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Systematic Review (Pages: 6741-6755)

The Effect of Electrical Nerve Stimulation in Management of Overactive Bladder in the Pediatric Population; A Systematic Review and Meta-Analysis

Fariba Roshdibonab[1], Seied Mohammadbager FazlJoo[1], Mohammadali Torbati[1], Ghadir Mohammadi[1], Mahboob Asadloo[2], *Hamid Noshad[3]

[1]Department of Iranian Traditional Medicine, Tabriz University of Medical Sciences, Tabriz, Iran.
[2]Department of Psychiatry, Tabriz University of Medical Sciences, Tabriz, Iran.
[3]Chronic Kidney Disease Research Center, Department of Nephrology, Tabriz University of Medical Sciences, Tabriz, Iran.

Abstract

***Background*:** In traditional medicine and recent years, nerve stimulation has been introduced as a replacement therapy for managing several disorders such as overactive bladder. However, there is still controversy in this regard. Therefore, the present meta-analysis aimed to assess the effectiveness of electrical nerve stimulation in treatment of overactive bladder.

***Materials and Methods*:** The present systematic review and meta-analysis attempted to gather the evidence existing in Medline, EMBASE, Scopus, Web of Sciences and CINHAL databases until the end of October 2017. Summarization of the articles was done by 2 independent researchers and finally, pooled effect size was reported as standardized mean difference (SMD) or overall odds ratio (OR) with 95% confidence interval (95%CI). In all analyses $p<0.05$ was considered as level of significance.

***Results*:** Data of 13 articles were entered. Analyses showed that using electrical nerve stimulation results in a significant decrease in wet days per week (SMD= -0.92; 95% CI: -1.47 to -0.37) and voiding frequency (SMD= -1.09; 95% CI: -2.15 to -0.03), and increase in maximum voided volume (SMD= 0.43; 95% CI: 0.13 to 0.73) and average voided volume (SMD= 0.78; 95% CI: 0.11 to 1.45). Finally, the success rate in the electrical nerve stimulation group was up to 2 times higher than the placebo or routine treatment group (odds ratio=2.11; 95% CI: 1.10 to 4.06; p=0.009).

Conclusion: Since the findings of the present study indicate the effectiveness of electrical nerve stimulation in improvement of overactive bladder symptoms in children, it is suggested to use it in routine practice.

Key Words: Neuromodulation, Overactive bladder, Pediatric, Urinary Incontinence.

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Corresponding Author:

Hamid Noshad, Chronic Kidney Disease Research Center, Tabriz University of Medical Sciences, Azadi Street, Tabriz, Iran,

Email: hamidnoshad1@yahoo.com

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1- INTRODUCTION

Overactive bladder is a common and complicated disorder consisting of various urinary symptoms, which manifests as a sudden need to urinate without the patient being able to control it. In Iranian traditional medicine, this disorder was more recognized and it was called "*Salas Alboul*" meaning urinary incontinence. Avicenna defines it as involuntary leakage of urine. He describes various etiologies for urinary incontinence including excessive use of diuretics, presence of pressure on the bladder such as during pregnancy as well as damage to the vertebra due to trauma (1).

The prevalence of this problem in children and adolescents is so much more than adults. Statistics show its 5% to 12% prevalence in children under the age of 10 years and 0.5% prevalence in 16 to 18 years old adolescents. The psychological and social effects of this problem are very serious and existing studies have expressed that those affected with overactive bladder have a greater odds of developing anxiety disorders, depression and other psychological conditions (2). A review performed on available evidence showed that both wet and dry overactive bladder lead to decrease in quality of life and social isolation. In addition to these points, the cost inflicted by this condition is very high and has been estimated to be 12.6 billion dollars in America (3).

Current treatments for overactive bladder emphasize on behavioral and cognitive approaches. Supportive and pharmaceutical treatments and even surgical therapy have been proposed as other choices for control and management of overactive bladder (4). In recent years, neuromodulation has been introduced as a replacement technique for management of treatment-resistant overactive bladder. The accurate mechanism of electrical nerve stimulation in controlling the symptoms of this disease is not fully known but it has been said that stimulation of peripheral nerves such as sacral and tibial nerves can inhibit the detrusor muscles of the bladder. In addition, stimulation of these nerves leads to activation of pelvic floor muscles, which in turn results in inhibition of bladder muscles (5). In Iranian traditional medicine, urinary incontinence (or *Salas alboul*) has been deemed related to shin cramps and in the book "Treasures dedicated to the king of Khwarazm" it has been said that bladder weakness is associated with shin problems (6). Based on this viewpoint of traditional medicine, acupuncture would be used as a treatment method for treating urinary incontinence by stimulating peripheral nerves (7).

However, there is still a lot of controversy in this field, especially regarding treating children with overactive bladder. One solution for overcoming this problem is performing a systematic review and meta-analysis (8-28). For this purpose, the present systematic review and meta-analysis is designed aiming to evaluate the efficacy of electrical nerve stimulation in treatment of overactive bladder in the pediatric population.

2- MATERIALS AND METHODS

2-1. Study design

The present systematic review and meta-analysis has gathered existing clinical evidence regarding the effectiveness of electrical nerve stimulation in treatment of overactive bladder. Search was done without time limitation and search deadline was determined to be the end of September 2017. Designing search strategy and summarizing method and reporting it were done based on the standard protocols and Cochrane and PRISMA guidelines (29, 30).

2-2. Inclusion and exclusion criteria

In the present study, clinical trials that had a control group (placebo or routine treatment) aiming to evaluate the effectiveness of electrical nerve stimulation in treatment of overactive bladder in children (under 19 years old) were included. Studies without a control group, review studies and studies performed on adults were excluded.

2-3. Search strategy

The search strategy was designed after consulting with a librarian. For this purpose, words relating to nerve stimulation in combination with overactive bladder were searched in Medline, EMBASE, Web of Sciences, Scopus and CINHAL databases. In addition, a manual search was performed in Google and Google Scholar, bibliography of related articles and review articles, and finally a search was done in the thesis section of ProQuest database. The search strategy used in Medline database (via PubMed) has been shown in **Table.1**.

2-4. Data synthesis and quality control

After finishing searching in databases and saving the obtained records in Endnote 7.0 software and deleting duplicate records, two researchers read the titles and abstracts of related articles, independently. Each researcher evaluated the related articles based on inclusion and exclusion criteria and record the required data. Data extracted from the articles are shown in **Table.2**. In the present study, the studied outcomes were success rate; average voiding volume; maximum voiding volume; maximum detrusor pressure; incontinence score; voiding frequency and wet per week. In the end, quality control of the studies was done using Cochrane guideline (29).

2-5. Statistical analysis

All analyses were done in STATA 14.0 software. It should be noted that analyses were done based on the evaluated outcomes. For this purpose, data of each article were summarized and using fixed or random effect models, a pooled effect size was introduced. Choosing either fixed or random effect model was done based on the presence or absence of heterogeneity (I^2 larger than 50% or p less than 0.1 were defined as heterogeneity). Finally, pooled effect size was reported as either standardized mean difference (SMD) or overall odds ratio (OR) with 95% confidence interval (95% CI). In all analyses, $p<0.05$ was considered as level of significance.

3- RESULTS

3-1. Characteristics of the included studies

Flowchart of selecting the studies has been presented in **Figure.1**. In the initial search, 1,739 non-duplicate articles were retrieved and after the screening performed, finally 13 articles were included in the present meta-analysis (31-43). These studies included the data of 422 children and adolescents 3 to 18 years old. Two hundred and two children were in the control group and 220 were in the group under treatment with electrical nerve stimulation; 47.64% of the population were boys. Transcutaneous electrical neural stimulation was the most common method for electrical nerve stimulation among the studies. The most important outcomes evaluated were success rate; average voiding volume; maximum voiding volume; maximum detrusor pressure; incontinence score; voiding frequency and wet per week.

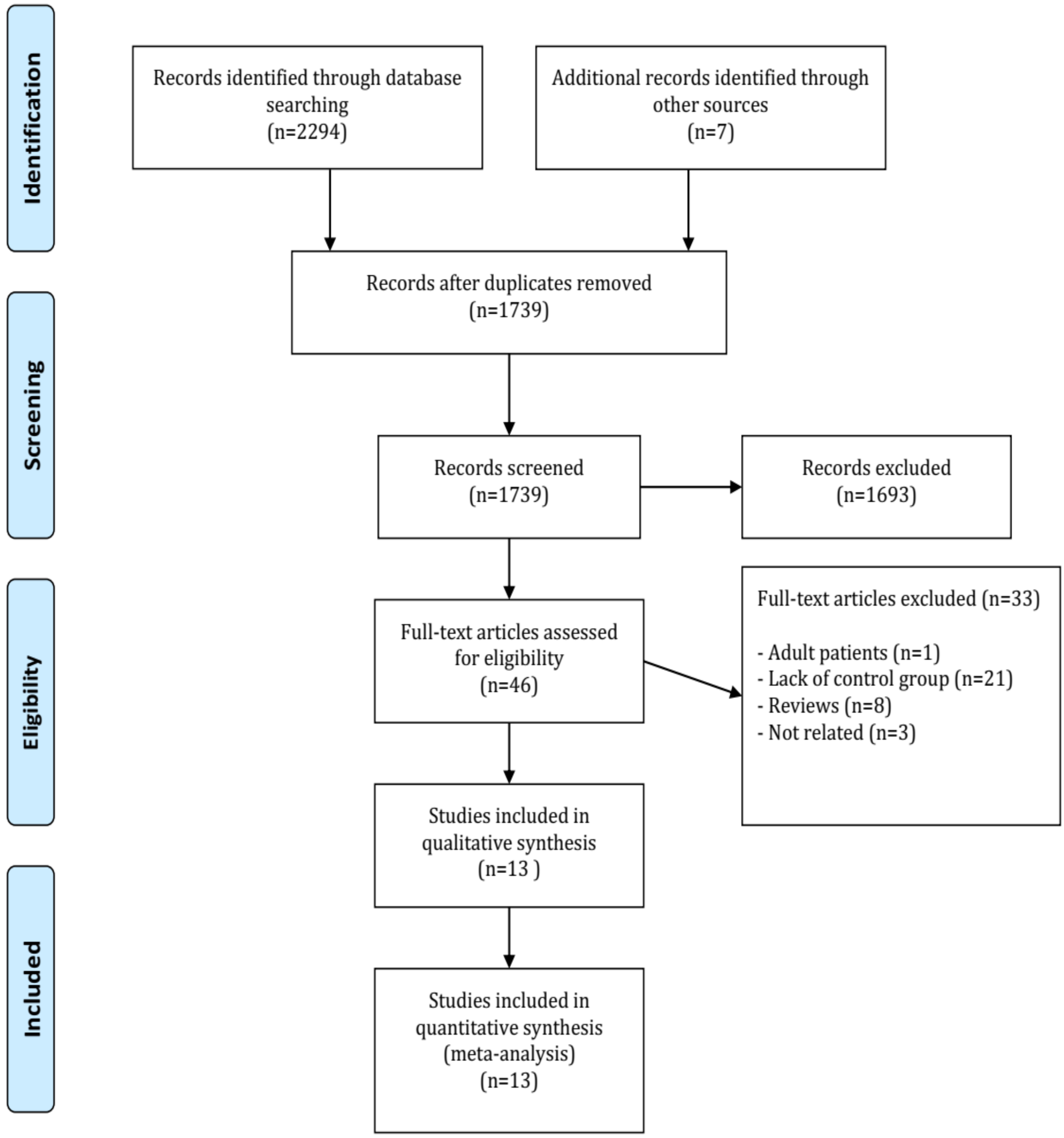

Fig.1: PRISMA flowchart of the present meta-analysis..

3-2. Risk of bias and heterogeneity between studies

Based on the evaluated outcomes, heterogeneity between the studies would change. As **Figures.3-5** show, in the section evaluating the effect of electrical nerve stimulation on incontinence severity (I^2=14.3%; p=0.321), wet days/week (I^2=37.6%; p=0.186), maximum voided volume (I^2=21.7%; p=0.257), and maximum detrusors pressure (I^2=0.0%; p=0.858) there was no heterogeneity, but in other evaluated outcomes significant heterogeneity was seen. However, there was no publication bias in the present study (**Figure.2**).

3-3. The effect of using electrical nerve stimulation on improvement of patients with overactive bladder

A) **Urinary incontinence score**

Four studies had attempted to evaluate the effect of electrical nerve stimulation on incontinence scores (33, 35, 36, 40). Overall, the analyses of this section showed that using this treatment modalitydoes not have an effect on improvement of urinary incontinence severity (standardized mean difference [SMD] = -0.35; 95% confidence interval [95%CI]: -0.77 to 0.08; p=0.108) (**Figure.3**).

B) Wet days per week

In this section of analyses, 4 studies were included (34-37). The analyses of this section showed that using nerve stimulation significantly reduces wet days per week (SMD= -0.92; 95% CI: -1.47 to -0.37; p=0.001) (**Figure.3**).

C) Voiding frequency

The search performed in the present meta-analysis led to inclusion of 6 studies that had assessed the effect of nerve stimulation on voiding frequency (35, 36, 38-40, 42). Analyses of this section showed that using this therapeutic technique can significantly reduce voiding frequency in patients with overactive bladder (SMD= -1.09; 95% CI: -2.15 to -0.03; p=0.044) (**Figure.3**).

D) Maximum voided volume

In this part of analyses, data of 8 studies were included (32, 33, 35-40). Analyses showed that nerve stimulation leads to increase in maximum voided volume in pediatric patients with overactive bladder (SMD= 0.43; 95% CI: 0.13 to 0.73; p=0.005) (**Figure.4**).

E) Average voided volume

Five studies had assessed the effect of the modality under evaluation on average voided volume (32, 35, 38-40). Analyses showed that using nerve stimulation results in an increase in average voided volume among children with overactive bladder (SMD= 0.78; 95% CI: 0.11 to 1.45; p=0.022) (**Figure.4**).

F) Maximum detrusors pressure

In this section of analyses, 3 original articles were included (33, 36, 37), and pooled analysis showed that electrical nerve stimulation does not have an effect on maximum detrusors pressure in children with overactive bladder (SMD= -0.42; 95% CI: -0.87 to 0.04; p=0.072) (**Figure.4**).

G) Success rate

The success rate of electrical nerve stimulation in children with overactive bladder was reported in 9 studies (31, 33-35, 38-41, 43). Result showed that success rate in the electrical nerve stimulation treated group was up to 2 times more than placebo or routine treatment method groups (odds ratio=2.11; 95% CI: 1.10 to 4.06; p=0.009) (**Figure.5**).

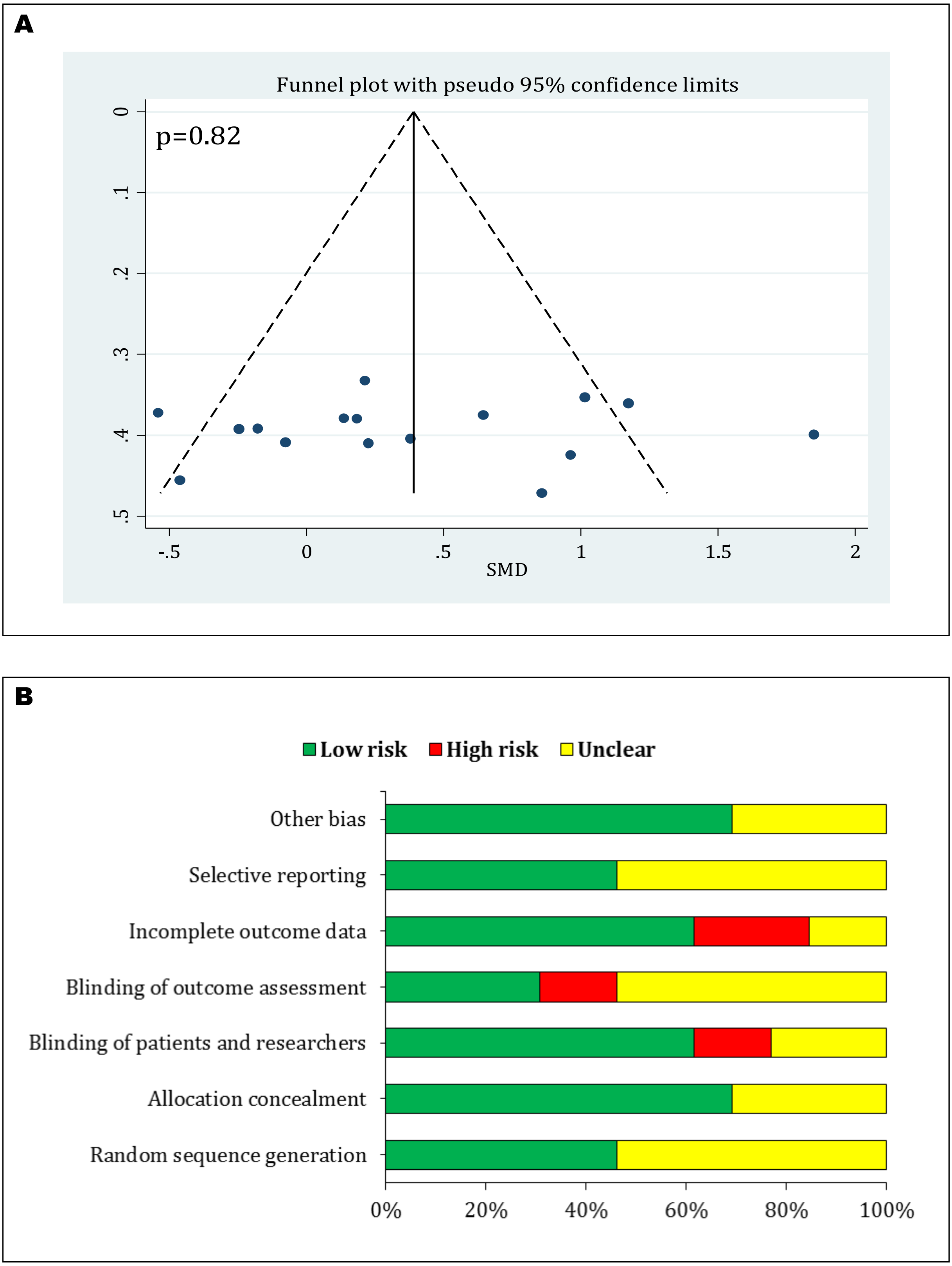

Fig.2: Assessment of publication bias (A) and risk of bias (B) in the present meta-analysis.

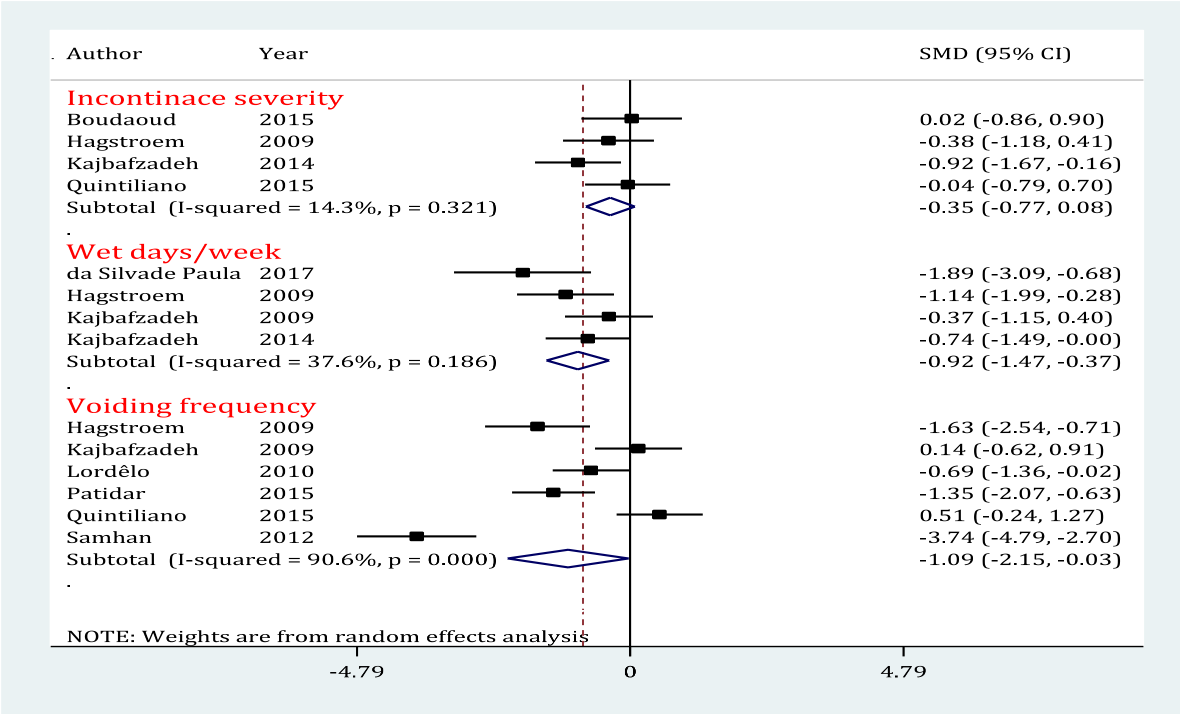

Fig.3: Forrest plot for efficacy of transcutaneous electrical nerve stimulation on incontinence score, wet days per week and voiding frequency in children with overactive bladder. CI: Confidence interval; SMD: Standardized mean difference.

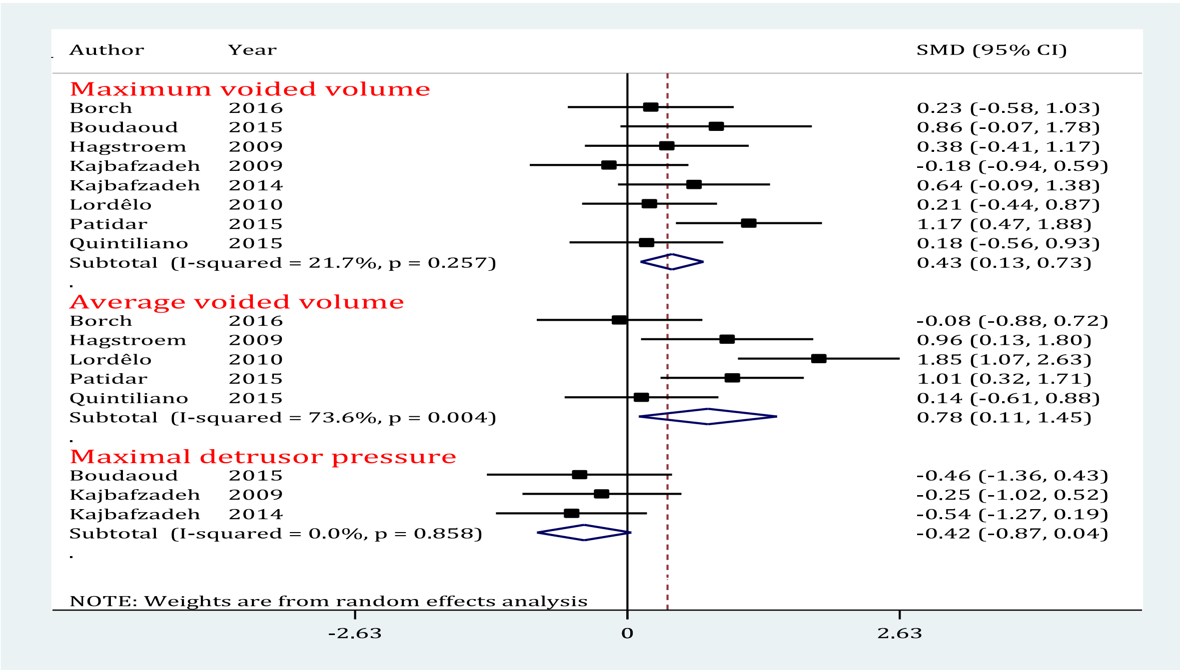

Fig.4: Forrest plot for efficacy of transcutaneous electrical nerve stimulation on manometry parameters in children with overactive bladder. CI: Confidence interval; SMD: Standardized mean difference.

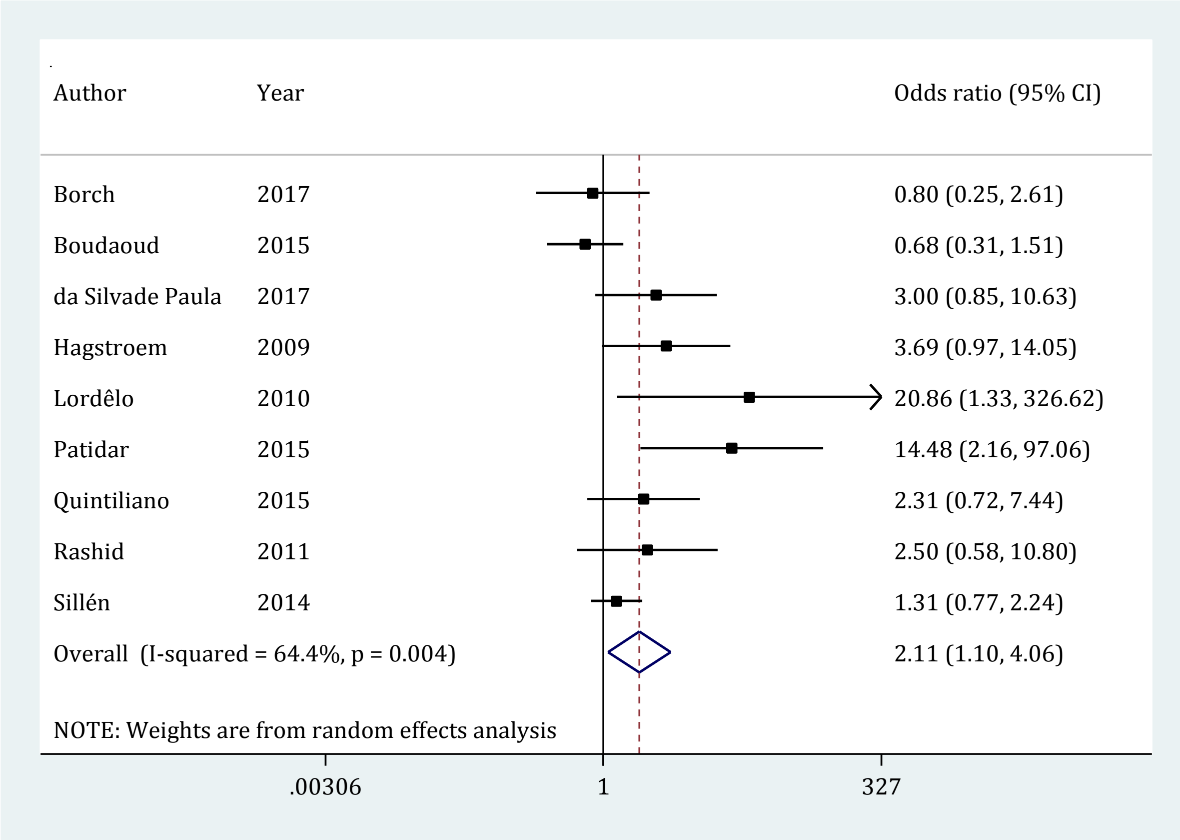

Fig.5: Forrest plot for success rate of transcutaneous electrical nerve stimulation in children with overactive bladder. CI: Confidence interval.

4- DISCUSSION

The present study attempted to reach a conclusion by gathering the existing evidence regarding the effect of electrical nerve stimulation in management of overactive bladder in children for the first time. Findings indicted that using this treatment intervention leads to decrease in the number of wet days per week and voiding frequency, and increase in maximum voided volume and average voided volume. Finally, pooled analysis showed that the rate of treatment success in the group under treatment with electrical nerve stimulation is significantly higher than placebo or standard treatment group. Decrease in the number of wet days per week is a reliable scale for assessing the effectiveness of urinary incontinence treatment. This scale reflects the individual's quality of life. Because presence of urinary incontinence inflicts serious psycho-mental stress on the patient and this in turn leads to social isolation, drop in self-esteem and even manifestation of mental illnesses (44). Therefore, a treatment modality that can decrease this problem can have a significant effect on improvement of the quality of life. Urodynamic scales are among other variables that have repeatedly been used in studies for evaluating the effectiveness of urinary incontinence treatment. These scales are indicators of the function of bladder and its sphincters (45-50). The present meta-analysis showed that voiding frequency decreases under the effect of neural stimulation. This variable, which is known as the need for urinating frequently throughout the day or night, is the indicator of the activity of bladder muscles. Therefore, it is evident that neural stimulation leads to a decrease in urinary urgency. This might be the reason that under the effect of this modality, average voiding volume and maximum voiding volume increase. In comparison to the findings of the present study, in a systematic review Barroso and Lordêlo showed that neural stimulation is an efficient method for treatment of overactive bladder and can be easily tolerated by children (51). However, that systematic review had limitations including not performing a meta-analysis and including various types of studies without considering the methodology of the study (for example including studies that lacked a control group). In addition, in 2011, by performing a systematic review with a similar goal, De Gennaro et al. showed that existing clinical evidence regarding the effectiveness of electrical nerve stimulation in management of overactive bladder are not sufficient and there is a need for designing standard clinical trials for this purpose (52). Gaziev et al. in their systematic review express that percutaneous tibial electrical nerve stimulation is a reliable and safe method in treatment of lower urinary tract dysfunctions in adults (53). Finally, Zhu et al. in their meta-analysis on adults showed that electrical stimulation definitely has an effect on improvement of overactive bladder (54).

4-1. Limitation

Among the limitations of the present study, presence of heterogeneity in evaluation of some of the evaluated outcomes can be pointed out. However, the cause of this heterogeneity is not known. It is probable that the origin of this heterogeneity is difference in electrical nerve stimulation treatment protocols or it could be caused by the differences in the population of the studied children. Another limitation of the present study is the difference between the definitions of success rate among the studies. This might somehow show the presence of bias in this section.

5- CONCLUSIONS

Available studies express that using electrical nerve stimulation may lead to improvement of overactive bladder symptoms in children. However, lack of a complete conclusion led to motivation of the researchers of the present study to perform a systematic review and meta-analysis in this regard. Findings indicate the effectiveness of this treatment intervention in decreasing the number of wet days per week and voiding frequency, and increase in maximum voided volume and average voided volume. Finally, pooled analysis showed that the rate of treatment success in the group under treatment with electrical nerve stimulation is significantly higher than placebo or standard treatment group. Based on these findings, it is suggested to use electrical nerve stimulation in treatment of overactive bladder in children.

6- CONFLICT OF INTEREST: None.

7- ACKNOWLEDGMENTS

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Table-1: Search strategy in Medline database (via PubMed)

1- "Transcutaneous Electric Electrical nerve stimulation"[MeSH] OR "tibial nerve"[MeSH] OR "Percutaneous Electric Electrical nerve stimulation"[tiab] OR "TENS"[tiab] OR "Electrical Stimulation, Transcutaneous"[tiab] OR "Stimulation, Transcutaneous Electrical"[tiab] OR "Transcutaneous Electrical Stimulation"[tiab] OR "Transdermal Electrostimulation"[tiab] OR "Electrostimulation, Transdermal"[tiab] OR "Percutaneous Electrical Electrical nerve stimulation"[tiab] OR "Transcutaneous Electrical Electrical nerve stimulation"[tiab] OR "Electric Stimulation, Transcutaneous"[tiab] OR "Stimulation, Transcutaneous Electric"[tiab] OR "Transcutaneous Electric Stimulation"[tiab] OR "Transcutaneous Electrical nerve stimulation"[tiab] OR "Electrical nerve stimulation, Transcutaneous"[tiab] OR "Stimulation, Transcutaneous Nerve"[tiab] OR "Analgesic Cutaneous Electrostimulation"[tiab] OR "Cutaneous Electrostimulation, Analgesic"[tiab] OR "Electrostimulation, Analgesic Cutaneous"[tiab] OR "Electroanalgesia"[tiab] OR "tibial nerve"[tiab] OR "Tibial Nerve"[tiab] OR "Tibial Nerves"[tiab] OR "Posterior Tibial Nerve"[tiab] OR "Posterior Tibial Nerves"[tiab] OR "tibial electrical nerve stimulation"[tiab] OR "percutaneous tibial electrical nerve stimulation"[tiab] OR "electrical electrical nerve stimulation"[tiab] OR "Electrical nerve stimulation"[tiab] OR "Transcutaneous posterior tibial electrical nerve stimulation"[tiab] OR "tibial neuromodulation"[tiab].

2- "Urinary Bladder, Overactive"[Mesh] OR "Urinary Bladder, Overactive"[tiab] OR "Overactive Bladder"[tiab] OR "Overactive Urinary Bladder"[tiab] OR "Bladder, Overactive"[tiab] OR "Overactive Detrusor"[tiab] OR "Detrusor, Overactive"[tiab] OR "Overactive Detrusor Function"[tiab] OR "Detrusor Function, Overactive"[tiab] OR "bladder overactivity"[tiab] OR "detrusor overactivity"[tiab] OR "urinary bladder, overactive"[tiab]

3- #1 AND #2

Table-2: Characteristics of included studies

Author, Year, Country	Sample size*	Age[#] (year)	Gender (male, n)	Type of stimulation	Frequency / Sessions duration / intensity / Pulse duration / number of sessions	Number of sessions	Control strategy	Outcome	Follow-up (day)
Borch, 2016, Denmark (32)	12/12	5 to 15	16	TENS	10 Hz / NR / 40 mA / 200 µs	Single session	Sham	MVV; AVV	1
Borch, 2017, Denmark (31)	23 / 23	7.3	29	TENS	10 Hz / NR / 40 mA / 200 µs	Daily for 10 weeks	Oxybutynin	Success rate (VAS score 50 to 99)	70
Boudaoud, 2015, France (33)	9 / 11	10	10	TENS	10 Hz / 30 min / 10 mA / 200 µs	Twice a week for 12 weeks	Sham	Success rate (6 to 8-point decreases in incontinence score); MVV; Maximum detrusor pressure Incontinence score.	7
da Silvade Paula, 2017, Brazil (34)	8 / 8	3 to 18	6	TENS	10 Hz / 20 min / 10 mA / 700 µs	Weekly for 20 weeks	Sham	Success rate (VAS score 50 to 99); Wet per week.	60
Hagstroem, 2009, Denmark (35)	12 / 13	5 to 14	10	TENS	10 Hz / 120 min / 40 mA / 200 µs	Daily for 4 weeks	Sham	Success rate (more than 50% decreases in incontinence score); Incontinence score; Wet per week; Voiding frequency; MVV; AVV.	28
Kajbafzadeh, 2009, Iran (36)	10 / 19	3 to 16	12	Interferential TENS	1 to 20 Hz / 20 min / 0 to 50 mA / 250 µs	3 times per week for 6 weeks	Sham	MVV; Maximal detrusor pressure; Voiding frequency; Wet per week.	180
Kajbafzadeh, 2014, Iran (37)	15 / 15	6.7	18	Functional electrical stimulation	40 Hz / 15 min / 25 to 65 / 250 µs	3 times per week for 5 weeks	Sham	MVV; Maximal detrusor pressure; Voiding frequency; Wet per week; Incontinence score.	180
Lordêlo, 2010, Brazil (38)	16 / 21	4 to 12	12	TENS	10 Hz / 20 min / MLT / 700 µs	3 times per week for 7 weeks	Sham	Success rate (full cure based on VAS); MVV; AVV; Voiding frequency.	486

Patidar, 2015, India (39)	16 / 21	8.02	16	TENS	20 Hz / 30 min / 0 to 10 mA / 200 µs	Weekly sessions for 12 weeks	Sham	Success rate (full continence or mild severity in incontinence score); MVV; AVV; Voiding frequency	84
Quintiliano, 2015, Brazil (40)	15 / 13	4 to 17	9	TENS	10 Hz / 20 min / MLT/ 700 µs	3 times per week for 7 weeks	oxybutynin	Success rate (full cure base on VAS); MVV; AVV; Voiding frequency; Incontinence score.	180
Rashid, 2011, Pakistan (41)	14 / 14	1 to 12	15	TENS	35 Hz / 20 min / MLT/ 200 µs	Daily for 12 weeks	α-Adrenergic Blocker and imipramine	Success rate (one grade improvement in incontinence score); Voiding frequency.	84
Samhan, 2012, Egypt (42)	20 / 20	5 to 10	14	TENS	10 Hz / 20 min / MLT/ 700 µs	3 times per week for 8 weeks	Sham	Voiding frequency.	60
Sillén, 2014, Sweden (43)	32 / 30	8	35	TENS	10 Hz / 20 min / MLT/ NR	Twice Daily for 12 weeks	Behavioural therapy	Success rate (Improvement in incontinence episodes).	84

TENS: Transcutaneous electrical nerve stimulation; MVV: maximum voided volume; AVV: average voided volume; VAS: visual analogue scale.