PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Electroacupuncture for stress-predominant mixed urinary incontinence: a protocol for a three-armed randomized controlled trial
AUTHORS	Sun, Yuanjie; Liu, Yan; Chen, Huan; Yan, Yan; Liu, zhishun

VERSION 1 – REVIEW

REVIEWER	Blayne Welk Western University, Canada
REVIEW RETURNED	23-Apr-2020

GENERAL COMMENTS	Grammatical review will be necessary. There are several instances through the paper. As examples: 1st paragraph, last sentence: “under one second” should be rephrased. Also in the introduction: “When it refers to surgery for MUI, other therapies might need to be combined with to conquer the urgency component.12 In addition, the existence of urgency symptoms might aggravate after surgery13, and even reduce the success rate of operation14.” Should read: “When surgery is considered for MUI, other therapies might need to be combined with surgery to control the urgency component.12 In addition, the existence of urgency symptoms might be aggravated after surgery13, and even reduce the success rate of stress incontinence operations14.” How will overactive bladder medications at baseline be handled? There is a mention of documentation at baseline, but would most women be expected to be on these, and how will patients be instructed: continue these medications or discontinue them and allow a washout period? Why is there is no assessment of OAB symptoms, such as one of the many validated OAB questionnaires? This would help document baseline and potential improvement in OAB symptoms. Please consider explaining in the discussion the rationale for including both a sham and a conservative management arm in this study. Please consider mentioning the potential adverse effects, if any associated with active/sham treatment.

REVIEWER	Arjun Nambiar Freeman Hospital, Newcastle-upon-Tyne, UK
REVIEW RETURNED	28-Apr-2020

GENERAL COMMENTS	The authors are commended on a well-planned and well written protocol for elec. It will be interesting to see the results of the study. The inclusion and exclusion criteria seem appropriate and the choice of primary outcome is reasonable. MUI is an area where there is a lack of high quality evidence and so the premise of the trial is sound. I have only minor comments to make: typo line 52 ("nature" should be "natural") typo line 242 ("charged" should be "charge of")

REVIEWER	Julien Renard Geneva University Hospital Division pf Urology Geneva, Switzerland EOC, Saint John Hospital Division of Urology and Neurourology Bellinzona, Switzerland
REVIEW RETURNED	17-Jul-2020

GENERAL COMMENTS	This paper represents an atipical topic which makes it interesting as it treats of treatment of incontinence by acupuncture. One of the main limitations of this paper lies in the fact that it is abôut the treatment of Mixed urinary incontinence. Maybe a paper adresing separately stress and urge incontinence and the benefits of acupuncture would be more appropriate. Furthermore I beleieve that authors should present an hypothesis on how acupuncture works especially in the setting of stress incontinence which is usually due to sphincter insufficiency. Treatment of urge incontinence with acupuncture and electrical stimulations seems more easy to accept as it may reproduce ptns . PLease provide an explanation on the mechanism of action

REVIEWER	William Gibson University of Alberta
REVIEW RETURNED	04-Sep-2020

GENERAL COMMENTS	Thank you for asking me to review this protocol for a trial of acupuncture for MUI in women. In my view there are two major revisions to consider. Firstly, there is no sample size calculation given. If this is an exploratory trial this should be explicitly stated with a discussion of the caliucuatkon of effect size and plans for a fully powered trial. Secondly, insufficient detail is given to the process for maintaining and assessing blinding. What training and instruction will be given to the acupuncturists to ensure they do not inadvertently or deliberately unblind participants? How will adherence to lifestyle intervention be assessed , other than subjectively? The section on adverse events also needs expanding - how will the acupuncturists determine if an adverse effect is trial related?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Blayne Welk
Institution and Country: Western University, Canada
Competing interests: None
1.Grammatical review will be necessary. There are several instances through the paper. As examples: 1st paragraph, last sentence: “under one second” should be rephrased. Also in the introduction: “When it refers to surgery for MUI, other therapies might need to be combined with to conquer the urgency component.12 In addition, the existence of urgency symptoms might aggravate after surgery13, and even reduce the success rate of operation14.” Should read: “When surgery is considered for MUI, other therapies might need to be combined with surgery to control the urgency component.12 In addition, the existence of urgency symptoms might be aggravated after surgery13, and even reduce the success rate of stress incontinence operations14.”
Response:
“Under one second” has been revised into “less than fifty percent of such population” (Page 4, Line 60-61). The instances mentioned above had been corrected per suggestion (Page 4, Line 73-76). The manuscript had been revised for English expression.

2. How will overactive bladder medications at baseline be handled? There is a mention of documentation at baseline, but would most women be expected to be on these, and how will patients be instructed: continue these medications or discontinue them and allow a washout period?
Response:
Patients with overactive bladder medications, such as antimuscarinic drugs, in the previous one month will be excluded from the trial, therefore, there is no need of a washout period. To make it explicit, the related exclusion criteria is revised, both in the manuscript and registry website, into: History of treatments targeted at UI, such as acupuncture, PFMT and medications in the previous one month. (Page 6, Line 130-131)

3. Why is there is no assessment of OAB symptoms, such as one of the many validated OAB questionnaires? This would help document baseline and potential improvement in OAB symptoms.
Response:
Overactive Bladder Questionnaire short form (OAB-q SF) will be used to assess the OAB symptom bother and the health-related quality of life at weeks 4, 8,20 and 32 (Figure 2. Study schedule). The introduction to the questionnaire has been added in Secondary outcomes section, as following: OAB-q SF is used to assess the OAB symptom bother and the health-related quality of life (HRQL) in the past 4 weeks24 25. The domains include coping, concern, sleep and emotional interactions. The scores are transformed to a 0- to 100-point scale, with higher scores indicating severe symptoms and better HRQL. (Page 10, Line 228-231)

In addition, the secondary outcome measure of “Change of total and sub-score of OAB-q SF from baseline to weeks 4, 8, 20 and 32” is also added in the manuscript (Table 1) and registry website.

4. Please consider explaining in the discussion the rationale for including both a sham and a conservative management arm in this study.
Response:
The rationale for including both a sham and a conservative management arm has been added in discussion (Page 13-14, Line 327-338), as following:
Since plenty of patients in China have received acupuncture before, the form of superficial insertion at non-acupoint area with minimal and transient electric current is applied as sham control to eliminate placebo effects. The superficial insertion enables participants to promptly percept the stimulation and

electric current, which may further enhance the blinding even if it lasts only about 30 seconds. It is argued that minimal acupuncture may evoke physiologic effects30, especially for pain and depression31 32. However, the pathology of MUI is mainly sphincter insufficiency and detrusor overactivity. Studies indicates the rheobase of the normal bladder was 1-5mA33. The transient and minimal current output may not produce effects on the function of bladder. In the WL group, participants only receive healthcare education and lifestyle modification. The WL-control is applied to eliminate the influence of disease's natural cause.

5. Please consider mentioning the potential adverse effects, if any associated with active/sham treatment.
Response:
The potential adverse events and the way to determine whether it is related to active/sham treatment have been added in Safety assessment section (Page 11, Line 251-259), as following:
Adverse events (AEs), associated with the intervention or not, will be monitored and documented by participants and research assistants in Adverse Event Record Form and CRF throughout the trial. Whether the events are related to the treatments will be decided by acupuncturists and related specialists in each site within 24 hours of occurrence. Acupuncture related AEs are defined as following: broken needle, needle phobia, intense pain that is unbearable, bleeding, hematoma, infection or abscess at the needling site, and other discomfort induced by acupuncture, such as pain, nausea, vomiting, palpitation, dizziness, headache, loss of appetite, or insomnia that lasts for one hour or longer after treatment.

Reviewer: 2
Reviewer Name: Arjun Nambiar
Institution and Country: Freeman Hospital, Newcastle-upon-Tyne, UK
Competing interests: None declared
Please leave your comments for the authors below
The authors are commended on a well-planned and well written protocol for elec. It will be interesting to see the results of the study. The inclusion and exclusion criteria seem appropriate and the choice of primary outcome is reasonable. MUI is an area where there is a lack of high quality evidence and so the premise of the trial is sound.
I have only minor comments to make:

typo line 52 ("nature" should be "natural")
typo line 242 ("charged" should be "charge of")
Response:
Sorry for our negligence, and the errors you mentioned have been corrected per suggestion in Page 3, Line 50 and Page 11, Line 267.

Reviewer: 3
Reviewer Name: Julien Renard
Institution and Country:
Geneva University Hospital
Division pf Urology
Geneva, Switzerland
EOC, Saint John Hospital
Division of Urology and Neurourology
Bellinzona, Switzerland
Competing interests: none
Please leave your comments for the authors below

This paper represents an atipical topic which makes it interesting as it treats of treatment of incontinence by acupuncture. One of the main limitations of this paper lies in the fact that it is abôut the treatment of Mixed urinary incontinence. Maybe a paper adresing separately stress and urge incontinence and the benefits of acupuncture would be more appropriate. Furthermore I beleieve that authors should present an hypothesis on how acupuncture works especially in the setting of stress incontinence which is usually due to sphincter insufficiency. Treatment of urge incontinence with acupuncture and electrical stimulations seems more easy to accept as it may reproduce ptns. Please provide an explanation on the mechanism of action.
Response:
The explanation on the mechanism of acupuncture on MUI, especially on SUI, has been added in DISCUSSION section (Page 13, Line 319-326) as following:
The physiology underlying MUI remains unclear. Intrinsic urethral sphincter deficiency caused by weak pelvic floor muscles have been proposed as the main pathophysiology of SUI28 and detrusor overactivity is one of the main reasons leading to UUI11. Via acupuncture point BL33 and BL35, electroacupuncture may stimulate the S3 nerve and both motor and afferent fibers of the pudendal nerve, which can not only strengthen the pelvic muscles and raise the patient's awareness of these muscles, but also decrease the sensation of urgency and inhibit parasympathetic activity and involuntary detrusor contractions29.

Reviewer: 4
Reviewer Name: William Gibson
Institution and Country: University of Alberta
Competing interests: None declared
Please leave your comments for the authors below
Thank you for asking me to review this protocol for a trial of acupuncture for MUI in women.

1. In my view there are two major revisions to consider. Firstly, there is no sample size calculation given. If this is an exploratory trial this should be explicitly stated with a discussion of the caliucuation of effect size and plans for a fully powered trial.
Response:
It is intended to be a fully powered clinical trial. The Sample size section (Page 12, Line 284-289) has been revised as following:
Sample size
Based on our previous study14 15, we assume that 25% participants in the SA group will have at least 50% reduction of mean stress IEF from baseline to week 8. To detect a difference of 23% between the EA and SA group, a sample size of 232 participants will need to provide the trial with 80% power with a two-sided significance level of 0.05 and 10% dropouts.

2. Secondly, insufficient detail is given to the process for maintaining and assessing blinding. What training and instruction will be given to the acupuncturists to ensure they do not inadvertently or deliberately unblind participants?
Response:
Details for maintain and assessing blinding have been added in Intervention section (Page 8-9, Line 184-199), as following:
Participants in the EA and SA groups will be blind to the group allocations. Acupuncturists and research assistants will be instructed not to tell the group allocation to participants. Addition, to avoid the occurrence of inadvertent unblinding, the contacts between participants and project staff during treatment will be reduced as much as possible, and the manipulation of acupuncture, connecting to electronic apparatus and withdrawal of needles will be separately undertaken by acupuncturists and another research assistant. Participants will be treated separately with curtain drawing and their companions waiting outside the clinic, if any. Before manipulation, participants will be told that during

the treatment they may feel the electrical stimulation fade down gradually, even to the degree that they cannot percept. That is because the body has built up a tolerance to the electrical stimulation during the treatment process. Within 5 minutes after either treatment at week 8, participants will be told that they may have received EA treatment with deep insertion, or SA treatment with shallow insertion, and asked to answer the question do you think you have received EA treatment, and choose the answer between the options of Yes and No.

3. How will adherence to lifestyle intervention be assessed, other than subjectively?
Response:
The methods to promote and assess lifestyle modification have been added in Quality control section (Page 11, Line 271-275), as following:
To promote the adherence on lifestyle modification, the research assistants will remind the participants to adjust their lifestyle per the suggestions and record the changes of condition and lifestyle on Lifestyle Record Form every week. On each outcome assessment visit, the forms will be collected and examined by outcome assessors, and recorded in CRF in time.

4. The section on adverse events also needs expanding - how will the acupuncturists determine if an adverse effect is trial related?
Response:
The Safety assessment (Page 11, Line 251-259) section has been expanded per suggestion as following:
Adverse events (AEs), associated with the intervention or not, will be monitored and documented by participants and research assistants in Adverse Event Record Form and CRF throughout the trial. Whether the events are related to the treatments will be decided by acupuncturists and related specialists in each site within 24 hours of occurrence. Acupuncture related AEs are defined as following: broken needle, needle phobia, intense pain that is unbearable, bleeding, hematoma, infection or abscess at the needling site, and other discomfort induced by acupuncture, such as pain, nausea, vomiting, palpitation, dizziness, headache, loss of appetite, or insomnia that lasts for one hour or longer after treatment.

VERSION 2 – REVIEW

REVIEWER	Blayne Welk Western University
REVIEW RETURNED	03-Oct-2020

GENERAL COMMENTS	The authors have addressed my comments. Some minor grammatical issues remain, which can be addressed in final editing. Two minor corrections: 1. "The scores are transformed to a 0- to 100-point scale, with higher scores indicated severe symptoms and better HRQL." A higher score meaning more severe symptoms would mean a worse HRQOL. 2. "Participants will be instructed to drink 500 ml solid-free water..." I think it is solute free water.

REVIEWER	Julien Renard ORBV Division or urology Bellinzona, switzerland
REVIEW RETURNED	23-Oct-2020

GENERAL COMMENTS	Eager to see results

REVIEWER	William Gibson University of Alberta
REVIEW RETURNED	08-Oct-2020

GENERAL COMMENTS	Thank you for asking me to review this revised manuscript. I note that my comments and those of my co-reviewers have been addressed. I have a few comments to address. Line 322: "detrusor overactivity is one of the main reasons leading to UUI(ref 11)" DO is a urodynamic finding and is not synonymous with nor the main reason for urgency incontinence, particularly in older adults. Lines 324-326 "which can not only strengthen the pelvic muscles and raise the patient's awareness of these muscles, but also decrease the sensation of urgency and inhibit parasympathetic activity and involuntary detrusor contractions29. " This is a generous interpretation of the reference provided, which concluded "there was some evidence that electrical stimulation enhanced the effect of PFMT in the short term but not after six months.". I would suggest that this paragraph is rephrased to better reflect the available evidence. There remain numerous instances of syntax and grammatical errors to correct.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Comments to the Author
The authors have addressed my comments. Some minor grammatical issues remain, which can be addressed in final editing.
Two minor corrections:
1. "The scores are transformed to a 0- to 100-point scale, with higher scores indicated severe symptoms and better HRQL." A higher score meaning more severe symptoms would mean a worse HRQOL.
Response:
Sorry for the inexplicit description. It has been revised in Page 10, Line 230-232, as follows:
The scores are transformed to 0- to 100-point scales, with higher scores on the symptom bother scale indicating severe symptoms and higher scores on the HRQOL indicating a better HRQOL.

2. "Participants will be instructed to drink 500 ml solid-free water..." I think it is solute free water.
Response:

Sorry for the negligence, we have consulted the original reference, and the “solid-free” has been corrected into “sodium-free” in Page 10, Line 234.

Reviewer: 3
Comments to the Author
Eager to see results
Response: Really thank you.

Reviewer: 4
Comments to the Author
Thank you for asking me to review this revised manuscript. I note that my comments and those of my co-reviewers have been addressed.
1. I have a few comments to address.
Line 322: "detrusor overactivity is one of the main reasons leading to UUI(ref 11)"
DO is a urodynamic finding and is not synonymous with nor the main reason for urgency incontinence, particularly in older adults.
Lines 324-326
"which can not only strengthen the pelvic muscles and raise the patient's awareness of these muscles, but also decrease the sensation of urgency and inhibit parasympathetic activity and involuntary detrusor contractions29. "
This is a generous interpretation of the reference provided, which concluded "there was some evidence that electrical stimulation enhanced the effect of PFMT in the short term but not after six months.".
I would suggest that this paragraph is rephrased to better reflect the available evidence.
Response:
Thank you for your constructive suggestion. The paragraph has been rephrased in Page 13, Line 320-333, as follows:
The physiology underlying MUI remains unclear. UUI is closely associated with physiological perturbations to bladder function, such as detrusor overactivity, poor detrusor compliance and bladder hypersensitivity11, while urethral hypermobility resulting from weak pelvic floor or poorly supported urethral sphincter, or intrinsic urethral sphincter deficiency have been proposed as the main pathophysiology of SUI28. Electroacupuncture may relieve the symptoms of MUI by modulate the function of related nerves. Acupuncture points of BL 33, BL35 and SP6 are located in the lumbosacral region and posterior tibial region, in the distribution area of sacral plexus and pudendal nerves. Either by direct stimulation or indirect stimulation via sacral roots or plexus, the pudendal afferent can be activated to induce a strong inhibition of the detrusor hyperreflexia and cause detrusor relaxation 29. Additionally, stimulation of pudendal nerves can contract the pelvic floor muscle and simulate PFMT30, which can improve urethral function and relieve SUI symptoms31.
Reference:
11. Aoki Y, Brown HW, Brubaker L, et al. Urinary incontinence in women. Nat Rev Dis Primers 2017;3:17042. doi: 10.1038/nrdp.2017.42 [published Online First: 2017/07/07]
28. Yoshimura N, Miyazato M. Neurophysiology and therapeutic receptor targets for stress urinary incontinence. International Journal of Urology 2012;19(6):524-37. doi: 10.1111/j.1442-2042.2012.02976.x
29. Bosch JL. Electrical neuromodulatory therapy in female voiding dysfunction. BJU Int 2006;98 Suppl 1:43-8; discussion 49. doi: 10.1111/j.1464-410X.2006.06316.x [published Online First: 2006/08/17]
30. Wang S, Zhang S. Simultaneous perineal ultrasound and vaginal pressure measurement prove the action of electrical pudendal nerve stimulation in treating female stress incontinence. BJU Int

2012;110(9):1338-43. doi: 10.1111/j.1464-410X.2012.11029.x [published Online First: 2012/03/16]
31. Deng K, Balog BM, Lin DL, et al. Daily bilateral pudendal nerve electrical stimulation improves recovery from stress urinary incontinence. Interface Focus 2019;9(4):20190020. doi: 10.1098/rsfs.2019.0020 [published Online First: 2019/07/03]

2. There remain numerous instances of syntax and grammatical errors to correct.
Response:
The manuscript has undergone extensive revision for its English expression. Hoping it can meet the standards of the journal this time.