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File: ■ Stinging Nettle (*Urtica dioica*, Urticaceae)
■ Benign Prostatic Hyperplasia
■ Systematic Review/Meta-analysis

HC 091773-590

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RE: Meta-analysis Supports Efficacy of Stinging Nettle for Benign Prostatic Hyperplasia

Men C, Wang M, Aiyireti M, Cui Y. The efficacy and safety of *Urtica dioica* in treating benign prostatic hyperplasia: a systematic review and meta-analysis. *Afr J Tradit Complement Altern Med*. 2016;13(2):143-150.

Benign prostatic hyperplasia (BPH) is a common problem in older men. BPH results in lower urinary tract symptoms (LUTS), including the need to urinate more often, the sensation of incomplete voiding, urgency, and difficulty initiating and stopping urination. BPH symptoms decrease quality of life by interrupting sleep and disrupting activities.

Studies have reported that stinging nettle (*Urtica dioica*, Urticaceae) root improves BPH clinical symptoms without significant adverse effects, which is consistent with its traditional use for that purpose. The purpose of this systematic review and meta-analysis was to evaluate the efficacy and safety of stinging nettle in treating BPH.

The authors searched the Medline (1966 to February 2015), Embase (1974 to February 2015), and Cochrane Controlled Trials Register databases to identify relevant studies. The search terms were *Urtica dioica*, lower urinary tract symptom (or symptoms), benign prostatic hyperplasia, and randomized controlled trial (or trials). To be included in the meta-analysis, the trial had to evaluate treatment with stinging nettle, include the number of patients and numerical values for measured indices, and be available in full text. The Jadad scale was used to rate quality.

The authors identified the following five qualifying studies: one from Germany, one from Italy, and three from Iran. Stinging nettle was compared to placebo in three studies; one tested Pluvio® (Lampugnani Farmaceutici S.p.A.; Nerviano, Italy), which contains a "high dose of *Urtica dioica*," in comparison to no treatment; and the fifth study evaluated stinging nettle and prazosin versus prazosin alone (prazosin is an α-1 blocker). [Note: An internet search for Pluvio revealed a product consisting of avocado (*Persea americana*, Lauraceae), soy (*Glycine max*, Fabaceae) oil, stinging nettle, saw palmetto (*Serenoa repens*, Arecaceae), vitamins E and B6, and zinc.] Median age of patients ranged from 56 to 66 years. Experimental sample size ranged from 50 to 281 patients, while control

sample size ranged from 50 to 271 patients. Treatment duration ranged from two to 12 months. Dosage ranged from 360 mg/day to 600 mg/day. On the Jadad scale, four studies were deemed to have low risk of bias and one to have moderate risk of bias. [Note: It is not clear why the 2010 trial of Bercovich and Saccomanni,[1] which compared an active treatment group with a group of untreated patients, was considered to be a blinded trial. It is not possible to compare an active treatment group with an untreated group under blinded conditions.]

The authors performed a meta-analysis of reported data for the International Prostate Symptom Score (IPSS), peak urinary flow rate (Q_{max}), and prostate volume to evaluate stinging nettle's effectiveness. Reported prostate-specific antigen (PSA) values were analyzed to evaluate safety, though they might have also been considered as an efficacy outcome. An overview about the efficacy measures used in the single trials and about the baseline values of the outcome measures is not given. Differences between groups were calculated as mean differences (MDs) since the same outcomes seemed to be used in the trials. In the Methods section, the authors wrote that they estimated relative risk for dichotomous outcomes and standardized mean differences (SMDs) for continuous outcomes. In the Results section, no results of dichotomous outcomes are reported, and for continuous outcomes, the authors reported MDs, which they erroneously refer to as SMDs. In the forest plots, the MDs of the individual trials can be calculated by subtracting the means without standardization. This proves that MDs were calculated rather than SMDs. As a consequence, the reported differences can be interpreted on the original scales.

All five trials seemed to have data on the IPSS, encompassing 1128 patients (n=573, interventional group; n=555, control group). There were two trials with extremely positive results for the experimental group compared to the control group. In the 2013 trial of Ghorbanibirgani et al.,[2] the mean of the placebo group did not change during eight weeks of treatment, while the active treatment group improved by 24 points (mean). In the trial of Bercovich and Saccomanni,[1] which cannot be considered as a blinded trial, the patients of the placebo group worsened by 2.5 points and the actively treated patients improved by 13 points. In all other trials, a mean improvement of at least 1.5 points was observed for patients of the placebo group. These noticeable findings were not commented on by the authors. The estimated pooled MD was −10.47, 95% confidence interval (CI) −18.12 to −2.82 (P=0.007); this result suggests that the intervention shows statistically significant reductions in the IPSS compared to controls. As a consequence of the findings mentioned above, the heterogeneity estimated by the I^2 statistic was very high (I^2=99%; P<0.00001). In the Methods section, the authors state that I^2 > 50% reflects significant inconsistency, but in the Results section, the extent of heterogeneity was described only in the forest plot. As a result, a random-effects model was chosen to perform the meta-analysis. The consequences of the high heterogeneity for the interpretation of the results obtained from the random-effects meta-analysis were not reflected. In a sensitivity analysis, the two trials with the noticeable treatment effects could have been excluded, but such an analysis was not presented. In the Discussion section, a result of a subset of trials (all trials except Bercovich and Saccomanni[1]) was presented but this analysis was not discussed in terms of heterogeneity. The treatment effect seems to be overestimated in the meta-analysis.

Q_{max} seemed to be evaluated in three trials, giving a cohort of 904 patients (n=461, interventional group; n=443, control group). The results of the single trials were not commented on by the authors. In the 2010 trial of Bercovich and Saccomanni,[1] which

was an open-label trial, the untreated patients worsened; in the other trials, patients having received placebo improved. Furthermore, the 2010 trial of Bercovich and Saccomanni[1] showed the highest effect of the intervention. The estimated pooled MD was 4.37, 95% CI 1.55 to 7.19 (P=0.002), indicating a statistically significant increase in Q_{max} in the interventional group compared to control. The heterogeneity among the trials was very high (I^2=96%; P<0.00001). This was not commented on by the authors. The treatment effect seems to be overestimated.

Two trials seemed to have prostate volume data on 678 patients (n=347, interventional group; n=331, control group). One of these trials was the 2010 open-label trial of Bercovich and Saccomanni.[1] In this trial, the mean prostate volume of untreated patients increased, while the prostate volume of placebo-treated patients of the other trial decreased. The pooled MD fixed-effects estimate was −3.63, 95% CI −4.67 to −2.57 (P<0.00001), suggesting that the intervention significantly decreased prostate volume compared to control. The treatment effect seems to be overestimated.

Three of the trials seemed to have PSA data on 802 patients (n=409, interventional group; n=393, control group). The pooled MD fixed-effects estimate was −0.08, 95% CI −0.23 to 0.07 (P=0.31), indicating no significant difference in PSA levels between stinging nettle and control.

No serious side effects attributable to nettle were reported in any study.

The authors conclude that stinging nettle appears to be a safe and effective treatment for BPH LUTS. However, they caution that their analysis could be biased because it included only five studies, making the statistical power limited. Further, not all trials included in the analysis reported prostate volume, Q_{max}, or PSA data, and one study used a combination product whose effects cannot be attributed entirely to stinging nettle. The authors did not mention that one of the included trials was an open-label trial. Quite the contrary, they state that all included trials were blinded. In an open-label design, the results are likely to be biased and effects are likely to be overestimated if an active treatment is compared to no treatment. Long-term outcomes cannot be determined from this analysis.

The authors declare no conflict of interest.

—Heather Anderson, MD

References

[1]Bercovich E, Saccomanni M. Analysis of the results obtained with a new phytotherapeutic association for LUTS versus control. *Urologia*. 2010;77(3):180-186.

[2]Ghorbanibirgani A, Khalili A, Zamani L. The efficacy of stinging nettle (*Urtica dioica*) in patients with benign prostatic hyperplasia: a randomized double-blind study in 100 patients. *Iran Red Crescent Med J*. 2013;15(1):9-10.

The American Botanical Council has chosen not to reprint the original article.