Efficacy of Neuromodulation in Fecal Incontinence in Children; A Systematic Review and Meta-Analysis

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Abstract

**Background:** The results of existing studies regarding the use of neuromodulation in fecal incontinence (FI) are contradictory and therefore, a definitive conclusion cannot be made in this regard. Therefore, the aim of the present study was to evaluate the effectiveness of neuromodulation in controlling FI in children through a systematic review.

**Materials and Methods:** A decision was made to perform the search in electronic databases of Medline, Embase, Web of Science, CINAHL, and Scopus until end of October 2017. In the second step, the abstracts of the extracted studies were evaluated by 2 researchers independently and recorded in the data extraction form. Finally, all studies were summarized and categorized based on the evaluated outcomes and overall effect size was presented.

**Results:** Five studies were included in the present meta-analysis (including 115 children and adolescent). Pooled analysis also showed that the odds of improvement in the group under treatment with nerve stimulation was up to 20 times higher (OR = 20.29; 95% CI: 8.67 to 47.45; p<0.0001). In addition, using nerve stimulation leads to a significant improvement in fecal incontinence score of patients (SMD = 2.32; 95% CI: 1.12 to 3.52; p<0.0001).

**Conclusion:** It can be concluded that neuromodulation can seemingly be an effective measure in controlling FI in children. However, the lack of standard clinical trials in this field is highly felt and it is suggested to assess the effect of neuromodulation on FI by performing blinded randomized clinical trials in future studies.

**Key Words:** Children, Fecal Incontinence, Neuromodulation; Sacral Nerve Stimulation.


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1- INTRODUCTION

Fecal incontinence (FI) is a common and important disorder among pelvic floor disorders, which brings about a complicated situation and deeply impacts personal health, mental status, and quality of life in affected individuals (1). The incidence of mental and social problems following FI in children is significantly higher than adults. This has a big impact not only the individual but also the child’s family (2, 3). FI in children is defined as involuntary passing of stool in underwear (in children over 4 years old), and occurs due to functional (such as constipation, prolapse, inflammatory bowel disease and neuropathy), or organic causes (such as anorectal malformation, Hirschsprung's (HIRSH-sproongz) disease, spinal cord injury, cerebral palsy and myopathy) (4). The prevalence of FI in children of western countries is 0.8% to 4.1% (5-8). However, recent studies in Asia have shown that in Iran, South Korea and Sri Lanka the prevalence is 2% to 7.8% (9-11).

The first line of treatment mainly includes medication, biofeedback and therapeutic regimen (12, 13). The second line of treatment includes surgery such as sphincteroplasty (14), bulking agents (15), artificial sphincter (16), and recently, regeneration of damaged sphincter muscle tissue using stem cells (17, 18) just like this method is used for regeneration of other tissues (19-26). Applying less invasive therapeutic strategies for management of FI is more acceptable because Forte et al. have recently shown that, contrary to the current belief, surgery is not necessarily the most effective treatment for FI (27). One of these less invasive methods is using neuromodulation, such as Sacral Nerve Stimulation (SNS), which was among the first non-surgical techniques applied for treatment of FI. Today, SNS is considered as the second line of treatment in patients who have not responded to drug therapy, biofeedback, and etc. Neuromodulation probably results in the control of FI symptoms by affecting the somatosensory-cortical centres of the anus (28, 29). Limitations such as the mentioned therapeutic method being expensive on one hand and need for a skilled and expert operator or therapist on the other has resulted in this therapeutic method being unavailable in many instances and this has prevented it from being widely used in clinic. The results of existing studies regarding the use of neuromodulation in FI are contradictory and therefore, a definitive conclusion cannot be made in this regard. One of the ways that a general conclusion can be made regarding the effectiveness of using peripheral nerve stimulation in treating FI is performing a systematic review and meta-analysis on the existing studies in this field. Therefore, the aim of the present study is to evaluate the effectiveness of neuromodulation in controlling FI in children through a systematic review.

2- MATERIALS AND METHODS

2-1. Study design and search strategy

The present study is a systematic review in which the effect of SNS on FI in children and adolescents has been evaluated. This study has been designed based on Cochrane guideline for performing meta-analysis on clinical trials. Patients with FI in the age range of 1 to 19 years were considered. In the beginning of the study, search strategy was designed. By consulting a librarian who was familiar with databases, a decision was made to perform the search in electronic databases of Medline, Embase, Web of Science, CINAHL and Scopus. Search was done to find the studies published until end of October 2017. To do the search, first keywords including words related to "fecal incontinence" and "neuromodulation" were selected. Keywords were selected as broad
as possible in order to avoid omission of relevant studies. Keywords and their combination method in databases have been presented in Table.1 (Please see the table in the end of paper). To find additional articles or unpublished data, a hand-search was also carried out in the list of relevant study references and related journals. In addition, three strategies were considered for searching in gray literature. First, search was performed in the thesis section of ProQuest. Second, attempts were made to contact corresponding authors of related articles in order to access unpublished data or in-press articles. Finally, Google and Google Scholar search engines were used to find additional resources. In cases where the data could not be extracted from the article, authors of the articles were contacted. If the corresponding author did not respond to the first email, a reminder email was sent to the author. If there was still no response a second reminder was sent (with 1 week interval). If the author did not respond in the third attempt, other authors of the article were contacted via social media such as Research gate and LinkedIn to provide the required data for the researchers.

2-2. Inclusion and exclusion criteria

In this study, randomized clinical trials or quasi experimental studies that evaluated the effect of neuromodulation on FI were included. The study population was selected to include children and adolescents with FI from both sexes. Studies lacking a control group and those in which the status of FI was not evaluated were excluded. It should be noted that review articles were also excluded.

2-3. Quality assessment and data extraction

Data collection method, summarization and quality control of articles have been reported in previous studies by the researchers (30-50). In summary, the results of search in the literature were combined and duplicate studies were eliminated using EndNote software. In the second step, the abstracts of the extracted studies were evaluated by 2 researchers independently and recorded in the data extraction form and in case of being excluded, the reason was mentioned. In case of disagreement between the 2 researchers, a third reviewer studied the findings and by discussing it with the 2 researchers the disagreement was resolved. The systematic search results were recorded in a checklist that was designed based on the guidelines of PRISMA statement (51). This checklist included data related to article characteristics (name of the first author and year of publication), sample characteristics (age, gender), number of studied samples, baseline characteristics of the patients, duration of follow-up, treatment protocol, evaluated outcomes and probable bias. When the mentioned values were not reported in a study, the corresponding author was asked to provide them for the researchers. Quality status of each study was evaluated using the Cochran guideline for human studies.

2-4. Data analysis

All studies were summarized and categorized based on the evaluated outcomes. Heterogeneity between the studies was evaluated using chi square and I² tests, and p-value less than 0.1 were considered significant (indicating heterogeneity). Results of the studies were pooled and an overall effect size was presented. Funnel Plot and Egger's test and Begg's tests were used for evaluating publication bias (52). Statistical analyses were performed by STATA version 14.0 (Stata Corporation, College Station, TX).

3. RESULTS
3-1. Summary of included studies

The systematic and manual search conducted in this study yielded 4,352 non-redundant records. After the initial screening and receiving full-text of the articles, 15 papers were studied in more detail and finally, 5 studies were included (53-57) (Figure 1). Four studies had a before-after design and one study had cross-over clinical trial design. In these studies, a total of 115 children and adolescents with FI who had not responded to common treatments underwent treatment with neuromodulation. The neuromodulation used was implanted sacral nerve stimulation in three studies (54, 56, 57), transcutaneous external-neuromyogenic electrostimulation in 1 study (53), and transcutaneous posterior tibial nerve stimulation in another one (55). Protocol of nerve stimulation was not fully described in most studies. Only one study had reported all three factors of nerve stimulation frequency, session duration and session number (55). Duration of follow-up ranged between 4.5 and 30 months. The evaluated outcomes included resting pressure, maximum squeezing pressure, incontinence score and success rate (Table 2) (Please see the table in the end of paper).

![Fig.1: PRISMA flowchart of present study.](image-url)
3-2. Risk of bias

There was a high risk of bias regarding allocation concealment, blinding of patients and researchers and blinding of outcome assessing in all studies. The status of selective reporting and other bias was unclear in all studies (Figure 2). In addition, publication bias was not observed in the present study (Figure 3) (Please see the figures in the end of paper).

3-3. Meta-analysis

3-3-1. Success rate of neuromodulation in treatment of FI

The success rate reported in the study is shown in Figure 4-A. As can be seen, all studies have expressed that the success rate of nerve stimulation in were higher before intervention or the control group. Pooled analysis also showed that the odds of improvement in the group under treatment with nerve stimulation was up to 20 times higher (odds ratio [OR]= 20.29; 95% confidence interval [95% CI]: 8.67 to 47.45; p<0.0001).

3-3-2. Fecal incontinence score

Data from four papers were included in analyzes of this section (53-57). This section of analyzes included 79 children under treatment with nerve stimulation. The findings indicated a significant heterogeneity in this section (I²=87.2%; p<0.0001). Therefore, a random-effect model was used to pool the data. As Figure 4-B shows, using nerve stimulation leads to a significant improvement in fecal incontinence score of patients (standardized mean difference [SMD]=2.32; 95% CI: 1.12 to 3.52; p<0.0001). In other words, using this therapeutic technique can improve the status of stool control in children and adolescents.

4- DISCUSSION

The results of the present systematic review and meta-analysis on the role of neuromodulation in controlling FI in children indicate that this treatment method increases the success rate of fecal continence up to 20 times and also significantly increases standard fecal incontinence score compared to before treatment. These results indicate the effectiveness of neuromodulation for controlling FI in children. The results of the present meta-analysis are in line with those of the systematic reviews performed in adults in this regard. In 2004, Jarrett et al. performed a systematic review on 106 studies and its results showed that SNS significantly improves FI, and shows some degree of improvement regarding constipation (58). In 2008, in a systematic review on FI and constipation, Mowatt et al. stated that despite the effectiveness of SNS in controlling FI, more studies are needed to reach a definitive conclusion (59). In a systematic review evaluating the mechanism of SNS in the control of FI and constipation in 2014, while demonstrating the efficacy of SNS in controlling FI, more studies are needed to reach a definitive conclusion regarding the role of SNS in controlling FI after surgery and radiotherapy, more studies are needed (61, 62). Despite the numerous studies on SNS mechanism of action in controlling FI, the exact mechanism is unknown. Evidence suggests that the third sacral foramen is the best level for SNS induction, although second and third sacral foramina are also used. SNS effects are related to stimulation of the sacral nerve root adjacent to the
corresponding sacral foramen. In addition to stimulating the nerve root, part of the sympathetic chain that is adjacent to the sacral foramen is also stimulated. A sacral nerve contains motor, sensory and autonomic fibers (sympathetic and parasympathetic), and during SNS all of these fibers are stimulated. The first fibers that are stimulated during SNS are alpha motor fibers that innervate the external anal sphincter (EAS) and levator ani (63-66); thus, increasing the contractile force of the EAS can be a logical reason for improvement and success in stool control. After the motor fibers, the sensory fibers that innervate the anal canal are stimulated. These fibers play a key role in sensory-motor reflexes, which are important in optimal performance of the anal canal (67). Therefore, modulating these reflexes via SNS can be part of SNS mechanism of action in controlling FI. Balance in activity of autonomous nerves is a key factor in colorectal health and optimal performance of the internal anal sphincter (IAS) (68). Therefore, changing this balance and affecting IAS function can also be part of SNS mechanism of action in controlling FI.

4-1. Limitation

In general, existing systematic reviews as well as the present systematic review express that the small number of studies, presence of bias, and high heterogeneity in the performed studies are obstacles to reaching a conclusion regarding the effectiveness of this treatment method in treatment and management of FI. In addition, most of the studies included in this study had a before-after design, which is also one of the limitations that prevent reaching a reliable final conclusion in this regard. Therefore, in the end, this study suggests that the final conclusions can be reached after further clinical trials. Many of the included studies have low quality, which definitely makes comparing the studies difficult.

5- CONCLUSIONS

From the results of the present systematic review, it can be concluded that neuromodulation can seemingly be an effective measure in controlling FI in children. However, the lack of standard clinical trials in this field is highly felt and it is suggested to assess the effect of neuromodulation on FI by performing blinded randomized clinical trials in future studies.

6- CONFLICT OF INTEREST

All the authors declare that they have no conflict of interest.

7- ACKNOWLEDGMENTS

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8- REFERENCES


52. Egger M, Smith GD, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.


Table 1: Search query in Medline, Embase and Scopus databases

<table>
<thead>
<tr>
<th>Database</th>
<th>Search query</th>
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</table>
| Medline  | ("Fecal Incontinence"[Mesh] OR "Fecal Incontinence"[tiab] OR "Fecal Incontinences"[tiab] OR "Incontinence, Fecal"[tiab] OR “Incontinences, Fecal"[tiab] OR “anal incontinence"[tiab] OR “anus incontinence"[tiab] OR “bowel incontinence"[tiab] OR “encopresis"[tiab] OR “faecal incontinence"[tiab] OR “faeces incontinence"[tiab] OR “fecal incontinence"[tiab] OR “fecal incontinency"[tiab] OR “incontinence, anal"[tiab] OR “incontinencia alvi"[tiab])) AND (“Transcutaneous Electric Nerve Stimulation"[Mesh] OR “Transcutaneous Electric Nerve Stimulation"[tiab] OR “Percutaneous Electric 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 “Percutaneous Electrical Nerve Stimulation"[tiab] OR “Stimulation, Transcutaneous Electric"[tiab] OR “Transcutaneous Electric Stimulation"[tiab] OR “Nerve Stimulation, Transcutaneous"[tiab] OR “Stimulation, Transcutaneous Nerve"[tiab] OR “Nerve Stimulation, Transdermal"[tiab] OR “Percutaneous Electrical Nerve Stimulation"[tiab] OR "Electroanalgesia" OR "Neuromodulation" OR "sacral nerve stimulation" OR "sacral nerve modulation" OR "analgesic cutaneous" OR "cutaneous electrostimulation" OR "analgesic cutaneous stimulation" OR "cutaneous electrical stimulation" OR "cutaneous neurostimulation" OR "cutaneous neurostimulation" OR "cutaneous transdermal stimulation" OR "cutaneous transcutaneous stimulation" OR "cutaneous transcutaneous electrical stimulation" OR "cutaneous transcutaneous nerve stimulation" OR "cutaneous transcutaneous nerve modulation" OR "cutaneous transcutaneous electrical nerve stimulation" OR "cutaneous transcutaneous nerve stimulation" OR "cutaneous transdermal electrical stimulation" OR "cutaneous transdermal nerve stimulation" OR “sacral nerve stimulation" OR “sacral nerve modulation" OR “sacral nerve stimulation" OR “analgesic 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Embasse (neuromodulation/exp OR 'sacral nerve modulation/exp OR 'sacral nerve stimulation/exp OR 'nerve stimulation/exp OR 'transcutaneous electrical nerve stimulation/exp) AND (‘feces incontinence/exp OR ‘fecal leakage/exp).

Scopus

Neuromodulation in Fecal Incontinence

**Table-2: Summary of eligible studies neuromodulation in fecal incontinence**

<table>
<thead>
<tr>
<th>Author; year</th>
<th>Study type</th>
<th>Type of stimulation</th>
<th>Frequency (Hz)</th>
<th>Sessions Duration (min)</th>
<th>Sessions number</th>
<th>Sample size</th>
<th>Age (year)</th>
<th>Males (n)</th>
<th>Outcome</th>
<th>Follow-up (month)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ergun; 2010</td>
<td>Before-after</td>
<td>Transcutaneous external neuromyogenic</td>
<td>NR</td>
<td>NR</td>
<td>84</td>
<td>17</td>
<td>5 to 22</td>
<td>10</td>
<td>Incontinence score; Success rate</td>
<td>6</td>
</tr>
<tr>
<td>Haddad; 2010</td>
<td>Cross-over</td>
<td>Implanted sacral SNS</td>
<td>10 to 20</td>
<td>28</td>
<td>NR</td>
<td>18 / 18</td>
<td>12.22</td>
<td>24</td>
<td>Success rate</td>
<td>6</td>
</tr>
<tr>
<td>Lecompte; 2015</td>
<td>Before-after</td>
<td>Transcutaneous PTNS</td>
<td>10</td>
<td>20</td>
<td>270</td>
<td>8</td>
<td>10 to 13</td>
<td>5</td>
<td>Incontinence score; Success rate</td>
<td>6</td>
</tr>
<tr>
<td>Lu; 2017</td>
<td>Before-after</td>
<td>Implanted sacral SNS</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>25</td>
<td>10</td>
<td>13</td>
<td>Incontinence score; Success rate</td>
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<tr>
<td>Sulkowski; 2015</td>
<td>Before-after</td>
<td>Implanted sacral SNS</td>
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<td>NR</td>
<td>NR</td>
<td>29</td>
<td>12.1</td>
<td>13</td>
<td>Incontinence score; Success rate</td>
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</tr>
</tbody>
</table>

NR: Not reported; SNS: Sacral nerve stimulation; PTNS: Posterior tibial nerve stimulation; n= number; min: minute.
Fig. 2: Assessment of risk of bias through eligible studies.
**Fig.3:** Assessment of publication bias according to outcomes; A) success rate; B) fecal incontinence score.
Fig. 4: Forrest plot for the success rate of neuromodulation in treatment of fecal incontinence (A) and effect of this treatment modality on fecal incontinence score (B) in pediatric patients. CI: Confidence interval; OR: Odds ratio; SMD: Standardized mean differences.