

# Neuromuscular electrical stimulation as an adjunctive therapy to drotaverine hydrochloride for treating patients with diarrhea-predominant irritable bowel syndrome

## A retrospective study

Jian-kui Wang, MM, Juan Liu, MB\*

### Abstract

This retrospective study investigated the effectiveness and safety of neuromuscular electrical stimulation (NMES) as an adjunctive therapy to drotaverine hydrochloride (DHC) in patients with diarrhea-predominant irritable bowel syndrome (BP-IBS).

A total of 108 patient cases with BP-IBS were included in this study. Of these, 54 cases were assigned to a treatment group and received NMES and DHC, whereas the other 54 subjects were assigned to a control group and underwent DHC alone. All patients were treated for a total of 4 weeks. Primary outcomes were measured by the visual analog scale (VAS), and average weekly stool frequency. Secondary outcome was measured by the Bristol scale. In addition, adverse events were documented. All outcome measurements were analyzed before and after 4-week treatment.

Patients in the treatment group did not show better effectiveness in VAS ( $P = .14$ ), and average weekly stool frequency ( $P = .42$ ), as well as the Bristol scale ( $P = .71$ ), compared with the patients in the control group. Moreover, no significant differences in adverse events were found between 2 groups.

The results of this study showed that NMES as an adjunctive therapy to DHC may be not efficacious for patients with BP-IBS after 4-week treatment.

**Abbreviations:** AEs = adverse events, BP-IBS = diarrhea-predominant irritable bowel syndrome, DHC = drotaverine hydrochloride, IBS = irritable bowel syndrome, NMES = neuromuscular electrical stimulation, VAS = visual analog scale.

**Keywords:** diarrhea-predominant, drotaverine hydrochloride, effectiveness, Irritable bowel syndrome, neuromuscular electrical stimulation

## 1. Introduction

Irritable bowel syndrome (IBS) is a common chronic functional gastrointestinal disorder, which was characterized by recurrent abdominal pain, diarrhea, and/or constipation, and so on.<sup>[1–3]</sup> Previous studies have reported that its prevalence varied from 3.7% to 22% in Asian population.<sup>[4,5]</sup> The other study also reported that it has 24.0% prevalence at a sex ratio of 3:1 with female predominance.<sup>[6,7]</sup> This condition has 4 types with diarrhea predominant IBS (BP-IBS), constipation-predominant IBS, mixed diarrhea, and constipation-predominant IBS, and

alternating diarrhea and constipation-predominant IBS.<sup>[8–9]</sup> Of these, BP-IBS is the most common type.<sup>[10–12]</sup>

The current strategy for IBS treatment is to relieve its symptoms, and to improve the quality of life for the patients. Unfortunately, most patients who received long-term medication experienced poor efficacy and serious adverse events (AEs).<sup>[12–14]</sup> Thus, it is very urgent to seek alternative intervention to treat such condition.<sup>[15]</sup>

Complementary and alternative medicine including electroacupuncture, moxibustion, yoga, and neuromuscular electrical stimulation (NMES) is recommended to treat IBS more and more by physician.<sup>[16–18]</sup> However, limited data of NMES for the treatment of BP-IBS are still available currently. Thus, in this retrospective study, we investigated the effectiveness of NMES as an adjunctive therapy to drotaverine hydrochloride (DHC) for treating patients with BP-IBS.

## 2. Methods and materials

### 2.1. Study design

This study was approved by the ethics committee of The People's Hospital of Yan'an. Written informed consent was provided for all patients. All the cases were collected at the People's Hospital of Yan'an between December 2015 and November 2017. A total of 108 eligible patient cases with BP-IBS were included in this retrospective study. Of these, 54 cases received NMES plus DHC, whereas the other 54 subjects underwent DHC alone. All patients

Editor: Qinrong Zhang.

The authors report no conflicts of interest.

Department of Gastroenterology, The People's Hospital of Yan'an, Yan'an, 716000, China.

\* Correspondence: Juan Liu, Department of Gastroenterology, The People's Hospital of Yan'an, No.57 Qilipu Street, Baota District, Yan'an 716000, China (e-mail: Juanliu201501@yeah.net).

Copyright © 2018 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

Medicine (2018) 97:29(e11478)

Received: 29 April 2018 / Accepted: 15 June 2018

<http://dx.doi.org/10.1097/MD.00000000000011478>

were treated for a total of 4 weeks. Outcomes were measured before and after 4-week treatment.

## 2.2. Patients

Patient cases were included if they met the eligible criteria as follows: patients aged more than 18 years old; and confirmed diagnosis of BP-IBS based on the criteria of the Rome II diagnostic criteria for IBS.<sup>[19]</sup> However, the cases were excluded if the patients had other gastrointestinal tract diseases, pregnancy, unconsciousness, psychiatric problems, severe organ diseases, and incomplete outcome data. Additionally, cases were also excluded if the patients had a cardiac pacemaker, received DHC or NMES 1 month before they underwent these 2 interventions.

## 2.3. Treatment schedule

Patients in both groups received DHC 80 mg tablet, 2 times daily, 7 days weekly for a total of 4 weeks. Additionally, patients in the treatment group also received NMES at bilateral acupoints Shangjuxu (ST37, 6 *cun* below the lower border of the patella, one finger width lateral from the anterior border of the tibia), and Tianshu (ST25, 2 *cun* lateral to the belly button), 20 minutes for a pair of acupoints in one session, once daily, and 2 sessions weekly for a total of 4 weeks. NMES intervention was applied by the NMES device (HANS-100, Nanjing Jisheng Medical Technology Co., Ltd) at a frequency of 2 to 100 Hz. This device has 2 pairs of gel pads attached to a silicon patch. The patch was attached to the selected acupoint areas. The current intensity was gradually increased to the maximum of each patient's tolerance.

## 2.4. Outcome measurements

Primary outcomes were measured by visual analog scale (VAS),<sup>[20]</sup> and average weekly stool frequency. The VAS ranges from 0 to 10, with a higher score indicating a worse pain. Secondary outcome was assessed by the Bristol scale.<sup>[21]</sup> It consists of 7 types, from type 1, severe constipation, to type 7, severe diarrhea. Additionally, AEs were also documented in this study. All outcome measurements were evaluated before and after 4-week treatment.

## 2.5. Statistical analysis

In this study, all outcome measurements were analyzed by the SAS package (Version 9.1; SAS Institute Inc., Cary, NC). Continuous values were analyzed by the *t* test or Mann–Whitney rank test, whereas the categorical values were performed by Pearson  $\chi^2$  test or Fisher exact test. The level of statistical significance was defined as  $P < .05$ .

## 3. Results

In this retrospective study, a total of 108 eligible patients were included. The patient characteristics are summarized in Table 1. There were no significant differences regarding all the characteristic values between 2 groups (Table 1).

The results of primary and secondary outcome measurements are shown in Tables 2 to 4. Patients in the treatment group did not exert better outcomes in reducing pain, measured by the VAS scale ( $P = .14$ , Table 2), and stool frequency, measured by the average weekly stool frequency ( $P = .42$ , Table 3), as well as the Bristol score ( $P = .71$ , Table 4), compared with the patients in the control group after 4-week treatment.

**Table 1**

### Patients characteristics.

Characteristics	Treatment group (n = 54)	Control group (n = 54)	P
Age, y	40.6 (16.4)	41.3 (16.8)	.83
Sex			
Male	17 (31.5%)	21 (38.9%)	.42
Female	37 (68.5%)	33 (61.1%)	.42
BMI, kg/m <sup>2</sup>	21.7 (3.0)	21.4 (2.8)	.59
Diarrhea duration, y	2.1 (0.7)	2.0 (0.8)	.49
IBS type			
BP-IBS	54 (100.0%)	54 (100.0%)	—
VAS	6.1 (2.0)	5.8 (1.9)	.42
Average weekly stool frequency	17.9 (7.5)	17.2 (7.1)	.83
Bristol score	6.2 (1.0)	6.2 (0.9)	1.00

Data are present as mean  $\pm$  standard deviation or number (%). BMI = body mass index, BP-IBS = diarrhea-predominant irritable bowel syndrome, IBS = irritable bowel syndrome, VAS = visual analog scale.

**Table 2**

### Comparison of VAS after 4-week treatment between 2 groups.

VAS	Treatment group (n = 54)	Control group (n = 54)
Difference from baseline	2.0 (0.9, 3.2)	1.6 (0.7, 2.8)
P	<.01	<.01
Difference between groups		0.4 (0.1, 0.7)
P		.14

Data are present as mean and range. VAS = visual analog scale.

AEs of all included patients are listed in Table 5. No serious AEs occurred in either group. No treatment related death was found in both groups. No significant differences regarding AEs were found between both groups (Table 5).

## 4. Discussion

IBS is a very common chronic digestive issue among the youth and female population.<sup>[22,23]</sup> It often seriously impacts the quality of life in patients with such condition.<sup>[22]</sup> Previous published studies have reported that DHC can relieve the symptoms for this condition.<sup>[24]</sup> However, they also experienced lots of AEs when they underwent this medication.<sup>[24]</sup> Alternative intervention, such as NMES, is a potential adjunctive candidate to treat such kind of condition.<sup>[15]</sup>

To our best knowledge, no study specifically focused on NMES as an adjunctive therapy to DHC for treating patients with IBS in China, especially for BP-IBS. The results of this study can provide the potential evidence for the clinical practice, as well as the further study of this issue.

**Table 3**

### Comparison of average weekly stool frequency after 4-week treatment between two groups.

Stool frequency	Treatment group (n = 54)	Control group (n = 54)
Difference from baseline	2.8 (1.3, 4.0)	2.5 (1.6, 3.7)
P	.07	.11
Difference between groups		0.4 (0.1, 0.7)
P		.42

Data are presented as mean and range.

**Table 4****Comparison of Bristol score after 4-week treatment between 2 groups.**

Bristol score	Treatment group (n=54)	Control group (n=54)
Difference from baseline	-0.6 (-1.0, -0.2)	-0.4 (-0.7, -0.1)
<i>P</i>	.38	.59
Difference between groups		-0.2 (-0.5, -0.1)
<i>P</i>		.71

Data are present as mean and range.

**Table 5****Adverse events between 2 groups.**

Adverse events	Treatment group (n=54)	Control group (n=54)	<i>P</i>
Nausea	3 (5.6)	4 (7.4)	.70
Headache	3 (5.6)	2 (3.7)	.65
Dizziness	3 (5.6)	2 (3.7)	.65
Weakness	2 (3.7)	1 (2.7)	.57
Fatigue	1 (2.7)	2 (3.7)	.57
Insomnia	1 (2.7)	2 (3.7)	.57
Hot flash	1 (2.7)	0 (0)	.50

Data are present as number (%).

The results of this study demonstrated that NMES as an adjunctive therapy to DHC did not exert better outcomes in pain relief, measured by VAS scale, and the stool frequency, measured by average weekly stool frequency, compared with DHC alone. Furthermore, NMES and DHC did not show significant differences in the Bristol scale, when compared with DHC alone. These results indicate that NMES may be not an effective adjunctive candidate for patients with BP-IBS after 4-week treatment.

This study has its own unique advantages and limitations. On the one hand, this study firstly explored the effectiveness of NMES plus DHC for the treatment of patients with BP-IBS, which can provide potential evidence for the future studies. On the other hand, the treatment period was only 4 weeks and the sample size was quite small in this study, which may affect the results of this study. In addition, this study is a retrospective study with an intrinsic limitation, which may increase the selection bias. Future studies should avoid these limitations.

## 5. Conclusion

The results of this study found that NMES as an adjunctive therapy to DHC may not benefit for patients with BP-IBS after 4-week treatment. Further studies with larger sample size and longer treatment period are still needed to warrant the results of this study.

## Author contributions

**Conceptualization:** Juan Liu, Jian-kui Wang.

**Data curation:** Jian-kui Wang.

**Formal analysis:** Jian-kui Wang.

**Investigation:** Juan Liu.

**Methodology:** Jian-kui Wang.

**Project administration:** Juan Liu.

**Resources:** Juan Liu, Jian-kui Wang.

**Software:** Jian-kui Wang.

**Supervision:** Juan Liu.

**Writing – original draft:** Juan Liu, Jian-kui Wang.

**Writing – review & editing:** Juan Liu, Jian-kui Wang.

## References

- [1] Leyer P, Stanghellini V. Review article: Linaclotide for the management of irritable bowel syndrome with constipation. *Aliment Pharmacol Ther* 2014;39:371–84.
- [2] Li DY, Dai YK, Zhang YZ, et al. Systematic review and meta-analysis of traditional Chinese medicine in the treatment of constipation-predominant irritable bowel syndrome. *PLoS One* 2017;12:e0189491.
- [3] Defrees DN, Bailey J. Irritable Bowel Syndrome: Epidemiology, Pathophysiology, Diagnosis, and Treatment. *Prim Care* 2017;44:655–71.
- [4] Rey E, Talley NJ. Irritable bowel syndrome: novel views on the epidemiology and potential risk factors. *Dig Liver Dis* 2009;41:772–80.
- [5] Gwee KA, Wee S, Wong ML, et al. The prevalence, symptom characteristics, and impact of irritable bowel syndrome in an Asian urban community. *Am J Gastroenterol* 2004;99:924–31.
- [6] Cañón M, Ruiz AJ, Rondón M, et al. Prevalence of irritable bowel syndrome and health-related quality of life in adults aged 18 to 30 years in a Colombian University: an electronic survey. *Ann Gastroenterol* 2017;30:67–75.
- [7] Cremonini F, Talley NJ. Irritable bowel syndrome: epidemiology, natural history, health care seeking and emerging risk factors. *Gastroenterol Clin North Am* 2005;34:189–204.
- [8] Bijkerk CJ, Muris JW, Knottnerus JA, et al. Systematic review: the role of different types of fibre in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 2004;19:245–51.
- [9] El-Salhy M, Ystad SO, Mazzawi T, et al. Dietary fiber in irritable bowel syndrome. *Int J Mol Med* 2017;40:607–13.
- [10] Lacy BE. Diagnosis and treatment of diarrhea-predominant irritable bowel syndrome. *Int J Gen Med* 2016;9:7–17.
- [11] Lacy BE, Moreau JC. Diarrhea-predominant irritable bowel syndrome: diagnosis, etiology, and new treatment considerations. *J Am Assoc Nurse Pract* 2016;28:393–404.
- [12] Simrén M, Törnblom H, Palsson OS, et al. Management of the multiple symptoms of irritable bowel syndrome. *Lancet Gastroenterol Hepatol* 2017;2:112–22.
- [13] Spiller R, Aziz Q, Creed F, et al. Guidelines on the irritable bowel syndrome: mechanisms and practical management. *Gut* 2007;56:1770–98.
- [14] Li CY, Li SC. Treatment of irritable bowel syndrome in China: a review. *World J Gastroenterol* 2015;21:2315–22.
- [15] Grundmann O, Yoon SL. Complementary and alternative medicines in irritable bowel syndrome: an integrative view. *World J Gastroenterol* 2014;20:346–62.
- [16] Kavuri V, Raghuram N, Malamud A, et al. Irritable bowel syndrome: yoga as remedial therapy. *Evid Based Complement Alternat Med* 2015;2015:398156.
- [17] Zhao JM, Chen L, Zhou CL, et al. Comparison of electroacupuncture and moxibustion for relieving visceral hypersensitivity in rats with constipation-predominant irritable bowel syndrome. *Evid Based Complement Alternat Med* 2016;2016:9410505.
- [18] Ma X, Wang X, Kang N, et al. The effect of Tong-Xie-Yao-Fang on intestinal mucosal mast cells in postinfectious irritable bowel syndrome rats. *Evid Based Complement Alternat Med* 2017;2017:9086034.
- [19] Lea R, Hopkins V, Hastleton J, et al. Diagnostic criteria for irritable bowel syndrome: utility and applicability in clinical practice. *Digestion* 2004;70:210–3.
- [20] Crichton N. Visual analogue scale (VAS). *J Clin Nurs* 2001;10:706–16.
- [21] Riegler G, Esposito I. Bristol scale stool form. A still valid help in medical practice and clinical research. *Tech Coloproctol* 2001;53:163–4.
- [22] Hungin AP, Whorwell PJ, Tack J, et al. The prevalence, patterns, and impact of irritable bowel syndrome: An international survey of 40,000 subjects. *Aliment Pharmacol Ther* 2003;17:643–50.
- [23] Ruigomez A, Wallander MA, Johansson S, et al. One-year follow-up of newly diagnosed irritable bowel syndrome patients. *Aliment Pharmacol Ther* 1999;13:1097–102.
- [24] Rai RR, Dwivedi M, Kumar N. Efficacy and safety of drotaverine hydrochloride in irritable bowel syndrome: a randomized double-blind placebo-controlled study. *Saudi J Gastroenterol* 2014;20:378–82.