Using meta-regression approach to explore the dose-response association between acupuncture sessions and acupuncture effects on chronic prostatitis/chronic pelvic pain syndrome

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Background: The benefits of acupuncture on chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) have been well established according to previous studies. However, uncertainty exists regarding the dose-response relationship between acupuncture sessions and acupuncture effects for CP/CPPS. The objective of this study is to explore the association between the acupuncture sessions and its effects based on previously published data.

Methods: A non-linear meta-regression approach with restricted cubic spline (RCS) was used to investigate the dose-response relationship between acupuncture sessions and its effects on the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI). PubMed, EMBASE, and Cochrane CENTRAL were searched up to May 20, 2018. Randomized controlled trials (RCTs) and case series studies (CSSs) reported the treatment sessions of acupuncture for CP/CPPS with at least two categories were eligible for inclusion.

Results: Ten studies involving 329 participants were included, the results showed a J-shaped dose-response association between acupuncture sessions and NIH-CPSI score (range 0 to 43, with higher score indicating greater CP/CPPS symptoms). Overall, more acupuncture sessions received for CP/CPPS patients is associated with increased symptom relieving. After 6 acupuncture sessions, the NIH-CPSI decreased from 26.1 (95% CI: 25.3–27.0) to 18.5 (95% CI: 11.6–25.4), with a between-session difference of –7.6 (95% CI: –14.6 to –0.7). Considering the 95%CI, both robust-error meta-regression modeling [MD: –8.3 (95% CI: –10.4 to –6.3)] and sensitivity analysis without CSSs [MD: –8.1 (95% CI: –9.5 to –6.7)] demonstrated that 18 acupuncture sessions could reach a clinically meaningful improvement regarding NIH-CPSI score.

Conclusions: There appear to be dose-response relationship between acupuncture sessions and CP/CPPS outcome. Prolonged acupuncture sessions were associated with less NIH-CPSI score. According to current evidence, six acupuncture sessions might be the minimal required 'dose' to reach its clinical effects.

Keywords: Acupuncture; chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS); dose-response; meta-analysis

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Introduction

Category III prostatitis, also known as chronic prostatitis/ chronic pelvic pain syndrome (CP/CPPS) presents as chronic pain in the region of the pelvis, and often associated to ejaculatory pain, erectile dysfunction, and psychosocial symptoms, lasting for at least 3 to 6 months (1). As the most common type of prostatitis, CP/CPPS affects approximately 90% to 95% of men worldwide (2,3). Owing to its long-lasting symptoms that are tough to treat and quantify, indeed both patient and physician frustration is high in dealing with this disorder.

The benefits of acupuncture on CP/CPPS have been well established according to clinical trials (4-8), and guideline also supported its effectiveness for CP/CPPS (5,9,10). However, the existence of a possible dose-response association between acupuncture and its effects has not been well investigated. Currently, the acupuncture sessions of published studies ranged from 6 to 24 times, optimal dosing for acupuncture is not fully understood and clinical guidelines including acupuncture do not describe minimum treatment session that would constitute a full course of treatment for given condition (7).

As which is particularly important in pharmacology and epidemiology, dose-response relationship should be considered in the acupuncture clinical practice and research. White and colleagues realized question of "dose-response" for acupuncture study decade ago (11), suggesting that there is an urgent need for studies to guide decisions about what is an "adequate" dose of acupuncture for different conditions. To date, few studies examined factors associated with the number of acupuncture sessions completed, considered the question of adequate acupuncture sessions and applied criteria. Research into what constitutes an adequate dose of acupuncture has long been neglected and uncertainty exists regarding the dose-response relationship between treatment sessions and the effect of acupuncture (11). This study also demonstrated that there appear to be relationships between treatment timing, treatment frequency, and mode of needle stimulation, albeit these conclusions were drawn by qualitative approaches instead of quantitative analyses (11).

To address the aforementioned shortfalls and develop evidence-based recommendations, we introduced meta-regression approach into dose-response association between acupuncture sessions and acupuncture effects on CP/CPPS.

Methods

This meta-analysis was reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement and recommendations for improving the methodological quality of dose-response meta-analysis (12,13).

Literature search

Two reviewers independently searched PubMed, EMBASE, and Cochrane CENTRAL Register for Clinical Trials for English-language publications from their inception through December 8, 2017 and updated at May 20, 2018 using the search terms: "chronic prostatitis" OR "chronic pelvic pain syndrome" OR "CP/CPPS" AND "acupuncture" (see *Table S1*, which describe the search terms and strategies). In addition, a manual search was performed for relevant systematic reviews and guidelines. Both two authors have over 3 years' experience in evidence-based practice. Another author (C Xu) checked the excluded records to ensure there was no mis-operation.

Study selection

Trials were included if (I) patients diagnosed with CP/CPPS or chronic nonbacterial prostatitis; (II) efficacy data were available for acupuncture participants for at least one time point other than baseline and endpoint; (III) the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI) was utilized as outcome measurement of CP/CPPS (14). Trials were excluded if (I) patients with acute bacterial prostatitis, benign prostatic hyperplasia, prostate cancer or other prostate diseases; (II) non-invasive acupuncture was used (laser acupuncture, acupressure *et al.*); (III) secondary analysis using the published clinical sample; (IV) adjunctive therapy was provided to the acupuncture group.

We defined the total acupuncture sessions as the total counts of acupuncture therapy; we use the acupuncture sessions as primary intervene because compared with other variable it significantly varies with different studies; the primary outcome, NIH-CPSI, refers to the total score corresponding to each time point.
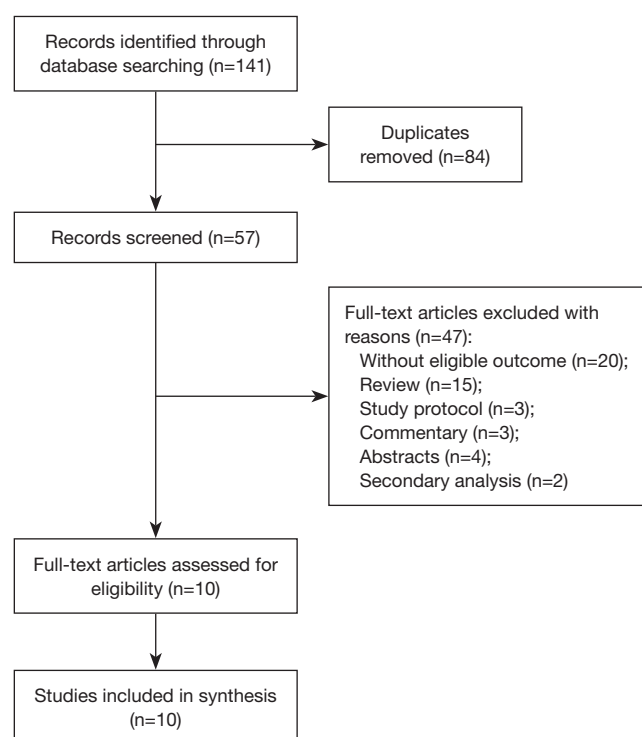
Figure 1 Study flow chart.

Data extraction and risk of bias assessment

Two authors extracted data from selected studies using an electronic standardized data extraction form. Any disagreements were solved by consensus. Study characteristics, patient characteristics, acupuncture sessions, acupuncture types, acupoints selection, and the NIH-CPSI score (range from 0 to 43). Included trials provided NIH-CPSI for at least two time points (baseline, first visit point). Additionally, if trials reported outcomes in a figure rather than in a table, GetData Graph Digitizer version 2.26 was used to extract data from the figures (software available at http://getdata-graph-digitizer.com).

Two authors evaluated the quality of included studies independently. We used the Cochrane Collaboration tool to evaluate the risk of bias for the RCTs. For assessing CSSs, a tool developed by Moga *et al.* was used , which consists of 20 items and can systematically evaluate the CSSs (15,16).

Statistical analysis

To build the relationship of acupuncture treatment sessions and NIH-CPSI score, we conducted dose-response meta-analyses using the approach of robust-error meta-regression

(REMR) (17). Based on the "one-stage" framework, REMR method treated each included study as a cluster, and fitted the meta-regression of treating sessions against the mean NIH-CPSI score within a whole data set. Additionally, we weighted each dose-specific effect for the pooling by using the inverse variance method, which, at the same time, can balance heteroscedasticity in REMR model and ensure the unbiasedness of parameter estimation.

Restricted cubic spline (RCS) was used for approximating non-linear relationship. This is reasonable since the data points of dose-specific effect are sufficient (at least four data points between two adjacent knots) to fit an RCS function (18). We set three fixed knots to place splines inserting values, with both tails of the curve restricted to linear. The step would generate two splines, in which, the first spline represents the initial "dose" and the second one would be the non-linear function (spline transformation) of dose (18). We forced the regression coefficient of the second spline to zero to test whether the trend correspond to non-linear, with the $P<0.1$ indicating the evidence of non-linear.

The mean value of NIH-CPSI score and the mean difference of NIH-CPSI score were used as effect estimators while the treatment sessions as "dose" in this meta-regression analysis. We illustrated the dose-response results in following two methods: initially, we synthesized the means of NIH-CPSI score to demonstrate association between the different acupuncture sessions and dose-specific NIH-CPSI score; then, we synthesized the change of means of NIH-CPSI score, with the mean difference equals zero as the reference.

Additionally, we undertook sensitivity analyses by omitting CSSs and studies with sample size less than ten participants. The subgroup analysis was classified by different acupuncture types (manual acupuncture *vs.* electroacupuncture). Because for one-stage dose-response meta-analysis, there were currently no valid measurement methods for assessing heterogeneity, we used the statistic $(1-R^2)$ as a rough estimation of heterogeneity. Analyses were performed using the Stata 13.0 software (Stata Corp., College Station, TX, USA), with a two-side test of $\alpha=0.05$ as the significant level.

Results

Characteristics of included studies

A flowchart describing the selection of eligible trials is presented in *Figure 1*. After removal of duplicates,

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Table 1 Characteristics of selected studies

Author	Study type	Patients in acupuncture group	Acupuncture type	Acupoints	Treatment session	Treatment time
Lee 2008 (8)	RCT	44	MA	CV1, CV4, SP6, SP9	20	30 minutes
Sahin 2015 (24)	RCT	50	MA	BL33, BL34, BL54, CV1, CV4, SP6, SP9	6	20 minutes
Zhou 2017 (26)	RCT	38	EA	BL30, BL35	6	30 minutes
Qin 2018 (6)	RCT	34	MA	BL23, BL33, BL35, SP6	24	30 minutes
Lee 2009 (23)	RCT	12	EA	BL32, BL33, GB30	12	20 minutes
Kucuk 2015 (22)	RCT	26	EA	BL28, GB41, LI3, LI4, SP6, SP8	14	Not report
Chen 2003 (20)	CSS	12	MA plus EA	BL10, BL23, BL28, BL35, BL39, BL40, BL54, BL67, KI1, KI10, CV3, CV4, SP6	12	20 minutes
Tugcu 2010 (25)	CSS	93	MA	BL33	6	20 minutes
Capodice 2007 (19)	CSS	10	MA	TE5, GB41, LR3, LI4, SP8, SP6	12	30 minutes
Honjo 2004 (21)	CSS	10	MA	BL33	4	10 minutes

RCT, randomized controlled trial; CSS, case series study; MA, manual acupuncture; EA, electroacupuncture; CV, conception vessel; SP, spleen meridian, BL, bladder meridian; KI, kidney meridian.

Table 2 Risk of bias assessment for included randomized controlled trials

Author	Sequence generation	Allocation concealment	Blinding	Incomplete outcome	Selective outcome report	Other source of bias
Lee 2008 (8)	Low	Unclear	Low	Low	Unclear	Low
Sahin 2015 (24)	Low	Unclear	Low	Low	Unclear	Low
Zhou 2017 (26)	Low	Low	Low	Low	Unclear	Unclear
Qin 2018 (6)	Low	Low	Low	Low	Low	Unclear
Lee 2009 (23)	Low	Unclear	High	Low	Unclear	Unclear
Kucuk 2015 (22)	Low	Unclear	High	Low	Unclear	Unclear

141 citations for eligibility with 57 full-texts were used. Finally, a total of ten studies (six RCTs and four CSSs) were included in qualitative review and meta-analysis (6,8,19-26). All studies were published in English. *Table 1* summarizes the parameters of included studies. In general, the quality items of included studies were generally acceptable. *Tables 2,3* present the quality assessment of included studies.

Acupuncture sessions and the NIH-CPSI score

Ten studies (six RCTs and four CSSs) were included in the meta-regression model and the results indicated that more acupuncture sessions were associated with greater therapeutic effects. A J-shaped association between acupuncture sessions and NIH-CPSI score was presented: after 6 acupuncture sessions, the NIH-CPSI decreased from 26.1 (95% CI: 25.3–27.0) to 18.5 (95% CI: 11.6–25.4), with a between-session difference of –7.6 (95% CI: –14.6 to –0.7). After 18 acupuncture sessions, the NIH-CPSI decreased to 17.8 (95% CI: 15.9–19.7), with a difference of –8.3 (95% CI: –10.4 to –6.3), and a 6-point decline of NIH-CPSI score have been used as the optimal threshold for minimal clinically important difference (27). After 24 acupuncture sessions, the NIH-CPSI increased to 19.0 (95% CI: 15.3–22.7), with a difference of –7.1 (95% CI: –10.9 to –3.4). Moderate heterogeneity was observed between included studies (1-R^2 =54.7%). *Figures 2,3* presented the results of NIH-CPSI score and changes of NIH-CPSI

Table 3 Quality assessment for assessing included case series studies (16)

	Tugcu 2010 (25)	Chen 2003 (20)	Capodice 2007 (19)	Honjo 2004 (21)
Study objective				
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes
Study design				
2. Was the study conducted prospectively?	Yes	Yes	Yes	Yes
3. Were the cases collected in more than one center?	No	No	No	No
4. Were patients recruited consecutively?	Unclear	Unclear	Unclear	No
Study population				
5. Were the characteristics of the patients included in the study described?	Yes	Yes	Yes	Yes
6. Were the eligibility criteria for entry into the study clearly stated?	Yes	Yes	Yes	Yes
7. Did patients enter the study at a similar point in the disease?	Yes	Yes	Yes	Yes
Intervention and cointervention				
8. Was the intervention of interest clearly described?	Yes	Yes	Yes	Yes
9. Were additional interventions (cointerventions) clearly described?	No	No	No	No
Outcome measures				
10. Were relevant outcome measures established a prior?	Yes	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	Yes	Yes	Yes	Yes
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes	Yes
Statistical analysis				
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes	Yes
Results and conclusions				
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes	Yes
16. Were losses to follow-up reported?	Yes	Yes	Yes	Yes
17. Did the study provided estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes	Yes	Yes
18. Were the adverse events reported?	Yes	Yes	Yes	No
19. Were the conclusions of the study supported by the results?	Yes	Yes	Yes	Yes
Competing interests and sources of support				
20. Were both competing interests and sources of support for the study reported?	No	No	No	No

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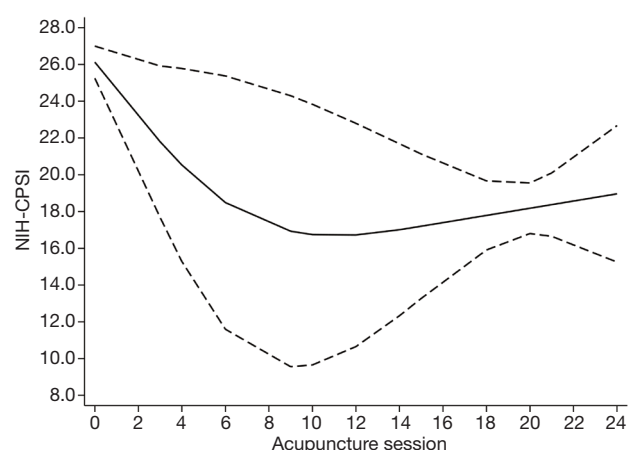

Figure 2 Dose-response relationship between acupuncture sessions and NIH-CPSI score.
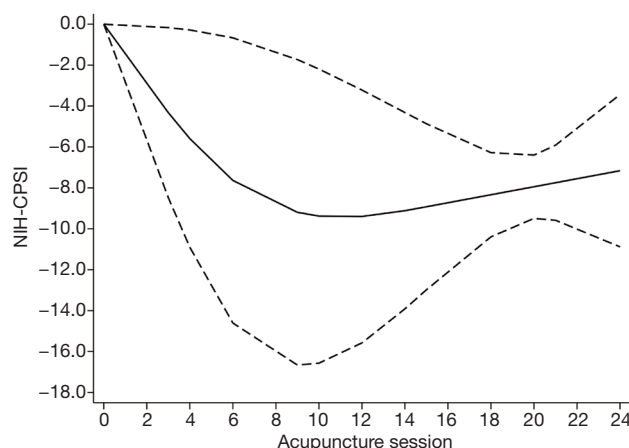

Figure 3 Dose-response relationship between acupuncture sessions and changes of NIH-CPSI score.

score, respectively.

In sensitivity analysis, when CSSs were omitted from the analysis, there remained a similar dose threshold in treatment sessions providing clinical effectiveness. Six RCTs were included in the meta-analysis showed the association between acupuncture sessions and NIH-CPSI score (6,8,22-24,26). The results from sensitivity analyses are congruent with the primary results. After 18 acupuncture sessions, the NIH-CPSI decreased from 26.3 (95% CI: 25.6–27.0) to 18.2 (95% CI: 16.3–20.2), with a difference of –8.1 (95% CI: –9.5 to –6.7). Sensitivity analysis by omitting studies with small sample size found no important changes compared with remaining studies (6,8,22,24-26).

After 18 sessions, the NIH-CPSI changed –8.3 (95% CI: –10.1 to –6.5). Subgroup analysis by classified studies using electroacupuncture found no significant difference compared with studies using manual acupuncture.

Discussion

Summary of main findings

To the best of our knowledge, this is the first study to explore the association between acupuncture sessions and acupuncture effects using dose-response methodology. We reported a dose-response association between acupuncture sessions and NIH-CPSI score, at least six acupuncture sessions might be recommended, and prolonged sessions of acupuncture may have clinically different effects.

Compared with existing studies

There is an urgent need for studies to guide decisions about what is an adequate dose of acupuncture for different conditions. In 1990s, a team from Dutch epidemiologists firstly considered the adequacy of acupuncture treatment in a series of systematic reviews, which suggested that a better understanding of adequate acupuncture treatment dose would support communication with patients and inform health policy (28,29). Despite with incomplete knowledge of acupuncture dosing, these studies have made more accessible to patients and stakeholders. In 2008, White and colleagues recommended that acupuncture systematic reviews should provide a subgroup analysis including only the studies that meet criteria for "adequate" acupuncture (12). Specifically, Ezzo and colleagues demonstrated that trails using ≥6 sessions of acupuncture for osteoarthritis were more likely to be positive than those using <6 sessions (30). However, the naïve subgroup analysis could not systematically exam dose-response relationship between variables and identify the existed cut-off value. Armour and colleagues investigated the relationship between components of acupuncture dose and menstrual pain (31). The results showed that there appear to be relationships between treatment timing and mode of needle stimulation, and menstrual pain outcomes; needle location, number of needles used and frequency of treatment showed dose-response relationships with menstrual pain outcomes. However, it was a narrative review without statistical model and quantitative analysis. Schwehr et al. surveyed the insurance system data belongs to National Health Interview Survey (NHIS), demonstrating that most

people who use acupuncture did not receive a full treatment course, which may affect the effectiveness of treatment (32). Although a short course of acupuncture treatment may be sufficient and effective in some cases, especially for acute pain. However, for other cases such chronic pain and internal disorders with long-term conditions, which are likely to require a series of treatments for optimal results.

Implications for practice and research

Increasing patients suffering from CP/CPPS seek acupuncture for help. However, the association between acupuncture sessions and its effects remain unclear, which limited the application of acupuncture regardless available evidence found that acupuncture could relieve the symptoms of CP/CPPS effectively. Every treatment involves a therapeutic relationship, and similar to drugs, the dose of acupuncture therapy should also be considered in clinical practice.

Limitations

Several limitations should be noted. First, the quantity of included studies is small, only ten studies with 329 participants were used for data synthesis. Second, to ensure a better trend approximating on the dose-response relationship, it is expected to include more dose categories with each study. However, most of the studies reported two time points such as baseline and endpoint which may influence the robustness of the results. Third, although the acupuncture time in different studies was similar, the "dose" in this study specific to the treatment sessions, and the treatment was not adjusted in our results. Fourth, owing to the characteristics of "one-stage" approach model, currently there is no valid method to estimate the heterogeneity. Instead, we reported the "$1-R^2$" of the model to quantitatively measure the heterogeneity, which may not precisely reflect the "true" heterogeneity.

Conclusions

The treatment session plays a vital role in acupuncture effects and prolonged acupuncture sessions (≥6 sessions) may have clinically relevant benefits for CP/CPPS. Further, large-scale, well-designed clinical studies reporting results from longitudinal data are strongly needed to explore the association between acupuncture treatment sessions and acupuncture effects.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Table S1 Search strategies

PubMed

  #1 "chronic prostatitis"[Title/Abstract]

  #2 "chronic pelvic pain syndrome"[Title/Abstract]

  #3 "nonbacterial prostatitis"[Title/Abstract]

  #4 "chronic prostatitis/chronic pelvic pain syndrome"[Title/Abstract]

  #5 "chronic prostatitis-chronic pelvic pain syndrome"[Title/Abstract]

  #6 "CP/CPPS"[Title/Abstract]

  #7 "CP-CPPS"[Title/Abstract]

  #8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

  #9 "acupuncture"[MeSH Terms]

  #10 "acupuncture therapy"[MeSH Terms]

  #11 "acupuncture points"[MeSH Terms]

  #12 "auriculotherapy"[MeSH Terms]

  #13 "acupuncture"[Title/Abstract]

  #14 "acupoint"[Title/Abstract]

  #15 "auriculotherapy"[Title/Abstract]

  #16 OR/1–15

  #17 #8 AND #16

EMBASE

  #1 'chronic prostatitis'/exp

  #2 'chronic prostatitis':ti,ab

  #3 'chronic pelvic pain syndrome':ti,ab

  #4 'nonbacterial prostatitis':ti,ab

  #5 'chronic prostatitis/chronic pelvic pain syndrome':ti,ab

  #6 'chronic prostatitis-chronic pelvic pain syndrome':ti,ab

  #7 'CP/CPPS':ti,ab

  #8 'CP-CPPS':ti,ab

  #9 OR/1–8

  #10 'acupuncture'/exp

  #11 'acupuncture':ti,ab

  #12 'acupoint':ti,ab

  #13 'auriculotherapy':ti,ab

  #14 OR/10–14

  #15 #9 AND #14