REVIEW

Interferential Electrical Stimulation Efficacy in the Management of Lower Urinary Tract Dysfunction in Children: A Review of the Literature

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Purpose: Lower urinary tract dysfunction (LUTD) is the most common problem of the referral children to the pediatric urology clinics. If this condition does not treat early in life, it will be a lifelong problem. During recent decades, electrical stimulation therapy has been expanded and extensively used for the treatment of LUTD in both adults and children. The aim of this review is to suggest clinicians an updated understanding of effects of interferential (IF) electrical stimulation therapy in management of LUTD in children.

Materials and methods: The search was performed in databases of Medline, PubMed, Google Scholar, ,and Scopus for information about IF electrical stimulation and its application using search words such as " IF electrical stimulation", "transcutaneous IF electrical stimulation" , "IF therapy " , " electrical stimulation", "voiding dysfunction" , " LUTD", " urinary incontinence" and " children". As this review focuses on the answer of this question "Does transcutaneous IF electrical stimulation has effect on management of LUTD in children?" we included the reference list of articles identified by this search strategy and selected those we judged relevant according to our keywords. Clinical trial studies in English were included. Categorical data were reported as frequencies and percentages.

Results: Eleven studies were included in this review. The success rate of IF therapy in these studies has been reported from 61% to 90% of children with LUTD and urinary incontinence.

Conclusion: IF electrical stimulation is an effective, safe and reproducible option to manage LUTD and urinary incontinence in children.

Keywords: electrical stimulation; children; lower urinary tract dysfunction; voiding dysfunction

INTRODUCTION

Lower urinary tract dysfunction (LUTD) is an exclusive term that contains different conditions such as dysfunctional voiding, urinary incontinence, overactive bladder (OAB), underactive bladder and etc.[1] Additionally, LUTD is the most common problem of the referral children to the pediatric urology clinics. If this condition does not treat early in life, it will be a lifelong problem. Accordingly, optimal clinical management and outcome measures for this condition are important to allow for the best allocation of office and healthcare system resources.[2] The first step in the treatment of LUTD, is patient and family education on voiding habits, pelvic floor muscles (PFM) function, hydration and timed voiding (standard urotherapy). In addition, many pharmacological treatments have been developed showing several side effects in children.[3] Nowadays PFM retraining and biofeedback therapy are the first-line treatment for the cases with dysfunction voiding after failure of simple conservative managements.[4] Furthermore, electrical stimulation has been used after failure of medication or biofeedback in several studies.[5] During recent decades, electrical stimulation therapy has been expanded and extensively used for the treatment of LUTD in both adults and children.[6,7] Several therapeutic electrical devices have been developed since Johann Gottlob Krüger reported the treatment of a patient by electricity in 1743. Electrical currents via stimulating nerves or muscles are used for pain relief, blood flow improvement, muscle spasm relief, wound healing, muscle retraining and strengthening.[8] On the other hand, electrical currents can affect sensory, motor, glandular, and secretory function as well. Some chemical changes have also been reported after electrical stimulation therapy, for example; increasing beta-adrenergic activity, reducing cholinergic activity and changes in neurotransmitter availability (dopamine, serotonin, vasopressin, and nitric oxide).[9] Moreover, electrical currents can cause reduction in detrusor pressure as well as increasing the bladder capacity or compliance.[10-13]

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Table1. Studies on interferential current therapy in children with lower urinary tract dysfunction

Author and year	Study purpose	Study design	Participants	Outcome measures	Intervention, frequency, duration	Results
Mauroy et al, 38 1992	Efficacy of IF current on bladder instability	Pilot study	10 children	Urodynamic parameters and resolution of incontinence	6 to 20 stimulation sessions once per week	90% of patients were clinically and urodynamically improved
Kajbafzadeh et al, 26 2009	Effect of IF on urodynamic parameters, and incontinency	RCT	30 children with myelomeni-ngocele	Urodynamic parameters and resolution of incontinence	18 stimulation sessions 3 times per week	78% of patients were clinically and urodynamically improved
Yazdanpanah et al, 39 2012	Comparing the effects of desmopressin and IF therapy on nocturnal enuresis in children	RCT	75 children	Symptoms improvement and recurrence rate	3 weeks (5 times /week) IF therapy or desmopresin	61% of patients in IF group were responded to the treatment
Lee et al,40 2013	Efficacy of IF on patients with medication-refractory enuresis	Pilot study	10 children	Symptoms improvement and resolution of incontinence	Six sessions (once a week)	90% of patients were completely or partially responded to treatment
Kajbafzadeh et al, 41 2015	Efficacy of IF on nocturnal enuresis	RCT	54 children	Symptoms improvement and resolution of incontinence	15 sessions (two times/week)	67 % of patients in IF group responded to the treatment
Kajbafzadeh et al, 42 2016	Efficacy of IF on non-neuropathic underactive bladder	RCT	36 children	Urodynamic parameters and resolution of symptoms	15 sessions (two times/week)	77 % of patients in IF group responded to the treatment
Zivkovic et al, 43 2017	fficacy of IF and diaphragmatic Ebreathing exercises on bladder and bowel dysfunction	RCT	79 children	Urodynamic parameters and resolution of symptoms	10 sessions (5 times/ week)	73 % of patients in IF group responded to the treatment
Rafaqat et al,44 2017	Effectiveness of IF current on overactive bladder syndrome	Quasi-Experimental study	40 children	Resolution of symptoms according to filled out questionnaires	8 weeks	Most of the patients responded to the IF therapy
Ladi-Seyedian et al, 45 2019	Effectiveness of IF current on non-neuropathic urinary incontinence	RCT	46 children	Urodynamic parameters and resolution of incontinence	10 sessions (once a week)	82% of patients in IF group responded to the treatment
Sharifi-Rad et al, 46 2019	Impact of IF therapy on primary bladder neck dysfunction	RCT	23 children	Uroflowmetry/EMG and resolution of symptoms	10 sessions (once a week)	Most of the patients responded to the treatment
Abdelhalim et al, 47 2019	A comparative study of IF therapy and TENS on children with primary nocturnal enuresis	RCT	52 children	Quality of life and resolution of enuresis	18 sessions (3 sessions per Week)	Most of the patients responded to the treatment

Interferential (IF) electrical stimulation as a medium frequency current penetrates with low skin impedance, delivers without pain and targets deeper tissue, has been utilized more than two decades to treat OAB, urinary incontinence and to reinforce the pelvic floor in women patients.[14] Recently, application of IF electrical stimulation for treatment of slow transient constipation in children was reported.[15,16]

IF currents are produced after crossing of two different medium-frequency currents of 4000 Hz by applying four surface electrodes on the body (**Figure 1**). Thus an amplitude-modulated current will be generated in the deep tissue such as bladder or the pelvic floor.[17]

Despite the lack of certainty about the mechanism of action of IF electrical stimulation, in the last decade this technique has been widely used for the treatment of OAB syndrome, urinary incontinence and chronic pelvic pain/painful bladder syndrome in women patients. This review aimed to address the answer of this question "Does transcutaneous IF electrical stimulation has effect on management of LUTD in children?"

MATERIAL AND METHODS

The search was performed in databases of Medline, PubMed, Google Scholar, ,and Scopus for information about IF electrical stimulation and its application using search words such as " IF electrical stimulation", "transcutaneous IF electrical stimulation" , "IF thera-

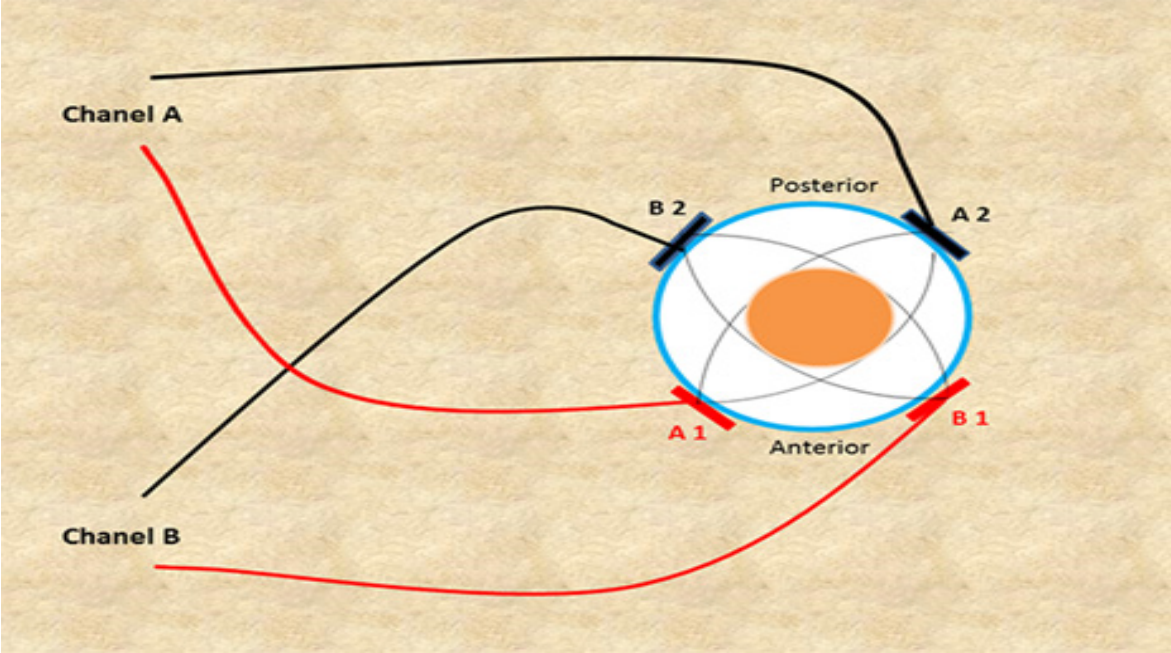

Figure 1. Pattern of interference currents in IF therapy

py " , " electrical stimulation", "voiding dysfunction" , " LUTD", " urinary incontinence" and " children". As this review focuses on the effects of transcutaneous IF electrical stimulation in the management of LUTD in children, we included the reference list of articles identified by this search strategy and selected those we judged relevant according to our keywords. We only included studies with participants up to 18 years of age. Outcomes of interest included patient-reported outcomes, such as change in symptoms, change in scores of validated questionnaires, or uroflowmetric parameters, and the episodes of urinary incontinence. Eligibility assessment was performed independently by two reviewers who screened papers titles and abstracts. Clinical trial studies that publishing in English were included. Case reports were excluded. One review author extracted the following data from included studies and the second author checked the extracted data. Disagreements were resolved by discussion between the two review authors; if no agreement could be reached, it was planned a third author would decide. As there were limited studies on the application of transcutaneous IF electrical stimulation for management of different kinds of LUTD in children, eleven studies were included in this review. Categorical data were reported as frequencies and percentages.

RESULTS

Physiological and therapeutic effects of interferential current

The exact mechanism that IF electrical stimulation affects the lower urinary tract function is not completely clear. It is suggested that the IF therapy decreases the stimulation of cutaneous sensory nerves near the electrodes in contrast to raising the stimulation of deep nerves.[18] IF current is often remarked to be more acceptable, as it generates lower discomfort than some other types of electrical stimulation. This current causes vasodilatation in the peripheral vasculature through chemical changes and sympathetic reflex inhibition.[19] Many investigators believe that low frequency currents can selectively use to stimulate the autonomic nervous system.[20,21] Also, IF therapy is an effective modality for the treatment of patients with urinary incontinence such as stress and urge incontinence in adults.[22,23] It is suggested that pelvic floor IF electrical stimulation can result in reflex inhibition of the pelvic nerves and increasing bladder capacity (**Figure 2**). In addition, afferent pudendal nerve stimulation will activate hypogastric efferent and causes reduction in sympathetic activity in order to stop or delay involuntary contractions. [24]
The pelvic floor plays a significant role in this system of sacral reflexes. The activated efferent fibers of the pelvic floor influence the sacral level of the neural network that controlling bladder and bowel function. Moreover, rhythmic contraction and stimulation of the pelvic floor can coordinate voiding function (**Figure 3**).[25-27]
An incompetent urethral sphincter can cause stress urinary incontinence whilst urge incontinence is resulted from uninhibited detrusor muscle contractions. Recent studies have reported that IF therapy has considerable results in the treatment of patients with stress incontinence, urge incontinence, or both.[28] Laycock and Green demonstrated the best frequency of stimulation and position of the electrodes for treatment of incontinence.[29] They reported that specific electrode positions can cause higher circulation of the currents in the pelvic floor. Therefore, it causes the greater muscle activity compared to a pressure probe method.[29] The possible mechanisms that IF therapy could improve OAB have been previously described.[30] It is including (1) stimulation of the somatosensory nerve in the pudendal region that inhibiting the efferent activities of the pelvic nerve (action on the micturition center in the brainstem and the spinal cord) (2) increasing the pelvic blood flow and (3) improving the urine pooling function of the bladder by sympathetic nerve inhibition.[30] The lower rate of stimulation frequency represents an attempt to excite

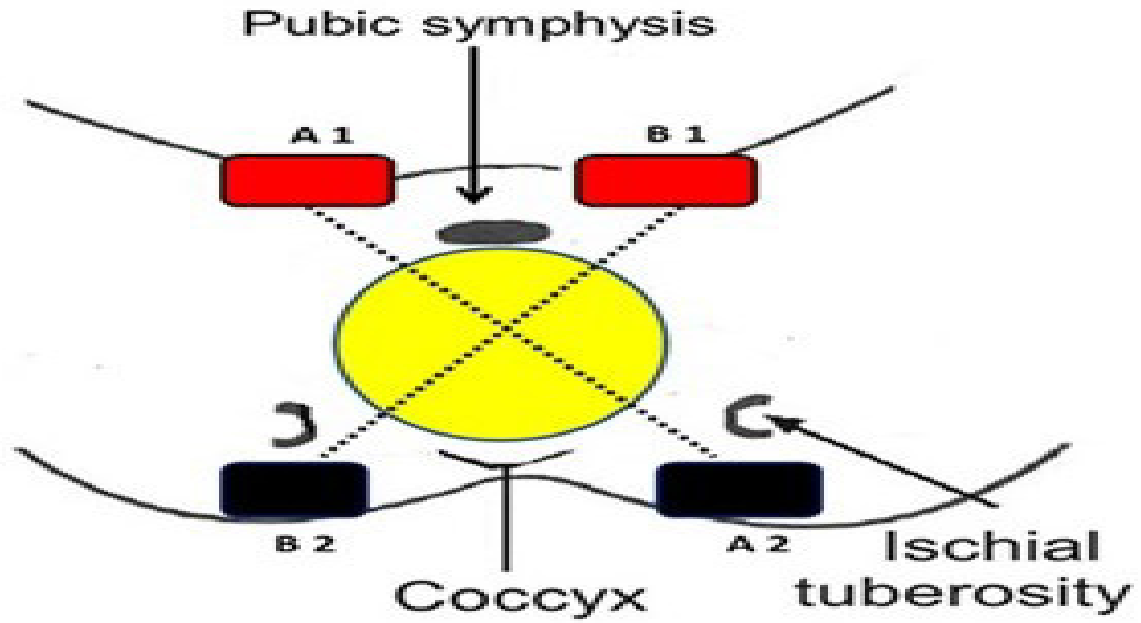

Figure 2. View of crossing currents from each channel along the pelvic floor.

small afferent fibers in the pudendal nerve that have a slow conduction velocity. This modulated low frequency current will generate reflex inhibition of detrusor following contraction of the slow twitch fibers in the PFMs.[17,31] Also, some investigators evaluated the role of IF therapy in the treatment of anorectal incontinence.[32,33] Nowadays, IF current is used more and more to treat some of bowel motility disorders including: dyspepsia[34], irritable bowel syndrome[35], functional constipation[36], neuropathic constipation[37] and slow transit constipation in children and adults.[22]

Application of interferential current in children with LUTD

There are limited studies on the application of transcutaneous IF electrical stimulation for the management of LUTD and urinary incontinence in children (**Table 1**). As the results of IF therapy for management of OAB and urinary incontinence in adult patients were favorable, use of IF current in pediatric patients seems to be effective.

1. In a study by Mauroy et al. 20 patients with unstable bladder who had no response to medical therapy (anticholinergic) were treated by IF current.[38] Each patient received 6 to 20 IF stimulation sessions for once a week in children and twice a week in adults. Authors reported that urinary incontinence improved in 18 patients. Moreover, no adverse effects and recurrences of the symptoms were observed at 18 months of follow up. They believed that this reliable technique constitutes an alternative to other retraining stimulation methods.[38]

2. In 2009, the first study on the efficacy of IF electrical stimulation in children with neuropathic bladder was published.[27] In this study 30 myelomeningocele children with intractable urinary incontinency due to neuropathic detrusor overactivity had been enrolled and randomly allocated into case group (20 children) who underwent IF electrical stimulation and control group (10 children) who underwent sham stimulation. Eighteen-session of pelvic IF electrical stimulation for 20 minutes 3 times per week was performed. The results revealed that 78% of patients in the case group obtained continence immediately after IF therapy which was maintained in 60% of them at 6 months of follow up. [27]

3. The positive results of this study in children with neuropathic bladder led to performing other studies during the next few years on children with lower urinary tract symptoms and voiding disorders. Yazdanpanah et al. compared the effect of desmopressin on 39 children who had primary nocturnal enuresis with 36 enuretic children who underwent IF therapy.[39] They reported that IF group had a complete response in 25%, partial response in 36.1% and no response in 38.9% of patients while the desmopressin group had a complete response in 87.2%, and no response in 12.8% of patients. Also, the relapse rate in IF and desmopressin groups were 61% and 87.2%, respectively. The author concluded that although the success rate in desmopressin group was higher than IF group, IF therapy is a cost-effective and safe modality in the treatment of primary enuresis in children due to limited treatment courses (three weeks IF therapy in contrast to 6 months of desmopressin therapy), lower relapse rate, and no side effects. [39]

4. Lee and Park evaluated the effect of salvage IF therapy on 10 children with medication-refractory enuresis.[40] Treatment was performed once a week, 20 minutes per treatment session, 6 times per cycle. After each cycle, an interview was performed and voiding diaries were filled out. They observed a full response in 1 patient (10%); a good response in 1 patient (10%); a partial response in 7 patients (70%); and no response in 1 patient (10%). The authors concluded that IF therapy is a safe treatment and would have beneficial effects in carefully selected patients.[40]

5. The efficacy of transcutaneous IF electrical stimulation and standard urotherapy in the treatment of children with primary nocturnal enuresis was studied in 2015.[41] Fifty four children with primary nocturnal enuresis were enrolled and divided into two groups. Children in

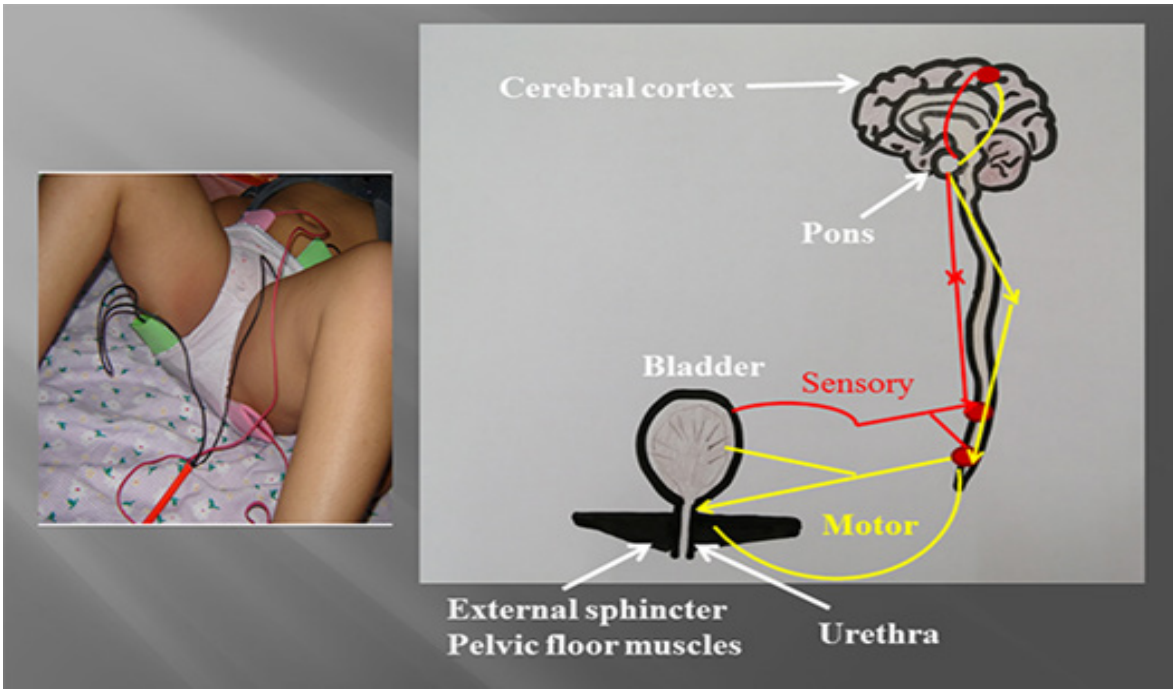

Figure 3. Mechanism of action of IF current in the lower urinary tract, spine and brain.

the control group underwent only standard urotherapy. Children in the case group were treated with standard urotherapy plus 15 courses of IF electrical stimulation. Generally, 15/27 (55.5 %) and 6/27 (22 %) of children in the case and control groups respectively responded to the treatment at the 1-year follow up.[41] Different results of these three studies on children with primary nocturnal enuresis probably relate to various positions for placement of the electrodes on the body, different amplitude frequency, number of treatment sessions and solely usage or combination of IF therapy with other treatments.

6. Underactive bladder is a form of LUTD that is defined as impaired detrusor contractility and the need to increase intra-abdominal pressure for complete voiding.[1] Children with underactive bladder usually have a low voiding frequency, episodes of hesitancy, urge urinary incontinence or overflow incontinence, a large-capacity bladder with incomplete emptying and high post-void residue urine volume which often present with urinary tract infections.[1] In a recent randomized clinical trial, IF electrical stimulation was used to manage this type of LUTD in children.[42] Thirty six children were enrolled and assigned into two equal treatment groups. The control group underwent only standard urotherapy including diet, hydration, scheduled voiding and toilet training, plus pelvic floor and abdominal muscles relaxation exercises. Children in the IF group not only underwent standard urotherapy and pelvic floor and abdominal muscles relaxation exercises, but also received IF stimulation for 15 sessions, 2 times per week. The authors reported that the voiding frequency significantly increased after IF therapy in the IF group, compared with the control group. Nighttime wetting was improved in all children who had this symptom before the treatment in the IF group. Overall, the IF group had significantly better outcomes compared to the control group.[42]

7. The significant improvement of bladder and bowel dysfunction in children was recently reported by adding trans-abdominal IF electrical stimulation to the diaphragmatic breathing exercises and behavioral modification compared to only diaphragmatic breathing exercises and behavioral modification.[43] Since bowel and bladder are likewise innervated, this experiment can support the concept that electrical stimulation is able to affect the function of both sympathetic and parasympathetic nerve fibers in the sacral nerves. It was shown that treatment of constipation significantly reduced lower urinary tract symptoms in children with bladder dysfunction.[43] They reported a significant improvement in defecation frequency and fecal incontinence only in children who underwent IF therapy. Additionally, a significant improvement in lower urinary tract symptoms and post-void residual urine was seen in these patients. Bell-shaped uroflowmetry curve was observed in 73.3% of children who underwent IF therapy and exercise.[43]

8. In addition, the effects of IF current on OAB in children were newly studied.[44] In this study, a total of 40 children with mild, moderate and severe OAB symptoms score underwent 8 weeks of IF therapy. This was a quasi-experimental study. Standard questionnaire was used for measurement through which results were calculated in this study. Complete information about the patients including their bio data, symptomatology was entered in a Performa and then data was entered on the basis of Overactive Bladder Symptom Score scoring system. In this study, IF current was used on S2 and S3 dermatome. The data was collected before and after the treatment. The study showed improvement of lower urinary tract symptoms such as daytime wetting, frequency and urgency in most of the patients after the treatment.[44]

9. Functional urinary incontinence in children improved with additional pelvic IF electrical stimulation compared to biofeedback therapy alone in a recent study.[45]

In this study, 46 anatomically and neurologically normal children with functional urinary incontinence were evaluated. Children were allocated into two treatment groups. Twenty three patients underwent biofeedback therapy in addition to IF electrical stimulation while 23 patients received only biofeedback therapy for 10 sessions, once a week. Improvement of urinary incontinence was significantly higher in IF + biofeedback group compared to only biofeedback therapy at 1 year follow up. Daytime wetting was improved in 19/23(82%) and 13/23(56.5%) of children in IF + biofeedback and biofeedback only groups respectively, after the treatment. No significant difference was observed in uroflowmetry measures between two groups after the treatment. This study demonstrated that combination of biofeedback and transcutaneous IF electrical stimulation was an effective method for the management of functional urinary incontinence in children.[45]

10. Primary bladder neck dysfunction defines as an impaired, delayed or incomplete opening of the bladder neck during micturition, resulting in a weak urinary stream without anatomical obstruction.[1] Newly, the impact of transcutaneous IF electrical stimulation on primary bladder neck dysfunction in children was studied. This survey was done on 23 neurologically and anatomically normal children. Included participants had different lower urinary tract symptoms such as hesitancy, straining, urinary incontinence and constipation with no sufficient response to medical treatment (α- blocker) for at least 6 months. IF electrical stimulation was performed for 20 minutes, 15 sessions, two times per week. All children were symptomatic and had abnormal urine flow pattern with an electromyography (EMG) lag time of more than 6 s on uroflowmetry with EMG. In addition, alpha blocker therapy was continued during IF therapy. The authors observed a significant improvement in mean maximum and average urine flow rates as well as mean EMG lag time and post-void residual volume after the treatment (all $P < 0.05$).[46] They concluded that increases in mean maximum and average urine flow rates in their patients indicated that pelvic IF therapy and behavioral modification improved voiding dysfunction in most of the patients and probably decreased bladder neck activity during voiding.[46]

11. In another new study the immediate and short-term effects of IF currents and transcutaneous electrical nerve stimulation (TENS) in the treatment of children with primary nocturnal enuresis was compared. Fifty two children at the age of 7 to 14 years old were randomly assigned into two groups (26 children for each group). Electrical therapy was performed for 20 minutes, 3 times per week until 6 weeks in both IF and TENS groups. The authors measured the patient's outcome with the number of wet nights, and quality of life through pediatric incontinence questionnaire before treatment, after the last session and 6 months later. They reported that the number of wet nights reduced significantly in both groups with better outcome in IF group. Also quality of life was significantly improved after the treatment in both groups with better outcome in IF group ($P < 0.05$). The authors concluded that, although IF therapy and TENS had immediate and short-term impact on improvement of primary nocturnal enuresis in children, the outcome was better in IF group than TENS group.[47]

We searched the literature up to May, 2020. There were a few studies with small sample sizes on the application of transcutaneous IF electrical stimulation in the management of LUTD and urinary incontinence in children, however, the success rate of IF therapy in these studies has been reported from 61% to 90%. Level 1 evidence is produced by few studies for the efficacy of IF current in the treatment of LUTD in children. It seems that IF therapy to be an efficacious and safe treatment for LUTD and urinary incontinence in children that could be highly recommended. (48) Nevertheless, this evidence needs to be confirmed by further good quality randomized controlled studies and meta-analysis of them. Little is known about the effects of the electric stimulation parameters and the stimulation protocols on IF electrical stimulation efficacy in children. Further studies are needed to identify the best electric parameters and the best protocols for every indication as well as possible effects of a combination therapy with drugs, standard urotherapy and exercises.

Additionally, different results of reviewed studies probably relate to various positions for placement of the electrodes on the body, different amplitude frequency, number of treatment sessions and solely usage or combination of IF therapy with other treatments. It is important the placebo effects of IF therapy to be considered. Few data are available on using of sham stimulation [28] in control group in order to offset placebo effects. According to the published data, IF therapy is a safe and well tolerated modality in children. Nevertheless, future studies will have to include safety data of the technique. Studies on subgroups of patients in the different indications considered are needed, to find patients more prone to respond to this treatment, with the aim to reduce the number of patients unsuccessfully treated, thus reducing the costs. No long term studies are available, therefore, further long term studies are needed. Further studies on alternative possible treatments (e.g. home based transcutaneous stimulation) are also needed. Moreover, few data are available about possible mechanisms of action of IF electrical stimulation. Therefore, studies on animal models and on humans, possibly using central nervous system functional imaging techniques are to be encouraged. Future studies with larger sample size, multicenter study and long term follow up are required to help better understanding of IF therapy. The main limitation of this review was that this study was not a systemic review with meta-analysis. A few numbers of studies was another limitation of this review.

CONCLUSIONS

IF electrical stimulation is an effective modality in the management of children with LUTD. Results from randomized controlled studies demonstrate that the success rate of IF therapy is statistically superior to that of placebo. IF therapy is safe, with no major complications reported in literature. Promising results, to be confirmed by randomized controlled studies, have been obtained in bowel and urinary disorders in children. Further studies are needed to assess the exact role of IF therapy in these indications and to evaluate the long term outcomes. Future studies are needed to obtain better understanding of IF therapy in children and bring the best application of it to the clinical setting.

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