

## ANSWERING REVIEWERS



June 4, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 10696-review.doc).

**Title: Factorial study of moxibustion in the treatment of diarrhea-predominant irritable bowel syndrome**

**Author:** Ji-Meng Zhao, Lu-Yi Wu, Hui-Rong Liu, Hong-Yi Hu, Ren-Jia Huang, Yin Shi, Shan-Ping Tao, Qiang Gao, Ci-Li Zhou, Jia-Ying Wang, Li Qi, Xiao-Peng Ma, Huan-Gan Wu

**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 10696

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

[Reply the first reviewer \(Reviewer code: 00068989\)](#)

(1) The reason for selection of only IBS-D patients is not clear.

Use of the Rome III criteria, along with a careful history and physical examination, allows IBS to be confidently diagnosed and appropriately subtyped by the predominant stool pattern. The stool symptoms include constipation, meaning IBS with constipation (IBS-C); diarrhea (IBS-D); or mixed constipation and diarrhea (IBS-M). According the recently study[1], 186 patients with IBS that met Rome III criteria were represented a mixture of IBS subtypes, with 45% meeting the criteria for IBS-D, 16% for IBS-C, and 38% for IBS-M. And in another study, 186 Asian patients with IBS defined by Rome III criteria, 47% presented with diarrhea and 29% present with constipation [2].

On the other side, previous studies have indicated that moxibustion can significantly improve abdominal pain, diarrhea, and other symptoms in IBS patients[3,4]. And recently clinical study also demonstrated herb-partitioned moxibustion appears to be a promising, efficacious, and well-tolerated treatment for patients with IBS-D [5].

Therefore, on the basis of moxibustion being effective for D-IBS, this study chose the subtype (IBS-D) with a higher prevalence to explore the effects of the cone number and frequency of herb cake-separated moxibustion on the efficacy of IBS-D, in order to get a better herb cake-separated moxibustion treatment for IBS-D and to provide a scientific basis for clinical practice.

## References:

- [1] Lacy BE, Everhart KK, Weiser KT, DeLee R, Strobel S, Siegel C, Crowell MD. IBS patients' willingness to take risks with medications. *Am J Gastroenterol*. 2012; 107(6):804-809. PMID: 22664841. Doi:10.1038/ajg.2011.485.
- [2] Lu W, Gwee KA, Siah KT, Kang JY, Lee R, Ngan CC. Prevalence of Anti-deamidated gliadin peptide antibodies in Asian Patients with irritable bowel syndrome. *J Neurogastroenterol Motil*. 2014;20(2):236-241. PMID:24840376. Doi:10.5056/jnm.2014.20.2.236.
- [3] Wu HG, Zhao C, Shi Z, Chen HP, Liu Y, Liu SM. Clinical study on spleen-stomach-reinforcing moxibustion treatment of diarrhea-type irritable bowel syndrome. *World Journal of Acupuncture-Moxibustion*, 2002, 1:10-15
- [4] Liu HR, Hua XG, Yang Y, Wu HG. Clinical study on 5-HT expression in colonic mucosa and the treatment of herb-partition moxibustion in diarrhea-predominant IBS. *Liaoning Journal of Traditional Chinese Medicine*, 2006, 33(8):984-985.
- [5] Ma YX, Liu X, Liu CZ, Wang LP, Guo G, Du DQ, Wang ZL, Ma H, Qi P, Li ZF, Guo YP, Yi HQ, Gao SZ. Randomized clinical trial: the clinical effects of herb-partitioned moxibustion in patients with diarrhea-predominant irritable bowel syndrome. *Evid Based Complement Alternat Med*. 2013:605460. PMID:24454500. Doi:10.1155/2013/605460.

(2) The authors did not compare their results to placebo group.

Our previously clinical and animal studies [1-4] have proved moxibustion being effective for abdominal pain, diarrhea and other symptoms in irritable bowel syndrome. Based on previous studies, this article is designed to compare different impacts of the cone number and frequency of herb cake-separated moxibustion on IBS-D, in order to get a better herb cake-separated moxibustion treatment for IBS-D.

## References:

- [1] Wu HG, Zhao C, Shi Z, Chen HP, Liu Y, Liu SM. Clinical study on spleen-stomach-reinforcing moxibustion treatment of diarrhea-type irritable bowel syndrome. *World Journal of Acupuncture-Moxibustion*, 2002, 1:10-15
- [2] Liu HR, Hua XG, Yang Y, Wu HG. Clinical study on 5-HT expression in colonic mucosa and the treatment of herb-partition moxibustion in diarrhea-predominant IBS. *Liaoning Journal of Traditional Chinese Medicine*, 2006, 33(8):984-985.
- [3] Zhou EH, Liu HR, Wu HG, Shi Y, Wang XM, Yao LQ, Zhong YS, Yang Y. Herb-partition moxibustion relieves chronic visceral hyperalgesia and 5-HT concentration in colon mucosa of rats. *Neurol Res.* 2009, 31(7):734-737 [PMID:19108755, DOI:10.1179/174313209X382313]
- [4] Liu HR, Qi L, Wu LY, Ma XP, Qin XD, Huang WY, Dong M, Wu HG. Effects of moxibustion on dynorphin and endomorphin in rats with chronic visceral hyperalgesia. *World Journal of Gastroenterology*, 2010, 16(32):4079-4083 [PMID:20731023]

### (3) Method described

Thank you for your comments. The description of method in the study is too simple for foreign readers to understand. The "treatment" section is revised as the following: aconite, Latin name: *Aconitum carmichaeli* Debx. Traditional Chinese medicine believes aconite can warm yang and tonify spleen. A cone is the period for a moxa to burn out (about 20 minutes). The treatment lasts two courses, with two weeks as a course and no interval between courses.

### (4) Language problems

There are some spelling and grammar mistakes in the article, which have been corrected and revised by the English native speaker. Thank you for your suggestion.

### (5) The problem of sample size calculation

The sample size calculation is too complicated and we have already shortened in the article.

[Reply the second reviewer \(Reviewer code: 01432186\)](#)

### (1) Why did you include only patients with diarrhea predominant IBS?

Use of the Rome III criteria, along with a careful history and physical examination, allows

IBS to be confidently diagnosed and appropriately subtyped by the predominant stool pattern. The stool symptoms include constipation, meaning IBS with constipation (IBS-C); diarrhea (IBS-D); or mixed constipation and diarrhea (IBS-M). According to the recently study [1], 186 patients with IBS that met Rome III criteria were represented a mixture of IBS subtypes, with 45% meeting the criteria for IBS-D, 16% for IBS-C, and 38% for IBS-M. And in another study, 186 Asian patients with IBS defined by Rome III criteria, 47% presented with diarrhea and 29% present with constipation [2].

On the other side, previous studies have indicated that moxibustion can significantly improve abdominal pain, diarrhea, and other symptoms in IBS patients [3, 4]. And recently clinical study also demonstrated herb-partitioned moxibustion appears to be a promising, efficacious, and well-tolerated treatment for patients with IBS-D [5].

Therefore, on the basis of moxibustion being effective for D-IBS, this study chose the subtype (IBS-D) with a higher prevalence to explore the effects of the cone number and frequency of herb cake-separated moxibustion on the efficacy of IBS-D, in order to get a better herb cake-separated moxibustion treatment for IBS-D and to provide a scientific basis for clinical practice.

## References:

- [1] Lacy BE, Everhart KK, Weiser KT, DeLee R, Strobel S, Siegel C, Crowell MD. IBS patients' willingness to take risks with medications. *Am J Gastroenterol*. 2012;107(6):804-809. PMID: 22664841. Doi:10.1038/ajg.2011.485.
- [2] Lu W, Gwee KA, Siah KT, Kang JY, Lee R, Ngan CC. Prevalence of Anti-deamidated gliadin peptide antibodies in Asian Patients with irritable bowel syndrome. *J Neurogastroenterol Motil*. 2014;20(2):236-241. PMID:24840376. Doi:10.5056/jnm.2014.20.2.236.
- [3] Wu HG, Zhao C, Shi Z, Chen HP, Liu Y, Liu SM. Clinical study on spleen-stomach-reinforcing moxibustion treatment of diarrhea-type irritable bowel syndrome. *World Journal of Acupuncture-Moxibustion*, 2002, 1:10-15
- [4] Liu HR, Hua XG, Yang Y, Wu HG. Clinical study on 5-HT expression in colonic mucosa and the treatment of herb-partition moxibustion in diarrhea-predominant IBS. *Liaoning Journal of Traditional Chinese Medicine*, 2006, 33(8):984-985.

[5] Ma YX, Liu X, Liu CZ, Wang LP, Guo G, Du DQ, Wang ZL, Ma H, Qi P, Li ZF, Guo YP, Yi HQ, Gao SZ. Randomized clinical trial: the clinical effects of herb-partitioned moxibustion in patients with diarrhea-predominant irritable bowel syndrome. *Evid Based Complement Alternat Med*.2013;605460. PMID:24454500. Doi:10.1155/2013/605460.

(2) Some spelling errors

There are some spelling errors in the article, and we have already corrected. Thank you for your advice.

[Reply the third reviewer \(Reviewer code: 00002649\)](#)

MAJOR:

(1)Introduction of herb cake-separated moxibustion

Moxibustion therapy [1] is one of the three major therapies such as acupuncture, moxibustion and traditional Chinese medicine. However, less attention is paid to moxibustion therapy than acupuncture. Moxibustion therapy is used to treat as many diseases as acupuncture in China. Moxibustion is a therapy in which burning moxa produces a heat stimulation to the human body. It affects the function of the meridians and points to prevent and treat disease. Herb-partition moxibustion or herb cake-separated moxibustion is one of moxibustion therapies. The moxa cylinder is burned to warm up herb-partition to stimulate acupuncture points instead of acupuncture needle. Moxibustion therapy is suitable for gastrointestinal tract diseases especially functional diseases such as IBS. Now more and more attentions are paid to moxibustion therapy in clinic in China.

Aconite is called *Aconitum carmichaeli* Debx in Latin. Traditional Chinese medicine believes that aconite can warm yang and tonify spleen and *Folium Artemisiae Argyi* can smooth meridians and eliminate cold. The heat of burnt moxa plus the effect of the herb in an aconite cake-separated moxibustion on an acupoint can warm the middle, disperse cold, tonify spleen, and stop the diarrhea. Modern research shows that partitioned moxibustion mainly conduct heat through heat conduction and heat radiation from the separator to the acupoint skin while through biological heat transfer from the acupoint skin to deep tissue and other parts[2]. It is also found that the spectrum of aconite

cake-separated moxibustion is amazingly the same with infrared radiation, with 7.51 $\mu$ m as their radiation peaks, which may be the material basis of moxibustion [3].

## References:

- [1] Zhou EH, Liu HR, Wu HG, Shi Y, Wang XM, Yao LQ, Zhong YS, Yang Y. Herb-partition moxibustion relieves chronic visceral hyperalgesia and 5-HT concentration in colon mucosa of rats. *Neurol Res* 2009;31(7):734-737. PMID: 19108755. Doi:10.1179/174313209X382313.
- [2] Wei JZ, Shen XY, Ding GH, Zhao L. Pathway and mechanism analysis of warm stimulation in partitioned moxibustion. *Chinese acupuncture*, 2007;27 (5) :391-394.
- [3] Ding GH, Shen XY, Chu JH, Huang ZM, Yao W, Zhou Y, Wei JZ, Chu LX, Zhang HM, Fei L. Comparison of infrared radiation spectrum of traditional moxibustion, substitute moxibustion and acupoints of human body. *Journal of Infrared and Millimeter Waves*, 2003;22(2):123-126.

(2) Explain all adverse events and reasons caused by aconite cake-separated moxibustion

Aconite cake-separated moxibustion is a relatively safe and effective treatment for irritable bowel syndrome. Adverse effects may be local skin burns. A small blister needs no treatment. A blister larger than 1cm<sup>2</sup> can be pricked and treated with burn ointment.

Patients didn't have nausea or vomiting in the study.

(3) This is a possible explanation for why all doses were very effective, but equally so. Are the acupuncture sites critical? Is heat transfer critical?

Traditional Chinese medicine believes that moxibustion is a therapy in which burning moxa produces a heat stimulation to the human body. It affects the function of the meridians and points to prevent and treat disease. Modern research shows that thermal stimulation, optical radiation and moxibustion product are three main factors in a moxibustion effect [1]. And the response to the thermal stimulation, optical radiation and its product is the scientific basis of moxibustion.

I agree with the reviewer's view of comparison with the placebo group, which is the focus in our following study. Now some studies of sham acupuncture for IBS have shown that sham acupuncture is as effective as acupuncture in relieving symptoms. Therefore, in the next study, reasonable and objective sham acupuncture group should be set for

comparison in order to provide a reliable basis for the treatment of IBS with acupuncture and moxibustion.

#### **References:**

[1] Wu HG, Yan J, Yu SG, Xu B, Chang XR, Ma XP, Mu GP, Liu HR. Current situation and development trend of moxibustion research [J]. Shanghai Journal of Acupuncture, 2009,28 (1) :1-6.

(4) When only one cone was applied, which of the 3 sites was chosen?

Three acupoints are left ST-25, right ST-25 and CV-6 (see Illustration 1). The burnt moxa are placed on the aconite cakes on these three acupoints. A cone is the period for a moxa to burn out, about 20 minutes.

(5) What was the durability of response—ie duration of symptom reduction before symptoms went back to normal?

We have already studied the clinical efficacy of treating IBS with moxibustion (including mild moxibustion and herb-separated moxibustion)[1]. A six-month follow-up shows 20 significantly effective cases (28.17%), 23 effective cases, 28 ineffective cases (39.44%) in 71 patients, with a total efficiency of 60.56%. On the basis of moxibustion being effective for IBS, the study believes that aconite cake-separated moxibustion is a better treatment for IBS-D.

#### **References:**

[1] Qi L, Li N, Liu HR, Ma XP, Wu LY, Wang XM, Zhou CL, Wu HG. Clinical and experimental studies on moxibustion for treatment of irritable bowel syndrome. China Journal of Traditional Chinese Medicine and Pharmacy, 2010,25 (12): 2224-2227

#### **MINOR:**

(1) What was the rationale that cake-separated moxibustion would improve depression or anxiety?

The study found a correlation among gastrointestinal symptoms, severity of psychological state and abnormal activation of specific brain areas in patients with IBS. The results of this study indicate that medicine-separated moxibustion can improve clinical symptoms in patients with IBS, with a linear correlation between improvement of SAS, SDS and symptoms, indicating that aconite cake-separated moxibustion can significantly improve mood disorders of IBS patients and improvement of mood can also significantly relieve

symptoms. Therefore, we hypothesized that improvement of gastrointestinal symptoms will reduce the psychological burden, and then anxiety and depression of the patient will be better.

(2) The grammar is good throughout, but what are “mental workers”?

Mental workers are personnel in the field of science and technology, arts, education, health, finance and trade, law, management and others, as well as those who need little physical strength but extremely nervous stress, such as personnel in observation, testing, and instrument operation. They are mainly engaged in mental work, with problems like irregular working hours and little muscle activity.

I have changed it into brainworker.

(3) I looked up references 20-21 and am not convinced that clinical trials have confirmed the efficacy of moxibustion in IBS patients.

Numerous previous studies have demonstrated that acupuncture can effectively alleviate visceral sensitivity in IBS patients, and reduce their abdominal pain, diarrhea, constipation and other symptoms. The results of Meta-analysis also confirmed the effectiveness of acupuncture and moxibustion in the treatment of IBS [1-3]. Methodological quality of treating IBS with acupuncture and moxibustion should be strengthened in future studies, and high-quality multi-center randomized controlled trials should be designed and implemented.

#### **References:**

[1] Zhao C, Mu JP, Cui YH, Yang L, Ma XP, Qi L. Meta-analysis of treating irritable bowel syndrome with acupuncture and moxibustion. *Journal of Chinese Medicine*, 2010,28(5):961-963

[2] Park JW, Lee BH, Lee H. Moxibustion in the management of irritable bowel syndrome: systematic review and meta-analysis. *BMC Complement Altern Med*, 2013,13:247

[3] Chao GQ, Zhang S. Effectiveness of acupuncture to treat irritable bowel syndrome: a meta-analysis. *World J Gastroenterol*, 2014,20(7):1871-1877

(4) Can the authors clarify the generic name for Smecta and Dicitel?

Smecta: Dioctahedral Smectite

Dicitel: Pinaverium Bromide Tablets

There may be some problems in translation, which have been corrected in the text.

(5) “frequency and number of cones.” (Needs the “s”).

Yes, thank you for your suggestion. I have revised and examined carefully.

(6) The pages are not numbered.

Yes, thank you for your suggestion. I have marked the page.

(7) Under Methods, the sentences above the description of the 4 groups...could be deleted (redundant).

Yes, the repeated parts have been removed.

(8) What is aconite?

Aconite is called *Aconitum carmichaeli* Debx in Latin. Traditional Chinese medicine believes that aconite can warm yang and tonify spleen and *Folium Artemisiae Argyi* can smooth meridians and eliminate cold. The heat of burnt moxa plus the effect of the herb in an aconite cake-separated moxibustion on an acupoint can warm the middle, disperse cold, tonify spleen, and stop the diarrhea.

(9) “Screened” probably means “sieved.”

Yes, I have corrected in the text.

(10) Each course lasted 2 weeks, but what was the interval in-between?

There is no interval between the two treatment courses.

(11) What is meant by “defecation feelings”-? Pain relieved by defecation?

Defecation feelings mean how the patient feels when he defecates. Many IBS patients suffer abdominal pain before or during defecation. After the treatment with moxibustion, the pain during defecation will be significantly reduced.

(12) Results are very strong compared with other reports of treatments for IBS, e.g. a decrease of 21 in IBS QOL, again highlighting the importance of studying a placebo group.

I agree with your suggestion about the placebo group. Although this study is a good argument of medicine-separated moxibustion in the treatment of IBS-D, we will design reasonable placebo group in future studies.

(13) Intro is a bit too long, yet is missing critical information about the technique.

Based on your suggestion, deletion and modification have been done in Introduction.

(14) Description of sample size estimation could be briefer

Based on your suggestion, deletion and modification have been done in the description of

sample estimate.

(15) RESULTS is misspelled.

Spelling errors have been corrected in Results. Thank you!

(16) The MS is much longer than it needs to be. Multiple comparisons always lead to small differences that may or may not be of importance.

Based on your suggestions, deletion and modification have been done in Manuscript.

(17) I don't see the need for Table 4.

Table 4 is to study the correlation between the improvement of gastrointestinal symptoms and improvement of anxiety and depression. The results show the correlation between improvement of gastrointestinal symptoms and mood, which further illustrates that aconite cake-separated moxibustion can relieve anxiety and depression through improvement of gastrointestinal symptoms in patients.

(18) The difference between "the degree of symptom improvement" and "SAS score improvement."

"The degree of symptom improvement" is the score obtained mainly based on Birmingham questionnaire of IBS symptoms, indicating the severity of gastrointestinal symptoms in patients with IBS. "SAS score" is the score mainly based on SAS Scale, reflecting the degree of anxiety in patients with IBS. Results of Table 4 indicates relevance of the two, suggesting that aconite cake-separated moxibustion can relieve anxiety through improvement of gastrointestinal symptoms in patients.

(19) How long did it take the mild burns to heal?

About 20min.

(20) Other treatments for IBS do indeed require cooperation between doctors and patients.  
Yes.

(21) No proof that thermal effects are required in this study.

Thermal effect is an important factor affecting the function of moxibustion. However, in the present study, we believe that 1 cone a time or 2 cones a time in the same group have the same thermal effects. Therefore, based on the same thermal effects, different amounts of moxibustion are studied for the treatment effect.

(22) Can delete "thus creating are ciprocal causation of the physical and psychological

symptoms of IBS.”

Studies have shown IBS patients are often accompanied by varying degrees of mental symptoms. This study aims to illustrate aconite cake-separated moxibustion can improve anxiety and depression while improving gastrointestinal symptoms of the patient.

(23) Discussion is too long.

Yes, I've deleted and modified.

(24) Since the group studied had D-IBS, what was the effect on diarrhea?

Yes. There are many ancient records on moxibustion in the treatment of diarrhea. Modern research also shows that moxibustion can treat diarrhea in children and adults [\[1-3\]](#).

### References:

[1] Yan FL, Li X, Fu HX. Infantile intractable diarrhea treated with moxibustion. *Zhongguo Zhenjiu*, 2013,33(7):631. PMID:24032200

[2] Chen RX, Chen MR, Fu Y, Zhang B, Chi ZH. Clinical study of moxibustion on ST-25 in the treatment of chronic diarrhea (spleen deficiency type). *Jiangxi Journal of Traditional Chinese Medicine*, 2011, 42 (337) :24-26.

[3] Ye Dan, Dong XZ, Zhu XD. Observation of 20 cases of aconite cake-separated moxibustion in the treatment of diarrhea of spleen and stomach deficiency type. *Zhejiang Journal of Chinese Medicine*, 2012,47 (10): 759.

(25)A CONSORT diagram was not included. This would show the number of dropouts, etc.

Figure 1 The flow chart of this investigation shown, six patients dropped out during the study. In particular, one case, two cases, two cases, and one case were lost from aconite cake-separated moxibustion groups 1, 2, 3, and 4, respectively.

(26)Much of the paper deals with describing scales that are already validated.

Yes, I will revise based on your suggestions, thank you!

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Ji-Meng Zhao

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