

## Section 2

## 10

## Physical Methods

# Electroacupuncture for Moderate and Severe Benign Prostatic Hyperplasia: A randomized controlled trial

China

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## Summary

A randomized controlled trial was carried out to evaluate the effects of electroacupuncture (EA) on moderate to severe benign prostate hyperplasia (BPH), and to explore the therapeutic effective difference between EA at the recommended acupoint BL33, and a non-acupoint for BPH.

Men with BPH and an International Prostate Symptom Score (IPSS)  $\geq 8$  were enrolled in the trial. One hundred participants were randomly allocated to receive EA at acupoint BL33 (treatment group) and EA at a non-acupoint (control group). The primary outcome was the change of IPSS at the sixth week. Secondary outcomes included

changes of post-void residual (PVR) urine and of urinary flow rate (Qmax) at the sixth week and change of IPSS at the eighteenth week. Treatment group patients had 4.51 points and 3.2 points greater decline in IPSS than the control group at week 6 and week 18 respectively ( $p < 0.001$ ,  $p = 0.001$ ). No significant differences were found in Qmax and PVR between two groups.

The results indicate that EA is effective in improving patient's quality of life and acupoint BL33 may have better therapeutic effects than non-acupoints in acupuncture treatments of BPH.

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## Background and Justification

Benign prostate hyperplasia (BPH) is an enlargement of the prostate gland due to progressive hyperplasia of the stromal and glandular cells of the prostate. The prevalence of this disease is as high as 40% in men in their fifties and 90% in men in their eighties (Nickel, 2006). BPH is one of the most common causes of lower urinary tract symptoms (LUTS). Current treatments for BPH include watchful waiting, lifestyle modifications, alpha blockers, 5 alpha-reductase inhibitors, phytochemicals, and BPH-related surgery (Tanguay *et al.*, 2009). Although most of the aforementioned therapies have various degrees of documented effectiveness in the management of BPH, the use of these interventions are limited to specific patient populations or have certain side effects that interfere with patients' quality of life.

Acupuncture is a traditional Chinese medicine treatment that has been commonly used in the management of LUTS in China for thousands of years. The effects of acupuncture on LUTS were well documented in Chinese medicine textbooks and are well-supported by modern research studies (Wang, 2003). Ricci *et al.* (2004) found that electroacupuncture (EA) had better effects in decreasing number of voiding times of urinary urgency that persisted after transurethral resection of the prostate. Kubista *et al.* (1976) found that EA could significantly increase the closing pressure in women with stress incontinence

compared with a placebo, and Philp *et al.* (1988) found that acupuncture increased the bladder capacity in patients with bladder instability. Besides effects on urinary storage problems, acupuncture was also found effective in the prevention of recurrent lower urinary tract infections in adult women (Aune *et al.*, 1998; Alraek *et al.*, 2002), and in improving the quality of life in patients with chronic prostatitis (Capodice *et al.* 2007).

BPH is clinically characterized by various LUTS which may include or be similar to urinary urgency, stress incontinence, bladder instability, and urinary tract infection (UTI). Therefore, we hypothesize that acupuncture may be effective in the management of BPH.

This hypothesis is supported by our previous studies in which we found that acupuncture at BL33 had better effects than terazosin in improving the International Prostate Symptom Score (IPSS), post-void residual urine (PVR), and maximum urinary flow rate (Qmax) on patients diagnosed with mild to moderate BPH (Yang *et al.*, 2008; Yang *et al.*, 2008a).

Theories of traditional Chinese medicine and results from modern studies indicate that acupoints of the fourteen meridians have specific functional regulatory effect on *zang-fu* organs (Shuran and Zhongsuan, 1987; Cheng and Han 2004; Xu *et al.*, 2010). However, studies in western countries found that dry needling, an acupuncture procedure at trigger points (including non-acupoints that do not belong to the meridian system), were effective in the management of various diseases (Diraçoğlu *et al.*, 2012; Kalichman and Vulfsons, 2010). Both dry needling and traditional acupuncture treat diseases via inserting stainless needles into the human body. However, differences between acupuncture at acupoints and acupuncture at non-acupoints have not been fully investigated. In the present study, we aimed to compare the therapeutic effectiveness of EA at bilateral acupoints of BL33 with EA at non-acupoints (2 cun [around 6.7 cm] lateral to BL33) in a randomized controlled pilot study. The results showed that correct acupoint EA was more effective than non-acupoint EA in reducing IPSS (Ding Y, 2011).

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## Description

Participants who met the trial criteria (Table 1, 2) were given a sequentially-numbered, opaque, sealed envelope. These envelopes were distributed to patients by an investigator who was not involved in acupuncture procedures and data analyses. Based on odd or even numbers assigned in the envelope, 50 participants were randomly allocated to receive either EA at acupoint BL33 (treatment group) and another 50 to receive EA at non-acupoint (control group).

<b><i>Inclusion criteria</i></b>	<b><i>Exclusion criteria</i></b>
<ul style="list-style-type: none"> <li>• 50–70 years old;</li> <li>• Moderate to severe BPH evaluated by IPSS; Patients having urinary dysfunction more than 3 months;</li> <li>• Patients with stable life signs;</li> <li>• Not on any <math>\alpha</math>1 receptor blocker, 5<math>\alpha</math>-reductase inhibitor or traditional Chinese medicine for over 1 week;</li> <li>• Volunteer to join this research and give informed consent prior to receiving treatment.</li> <li>• For safety reasons, patients were instructed of possible emergency conditions and were told to seek appropriate medical help if they should occur.</li> </ul>	<ul style="list-style-type: none"> <li>• Urinary dysfunction caused by gonorrhoea or urinary tract infection;</li> <li>• Oliguria and anuria caused by urinary calculi, prostate cancer, bladder tumor and acute/chronic renal failure;</li> <li>• Urinary dysfunction caused by neurogenic bladder, bladder neck fibrosis and urethral stricture;</li> <li>• Failure of invasive therapy for prostatic obstruction;</li> <li>• Injured local organs, muscle and nerve caused by pelvic operation or trauma;</li> <li>• Upper urinary obstruction and hydrocoele combined with damaged renal function due to BPH diagnosed by B-ultrasound;</li> <li>• Patients unable to commit to treatment because of commuting problems to the hospital.</li> </ul>

**Table 1:** The inclusion and the exclusion criteria for the clinical trial.

We used Huatuo brand needles (size 0.30 x 100 mm, manufactured by Suzhou Medical Appliance, Suzhou, Jiangsu Province, China) together with GB6805-2 Electro-Acu Stimulators (Huayi Medical Supply & Equipment Co., Ltd, Shanghai, China). For the treatment group, we needled at bilateral BL33 with a 45° angle. A feeling of soreness and distension is felt when needling into the third posterior sacral foramina (S3) with eventual radiation of the sensation to the perineum. Needles were inserted 60–80 mm without lifting, thrusting or rotating and, once in position, connected to the electric stimulator with a disperse-dense wave of 20 Hz. The current intensity was increased to the patients' maximum tolerance and then slightly reduced to a bearable level. For the control group, we took the site 2 cun lateral BL33 as the non-point. Manipulation methods and electric stimulator parameters were the same with those of the treatment group.

There were 16 sessions for all patients (five sessions in the first and second weeks and three sessions in the third and fourth weeks). Each session lasted 30 minutes. Acupuncture for the two groups was operated by the same acupuncturist who has more than ten years experience. This acupuncturist was blinded to the outcome assessment at baseline, week 6 and week 18.

All patients were evaluated during the first week for baseline values which included IPSS, PVR and Qmax. The primary outcome involved the change of IPSS from baseline at the 6th week; secondary outcomes included changes of PVR and Qmax at the sixth week and change of IPSS at the 18th week. Safety evaluation included haematoma, fainting, severe pain, and local infection during and after acupuncture. In addition, emergency conditions which require catheterization were also recorded if any.

The statistical analysis was performed by a statistician blinded to treatment allocation in the Clinical Evaluation Centre of China Academy of Chinese Medical Sciences.

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## Results

From September 2010 to May 2012, a total of 192 patients with LUTS visited the Acupuncture Department at Guang'anmen Hospital in Beijing. 92 patients were excluded from the present study because they either did not meet the inclusion criteria or met one or more of the exclusion criteria (Table 1).

One hundred of them were included and randomized to receive either acupoint acupuncture or non-acupoint acupuncture treatments (Figure 1). Figure 2 details the time frames of recruitment, treatment and follow-up periods.

## Study flow

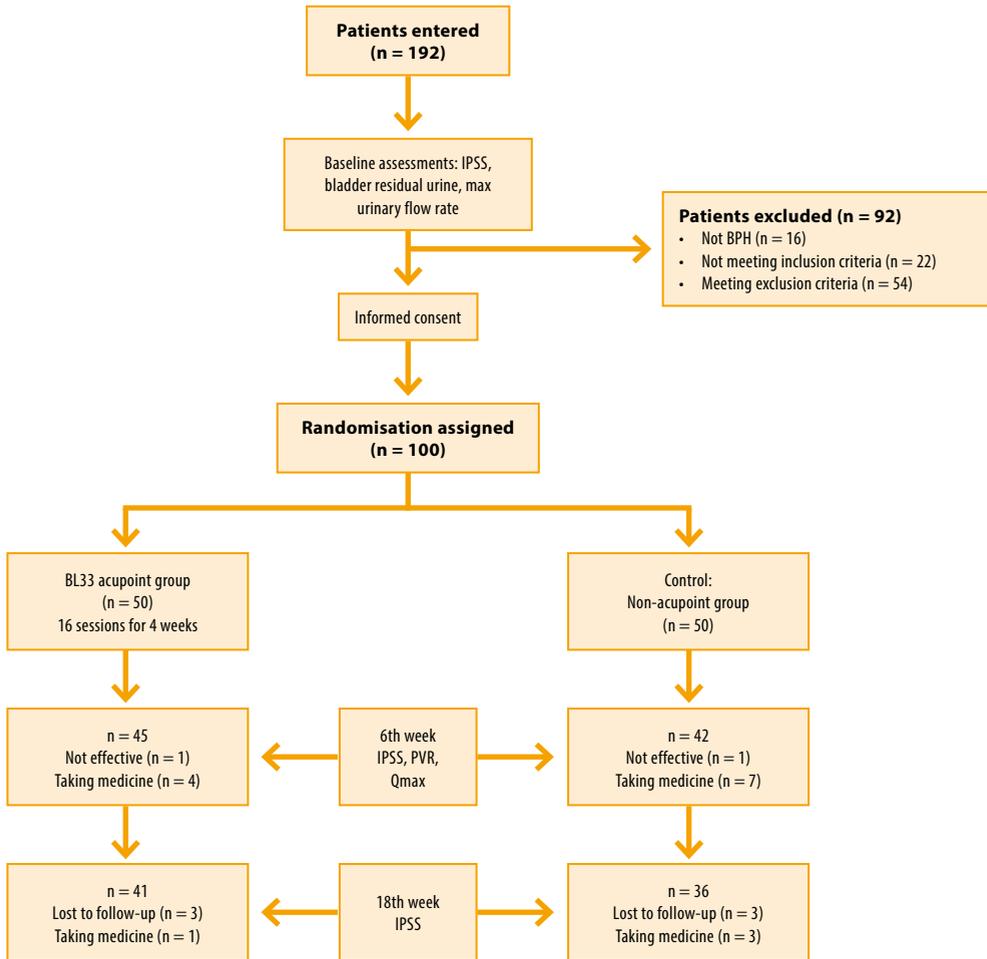


Figure 1: Flowchart for study participation.

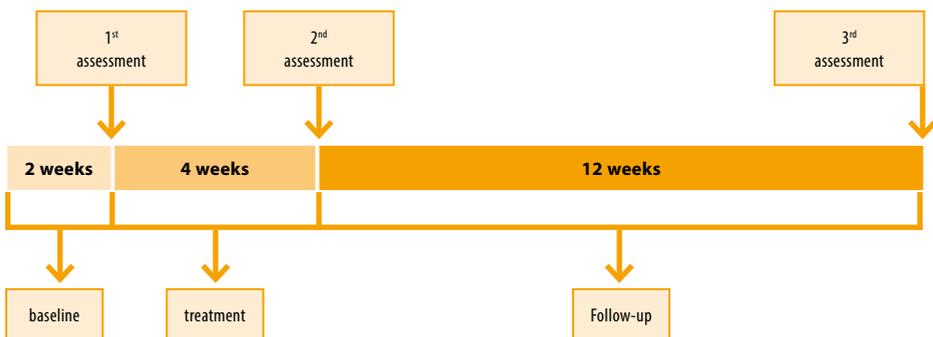


Figure 2: Time frame of each period of the trial.

Demographic characteristics and baseline information of the 100 participants are shown in Table 2. No statistically significant differences were found between the two groups in age, gender, and baseline values. The mean age of all participants was 65 years old.

	Acupoint group (n=50)	Non-point group (n=50)	P-value (two-tailed)
Age	64.80±7.05	65.94±6.74	0.411
Course of disease	76.08±57.59	73.66±57.72	0.834
IPSS	20.10±6.52	18.76±6.06	0.289
Qmax	13.04±6.73	15.93±7.33	0.051
PVR(ml)	20 (0,128)	16 (0,128)	0.260

**Table 2:** Demographic information and baseline characteristics.

Analyses of IPSS at the sixth week were based on both the intention-to-treat population (ITT) and the per protocol (PP) population (i.e. those who successfully completed the trial) (Table 3 and Table 4). At the sixth week, the ITT analysis indicated that IPSS reduced from 20.10±6.52 at baseline to 12.84±5.87 for the acupoint treatment group, and from 18.76±6.06 at baseline to 16.42±6.80 for non-point control group. With the PP analysis, IPSS of the two groups reduced to 12.60±5.85 and 16.05±6.83, respectively. At the sixth week, acupoint group patients had a 4.51 ( $p<0.001$ ) and 4.12 ( $p<0.001$ ) points greater decline than the non-acupoint control group in the ITT and PP populations, respectively (Table 5). At the 18th week, a 3.2 points ( $p=0.001$ ) greater decline was found for the acupoint treatment group compared to the non-acupoint control group.

		Acupoint group (n=50)	Non-point group (n=50)
IPSS	Baseline	20.10±6.52	18.76±6.06
	Week 6	12.84±5.87	16.42±6.80
	Change in IPSS	7.26±5.12	2.34±4.85
	Week 18	14.62±5.76	16.96±6.47
	Change in IPSS	5.28±5.16	1.8±5.06
PVR (ml)	Baseline	20 (0,128)	16 (0,128)
	Week 6	20 (0,300)	15 (0,180)
	Change in PVR	0 (-172,84)	0 (-120,80)
Qmax	Baseline	13.04±6.73	15.93±7.33
	Week 6	12.63±6.11	15.00±6.50
	Change in Qmax	0.36±4.51	0.98±4.05

**Table 3:** Descriptive statistics of ITT population.

		Acupoint group (n=45)	Non-point group (n=42)
IPSS	Baseline	19.84±6.46	18.83±6.00
	Week 6	12.60±5.87	16.05±6.83
	Change in IPSS	7.24±5.23	2.79±5.17

**Table 4:** Descriptive statistics of the per protocol (PP) population.

		Treatment effect estimate (Mean difference)	Standard error	P-value
IPSS (ITT)	Week 6	4.51	0.93	0.0000
	Week 18	3.20	0.93	0.0001
IPSS (PP)	Week 6	4.12	1.03	0.0000
Qmax (ITT)	Week 6	0.18	0.80	0.819

**Table 5:** Statistical analysis of the trial outcomes: ANCOVA test results. P-values less than 0.05 are considered significant.

*Qmax and PVR.* No significant differences were found between the two groups in Qmax at the sixth week ( $p=0.819$ , Table 5). PVR data followed a non-normal distribution and no significant difference was found ( $P=0.35$ ).

*Adverse events.* No serious adverse events happened in either group. Two cases of mild haematoma were reported in the non-acupoint control group during study. The patients were told to apply ice and compression within 24 hours and heat compression after 24 hours to the acupuncture treatment areas. The haematomas disappeared in about two weeks.

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## Impact

In this study, EA at BL33 had better effects on IPSS, but no difference on PVR and Qmax as compared with non-acupoint EA. The results indicate that EA is effective in improving patients' quality of life and acupoint BL33 may have better therapeutic effects than non-acupoints in acupuncture treatment of BPH.

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## Lessons Learned

Blinding is difficult in acupuncture studies, so real randomized placebo-controlled trials may seem impossible. In this randomised controlled trial, enrolled patients were distributed via sequentially numbered, opaque, sealed envelopes by an investigator who was not involved in acupuncture procedures and data analyses. For the blinding of outcome assessors, the staff in charge of the assessment and the statistician were all blinded to the patients' allocation. Acupuncture operation (performed by an experienced acupuncturist) and filling of case report forms (by a postgraduate) were done under strict supervision. Phone calls and e-mails were used to inform the patients for follow-up assessments. Any medicine taken and other treatment conducted during this time were recorded in detail. Although non-acupoint EA procedures were used as a control in the present study, they are still acupuncture procedures; thus we could not rule out the confounding factor of needling and placebo effects in the present study.

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## Future Plans

This randomised controlled trial was performed in only one hospital rather than multi-centres. Therefore, the results of the present study may not well-characterize the general response of patients with BPH around the world. In future, to further test the therapeutic effects of EA on BPH, additional large scale, multi-centre, international cooperative studies are warranted.

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## Publications

- Yang Wang, Zhishun Liu, Jinna Yu, *et al.* (2011). Efficacy of electroacupuncture at Zhongliao point (BL33) for mild and moderate benign prostatic hyperplasia: study protocol for a randomized controlled trial. *Trials*,12:211.
- Yang Wang, Zhishun Liu, Jinna Yu, *et al.* (2013). Electroacupuncture for Moderate and Severe Benign Prostatic Hyperplasia: A Randomized Controlled Trial. *PloS One*, 8(4).

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