of Lordelo et al. with children who suffer from NMNE, 63\% showed a partial or complete resolution, 32\% showed no change and 5\% showed increased urgency\(26\) The discrepancy between these result might be because of a different underlying physiological cause.

Children with OAB with or without daytime incontinence are a good indication for treatment with TENS, which should be considered as a second-line therapy after behavioral training. In contrast with medication, it has no side-effects.

Concerning nocturnal enuresis, we should be prudent, TENS would rather be a third-line treatment.

The reason why some children don’t response to TENS treatment remains an unanswered question. Pretreatment variables did not show to have an effect on TENS outcome. For example in our level I evidence study of Hagstroem et al. no differences could be found
between responders and non responders in regard to gender, age, uroflow configuration, fecal problem history, UTI history, pre-intervention incontinence scores, episodes of wet days per week, voiding frequency, VAS scores or fluid intake. Also no differences were seen in MVV or AVV. (30) Other studies came to the same conclusion. (26, 28)

*Meta analysis*

As we can see out of the meta-analysis, TENS is an effective treatment in decreasing symptoms. An overall of 70% of the patients shows a 50-100% decrease in symptoms. As when it comes to full response, the heterogeneity is big due to discrepancy between the studies. Below a table is outlined which can give us an explanation of these results. (table 7)

Three studies used subjective parameters to evaluate initial success. Discrepancy between objective improvement in incontinence, as reflected in measured parameters, and subjective relief of symptoms as reported by patients has the tendency to overestimate the cure rate in TENS studies. This can be supported as these studies show an overall higher rate in both full and full-partial response.

Only De Oliveira et al. did not support this probability. This can be because of his study population, which consisted of children with primary monosymptomatic enuresis. This population might not have the best indications for TENS treatment as outlined above. Lordelo et al. who also studied children with enuresis but more precisely non-monosymptomatic enuresis did show a subjective full response. This discrepancy might be explained due to other mechanisms involved in this dual pathology. Besides, enuresis can be present as a consequence of the daytime symptoms, who have a different pathophysiology. If these daytime symptoms are addressed, the nighttime symptoms will disappear as well.
Besides that we should also keep in mind that in many studies TENS has been used after other therapies were tried out, as for example anticholinergics. The majority of patient groups were refractory to treatment. They might be a more difficult group to cure.

The two studies that rely on objective outcome parameters differ in a big way. One of them is a retrospective study without control group where some patients continued on anticholinergics and others stopped. This can influence the results positively. Retrospective studies are also more prone to bias. Hagstroem et al. is the one with the most reliable study. The RCT has a level I evidence, used objective parameters to evaluate the initial success, stopped anticholinergics and showed results that are the least influenced by bias. Nevertheless as we can see out of these remarks, good objective standardized outcome parameters are needed.

TENS does show good results. The fact that the initial success may not lead to a full response, shouldn’t keep patients away from using it. A 100% guarantee may not be given, but for these children who are refractory to urotherapy, it is worth the try. Patients will be more happy to see progress. Progress is important in this condition as the patient is still maturing. TENS can give this process a helping hand to reach full bladder control.

Overall the lack of good quality studies and objective standardized parameters makes it impossible to see TENS as a “black or white” treatment. A good comparison between studies cannot be done. The bigger part of the studies show good effects and the more we’ll use TENS, the more we will know which people would benefit and which patients would not. It doesn’t do harm and positive results can be seen in the short term. Some patients, the fortunate few, will benefit from the first minute. Others will need combination therapy, more time, or a better follow-up to reach full recovery.
In summary those children, suffering from dysfunctional voiding and refractory to first-line treatment, should be given the opportunity to try TENS treatment because only with trial and hopefully not error, patients can be given the best possible treatment.

Table 7: Possible influential factors on the outcome

<table>
<thead>
<tr>
<th>References</th>
<th>Design</th>
<th>LUTD (Stage)</th>
<th>TENS (duration)</th>
<th>ACh</th>
<th>Outcome parameters</th>
<th>Full/partial response (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maim-Buatsi et al. (28)</td>
<td>Level IV</td>
<td>OAB (refractory)</td>
<td>2x20min/d (8±7mths)</td>
<td>Yes</td>
<td>Objective</td>
<td>11/61</td>
</tr>
<tr>
<td>Hagstroem et al. (30)</td>
<td>Level I</td>
<td>OAB (refractory)</td>
<td>2 hours/d (4 weeks)</td>
<td>No</td>
<td>Objective</td>
<td>0/62</td>
</tr>
<tr>
<td>Lordelo et al. (27)</td>
<td>Level IV</td>
<td>OAB (not stated)</td>
<td>3x20min/wk. (max 6.6wks)</td>
<td>No</td>
<td>Subjective</td>
<td>73/80</td>
</tr>
<tr>
<td>Lordelo et al. (26)</td>
<td>Level IV</td>
<td>NMNE (refractory)</td>
<td>3x20min/wk. (max 6.6wks)</td>
<td>No</td>
<td>Subjective</td>
<td>42/63</td>
</tr>
<tr>
<td>De Oliveira et al. (29)</td>
<td>Level I</td>
<td>MNE (primary)</td>
<td>3x20 min/wk. (3.3 wks.)</td>
<td>No</td>
<td>Subjective</td>
<td>0/70</td>
</tr>
</tbody>
</table>
CONCLUSION

Transcutaneous electrical nerve stimulation showed to be a good treatment. It was more effective than sham in randomized controlled trials treating OAB. An overall of 70% of the patients shows a 50-100% decrease in symptoms. Especially incontinence and urge show a significant decrease. For bladder capacity the results are less coherent, it looks like it remains unchanged but further studies are needed for confirmation. Most of the parents rated subjectively a significant improvement. This feeling is of importance for knowing how the patient experiences the treatment success. But we should keep in mind that people’s opinions vary from the moment and changes that occur. A long-term follow-up study would be the best solution as to know whether the effects remain or not.

As for nocturnal enuresis the results are less consistent and we should be prudent. The etiology is multifactorial. It can be caused by extrinsic factors which tend to respond good on behavioral therapy but also by intrinsic factor on which TENS would possibly have a positive effect. We could see that a marked population showed no improvement. Therefore after urotherapy, other treatments such as an alarm clock or medications, who have shown to be effective, should be the second-line treatment. As a third-line therapy, TENS can be taken into consideration.

Only 21% of the overall patients showed a full response. These results cannot be generalized due to the big heterogeneity between the studies. Some show full response, others don’t observe a 100% improvement. The big range makes it impossible to conclude that TENS shows a full response but neither can we say that it will never result in cure. Because of that we have to be careful of the promises we make to the patient. The goal that should be set out is cure, but the way to it can consist of more than TENS treatment.
More long term effect studies are necessary. Especially for those studies who only use subjective parameters as an outcome. According to the ICCS, we can only speak of complete success after a follow up of 2 years. Few studies followed their patients for a longer time, of which only one had a two year follow up.

Following remarks should be made. First of all, there is still a big lack of level I evidence studies. Only two were conducted concerning OAB, of which one used objective criteria. Secondly population groups differed through the several studies. Not only by characteristics but also by diagnosis. TENS application was diverse, for example some used sham, others didn’t, or the application duration varied among the studies. The study procedure was variable as well regarding pretreatment investigations, data collection, the follow-up period, medication,… Even the outcome parameters used are irregular between the studies. Despite this variety the results are consistent and indicate that TENS is effective in treating children with bladder dysfunctions.

There is a need for more level I evidence studies with population groups defined according to the ICCS criteria. As children suffering from OAB with or without incontinence seem to show the best indication, they might be our best point of interest. Urotherapy should remain the first-line treatment. If urotherapy fails, uroflow measurement is a necessary pretreatment investigation. Standardized objective outcome parameters are needed as the best study procedure can only be found by comparing studies who use the right and same indications. The ICCS recommends to use following 4 parameters namely incontinence, voiding frequency, voided volumes and fluid intake. On top of that it might be good to let the patients or parents fill in a validated questionnaire about the quality of life as to know what the child experiences before, during, and after treatment. Application of TENS at home or in the office can be conducted to patient preferences as no big differences were noted. Long-term effect outcome studies of two years are required and would give us more information on success rate, relapse and the placebo effect that could have been present at the initial response.
TENS is a non-invasive, easy to apply device with rarely side-effects that showed promising results. It deserves further research and a place in second-line treatment options.
REFERENCES
