Meta-analysis of the efficacy of Ningmitai capsule on the treatment of chronic prostatitis in China

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Abstract
Background: To evaluate the efficacy and safety of Ningmitai (NMT) capsule for treating chronic prostatitis (CP) in China.

Methods: Retrieving the China Journal Full-Text Database (CNKI), Wanfang database, China’s outstanding master’s/doctoral dissertation database, VIP Science and Technology Periodical Database, Cochrane library, PubMed, Embase, and Chinese academic conference papers. Collecting and selecting literatures of randomized controlled trials before March 2017 on NMT capsule for CP, evaluated by Jadad scale, and then analyzed with Stata software.

Results: Thirty randomized clinical trials including 6185 patients (3124 in the test group and 3061 in the control group) were included. The overall treatment risk ratios (RRs) were 1.19 (1.14, 1.24). The merged RRs were 1.05 (0.95, 1.15) and 1.22 (1.19, 1.26) for the single-drug group and the combined-drug group, respectively. The adverse events were found to be lower in all groups.

Conclusion: NMT is effective and safe on the treatment of CP, especially in combined-drug groups. High quality and a good design of multicentered, randomized, parallel-controlled and blinding trials are needed in order to make further studies, and deserve further examination for the treatment of CP with NMT.

Abbreviations: CI = confidence interval, CNKI = China Journal Full-Text Database, CP = chronic prostatitis, NMT = Ningmitai, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCT = randomized clinical trials, RR = risk ratio.

Keywords: chronic prostatitis, efficacy, meta-analysis, Ningmitai capsule, safety

1. Introduction

Chronic prostatitis (CP) is a common male genitourinary system disease with high morbidity. The average prevalence of CP in China was 8.4%,[1] which occurs in young males (20–40 years). A survey of CP in college students shows that the prevalence of CP in Chinese college students was up to 46.63%,[2] which significantly endangered the life and health in men. And it is also a disease with frequent recurrence and a cause of male sterility. CP was mainly caused by bacterial infection, therefore, antibiotics therapy had been thought as the mainstream therapy, for example, Ofloxacin, Roxithromycin, Doxycycline, and so on. However, with the increasing of using antibiotics, the resistance to antibiotics increased at the same time,[3] which provides the opportunity for Traditional Chinese Medicine or integrated traditional Chinese and Western medicine to treat CP.

Recently, Ningmitai (NMT) capsule, a pure Chinese medicine preparation, has been widely used for the treatment of CP, which is composed of Camellia azalea, Rhizoma Imperatae, Kadsura Pepper Stem, Barberry Root, Hairyein Agrimonia Herband Bud, Folium Hibisci Mutabilis, and Fructus Forsythiae. Several clinical trials had compared the NMT with kinds of antibiotics therapy,[4,5] in terms of their efficacy and adverse events in the treatment of CP. Although, NMT, alone or integrated with western medicine, has been widely used as an alternative and effective method for the treatment of CP in China, it is still necessary to evaluate which therapeutic method is effective in the treatment of CP by systematic review. The objective of this study is to appraise the efficacy and safety of NMT on CP treatment from the existing randomized clinical trials (RCTs), and provide evidence-based choice for the physicians on the treatment of CP.

2. Materials and methods

This meta-analysis was conducted strictly according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, and the ethical approval and informed consent were unnecessary since the meta-analysis was aimed to summarize the previous studies.

2.1. Study eligibility and outcomes

We retrieved the electronic databases PubMed, China National Knowledge Infrastructure Database(CNKI), Wanfang Database, Clinical Trials, the Cochrane Library, China Science and Technology Journal Database, Chinese Biomedical Literature Database, China’s outstanding master’s/doctoral dissertation database, and Chinese academic conference papers, collected and selected related literatures before March 2017 on NMT therapy for CP. Trials were eligible for inclusion if: the type of study was RCT; the participants were CP; the study was designed to compare the effectiveness and safety of NMT with antibiotics; the outcomes were contained at least one of the effective rate and adverse events. Trails were excluded if: nonoriginal research, reviews, comments, and articles unrelated to our analysis; lacking of basic information on participants, interventions of the
2.2. Data extraction and quality assessment

Data abstraction was conducted independently by 3 investigators according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, and any discrepancies among reviewers were resolved by consensus. Firstly, all studies with words such as “randomization” or “quasi-randomization” in their abstracts, whether they use blinding or not. For each study, we extracted the following information: name of the first author, year of publication, study design, participants’ characteristics, intervention, the effective rate of treatment and adverse events. The quality of the RCTs was evaluated by the Jadad scale.[6] The following items were assessed: Method to generate the sequence of randomization, randomization concealment, blinding, withdrawals, and dropouts.

2.3. Statistical analyses

Statistics analyses were estimated using Stata software 14.1. P values were two-sided, with significance at P < .05, and the 95% confidence interval (CI) was calculated from the data also. The risk ratio (RR) was estimated for the dichotomous data. Statistical heterogeneity among trials was estimated with the I-squared and P values. If heterogeneity existed (P < .05), data were analyzed using a random effects model. In the absence of heterogeneity, a fixed-effects model was used. Publication bias was evaluated by using Begg’s test.

3. Results

3.1. Characteristics of included trials

After a primary search of databases, 189 potentially eligible trials were screened out from electronic and manual searches. Records after removing duplicated publication, no data for extraction, case reports, inappropriate control, drug combination, no specific courses, intervention studies, and literature review, 30 RCTs were therefore eligible for inclusion. There were all trials comparing NMT with antibiotics. No trial applied placebo or no intervention as control. All of the 30 RCTs were conducted in China and published in Chinese between 1998 and 2017. Characteristics of the available eligible RCTs are shown in Table 1. Among the 30 RCTs that evaluate the efficacy and safety between NMT and antibiotics therapy for patients with CP, 11 RCTs reported the adverse events.

### Table 1

| Trial | Year     | Sample size | Age, mean (range) | Comparison       | Primary outcome | Efficiency (%) | Adverse events | Jadad score |
|-------|----------|-------------|-------------------|------------------|-----------------|----------------|---------------|-------------|
| Zhang L[7] | 2002 | 128 (75/52) | 33.2 (18–56) | NMT vs ST | NIH-CPSI | 78.9 vs 86.8 | N | 2 |
| Yu J[8] | 2012 | 92 (46/46) | 32.7 (18–51) | NMT vs SN | NIH-CPSI | 85.3 vs 81.5 | N | 1 |
| Lin YS[9] | 2016 | 200 (100/100) | 37.8 (21–53) | NMT vs SN | NIH-CPSI | 85.1 vs 65.9 | Y | 4 |
| Liu ZC[10] | 2010 | 60 (30/30) | 36.98 (19–58) | NMT vs TS | NIH-CPSI | 79.4 vs 75.7 | N | 2 |
| Wu L[11] | 2013 | 96 (48/48) | 37.4 (24–50) | NMT+MA vs MA | NIH-CPSI | 89.6 vs 68.8 | N | 2 |
| Huang XY[12] | 2011 | 462 (229/233) | 31 (17–63) | NMT+ML vs ML | NIH-CPSI | 84.7 vs 69.1 | N | 2 |
| Zhu HS[13] | 2014 | 90 (45/45) | 35.7 (22–65) | NMT+MM vs MM | NIH-CPSI | 89.9 vs 78.7 | N | 2 |
| Zhang XY[14] | 2004 | 307 (152/155) | 46 (29–56) | NMT+MO vs MO | NIH-CPSI | 89.2 vs 81.5 | N | 2 |
| Li H[15] | 2012 | 60 (30/30) | 35 (22–58) | NMT+MO vs MD | NIH-CPSI | 83.3 vs 66.7 | N | 2 |
| Zhang SL[16] | 2009 | 290 (150/140) | 33.47 (18–63) | NMT+SF vs SF | NIH-CPSI | 86.8 vs 82.4 | Y | 2 |
| Peng GP[17] | 2008 | 290 (150/140) | 32.65 (22–68) | NMT+SF vs SF | NIH-CPSI | 92.6 vs 86.9 | N | 2 |
| Zong Bo[18] | 2010 | 300 (150/150) | 30.87 | NMT+SF vs SF | NIH-CPSI | 84.4 vs 58.3 | N | 2 |
| Yu JM[19] | 2010 | 245 (125/120) | 32.6 (18–55) | NMT+SF vs SF | NIH-CPSI | 89.6 vs 69.2 | Y | 3 |
| Li H[20] | 2012 | 245 (120/125) | N/A | NMT+SF vs SF | NIH-CPSI | 88.7 vs 87.9 | Y | 2 |
| Che Y[21] | 2013 | 150 (75/75) | 33.6 (20–52) | NMT+SF vs SF | NIH-CPSI | 82.7 vs 85.3 | N | 2 |
| Xiang J[22] | 2013 | 288 (144/144) | 45.8 (20–76) | NMT+SF vs SF | NIH-CPSI | 84 vs 66.7 | N | 2 |
| Mu Q[23] | 2013 | 326 (178/148) | 31 (16–55) | NMT+SF vs SF | NIH-CPSI | N/A | N | 2 |
| Yu JM[24] | 2014 | 201 (101/100) | 37 (17–56) | NMT+SF vs SF | CPSI | 94.6 vs 80.4 | Y | 2 |
| Cai RS[25] | 2015 | 70 (35/35) | 48.2 (30–65) | NMT+SF vs SF | NIH-CPSI | 92.7 vs 74.3 | Y | 2 |
| Zhou RC[26] | 2015 | 110 (55/55) | 45.1 | NMT+SF vs SF | NIH-CPSI | 91.7 vs 78.2 | Y | 2 |
| Ma JQ[27] | 2015 | 116 (58/58) | 33.8 (18–59) | NMT+SF vs SF | NIH-CPSI | 93.1 vs 79.3 | N | 2 |
| Liu Q[28] | 2016 | 80 (40/40) | 33.7 (19–56) | NMT+SF vs SF | NIH-CPSI | 90 vs 67.5 | Y | 3 |
| Zhang Y[29] | 2016 | 120 (60/60) | 64.78 (36–78) | NMT+SF vs SF | NIH-CPSI | 96.7 vs 83.3 | N | 2 |
| Liu Z[30] | 2016 | 213 (107/106) | 30.6 (20–95) | NMT+SF vs SF | NIH-CPSI | 94.4 vs 81.9 | N | 2 |
| Su J[31] | 2016 | 186 (93/93) | 31.48 (18–59) | NMT+SF vs SF | NIH-CPSI | 90.3 vs 75.3 | Y | 3 |
| Yang JL[32] | 2012 | 98 (49/49) | 37 (17–54) | NMT+TS vs TS | NIH-CPSI | 73.3 vs 79.3 | Y | 2 |
| Liu ZL[33] | 2010 | 60 (30/30) | 35.33 | NMT+TS vs TS | NIH-CPSI | 83.3 vs 80 | N | 2 |
| Can HF[34] | 2008 | 158 (80/78) | 37.8 (21–57) | NMT+ZT vs ZA | NIH-CPSI | 75 vs 73.06 | N | 0 |
| Wang Q[35] | 2012 | 82 (41/41) | 37.8 (21–57) | NMT+ZT vs ZT | NIH-CPSI | 97.6 vs 89.1 | N | 0 |
| Fang ZJ[36] | 2016 | 126 (63/63) | 37.9 (20–50) | NMT+SF+TH vs SF+TH | NIH-CPSI | 87.3 vs 66.7 | Y | 3 |
| Zhong GQ[37] | 2014 | 378 (186/192) | 37.8 (18–58) | NMT+SF+TS vs SF+TS | NIH-CPSI | 93.5 vs 67.19 | N | 1 |

MA = azithromycin, ML = rifampicin, MM = minocycline hydrochloride capsules, MO = doxycycline hyclate tablets, NMT = Ningmitai, NIH-CPSI = NIH-Chronic prostatitis symptoms index, SF = doxycillin for injection, SN = norfloxacin, ST = prostat tablets, TH = tamsulosin hydrochloride, TS = tamsulosin hydrochloride sustained release capsules, ZA = alfuzosin hydrochloride tablets, ZT = terazosin hydrochloride.
3.2. Therapeutic efficacy of NMT on CP
In the single-drug group, 3 of the 4 articles, 95% confidence intervals (CI) of risk ratio (RR) included 1, which meant there was no evidence to show that NMT was superior to antibiotics. Only 1 article published in 2016 indicated that NMT was superior than antibiotics. As to the combined group, in the 26 RCTs, only 4 RCTs’ 95%CI of RR included 1, which might show that NMT was superior to antibiotics to treat CP.

Weighted quantitative synthesisization of NMT in the single-drug group was compared with antibiotics for CP treatment. The merged RR was 1.06 (95%CI: 0.92–1.21), 1 was included also, which means there was no significant difference between NMT and antibiotics on CP treatment.

Weighted quantitative synthesisization of NMT in the combined group was compared with antibiotics for CP treatment. The merged RR was 1.22 (95%CI: 1.19–1.26), the effective ratio of the NMT group was 1.22 times higher than the antibiotics group, 1 was not included, which means there was significant difference between NMT and antibiotics when combined drugs to treat CP (Fig. 1).

3.3. Adverse events
Eleven of the 29 RCTs reported the adverse events. The incidence of adverse events in NMT group was <5%. All the discomfort occurred during the treatment procedure was relieved and disappeared before the end of the treatment.

3.4. Publication bias
Egger’s test and the funnel plot were applied to assess the publication bias of the enrolled studies. The shapes of funnel plots were seemed symmetrical, indicating no bias in both the analysis of total enrolled studies (Fig. 2A) and that of the comparison between groups of NMT combined with antibiotics and antibiotics alone (Fig. 2B). The results of Egger’s tests exhibited slight bias for the overall efficacy rate of the total studies (P = .079, Fig. 3A) and no bias for the studies comparing the efficacy rate of antibiotics adjuvant with NMT and antibiotics only (P=.103, Fig. 3B). Since less than 10 studies comparing the NMT with antibiotics, we failed to perform Egger’s and funnel plot of the effective rate.

4. Discussion
CP is one of the most common urological diseases among men under the age of 50, and its etiology is still unclear and lacking of effective medications to treat. At present, antibiotics therapy was widely used to treat CP in clinical. With the increasing use of antibiotics, the resistance to antibiotics increased at the same time, which provides the opportunity for Traditional Chinese
Medicine or integrated traditional Chinese and Western medicine to treat CP. NMT, a classical traditional Chinese medicine, with the effect of heat-clearing and detoxicating, damp elimination and smoothing showering, was used to treat stranguria caused by damp and hot accumulate knot, difficult urination, dripping astringent pain, hematuria, lower urinary tract infection, CP and so on. This meta-analysis was conducted to appraise the efficacy and safety of NMT on CP treatment in China from the existing RCTs, and provide evidence-based choice for the physicians on the treatment of CP.

A total of 30 studies was selected and analyzed, the effective rate and adverse events were selected as indicators. Two groups were divided based on the published papers for the treatment of CP as follows: one is the single group which the CP patients orally NMT or antibiotics, and the other is combined drugs group which the patients were used NMT and antibiotics at the same times comparison with the patients used antibiotics only. In the single group, the merged RR was 1.06 and the 95%CI ranged from 0.92 to 1.21, concluded 1, which indicated that the effective rate of the treatment on CP was no significant between NMT and the antibiotics. For only 4 researches were included in the single group, and the published year was different. It seems that the effective rate of the CP treatment by NMT was better than antibiotics nowadays. It might because of the antibiotic resistance, on the other hand, it might also suggest that the advantages of NMT would more and more significant than antibiotic alone to treat CP. However, there were little literatures for the comparison of the treatment of CP between NMT and antibiotics alone currently. Hence, more researches were needed to test and verify the inference. In the combined drugs group, the merged RR was 1.22 and the 95%CI was 1.19–1.26 which indicated that the effective rate of NMT combined with antibiotics to treat CP was significantly higher than antibiotics alone.

The results of Begg’s rank correlation test and Egger’s regression test for small-study effects indicated that there was no significant publication bias in this study. Hence, we can think that the conclusion of this study is relatively robust. Using NMT to treat CP was not only beneficial to reduce the generation of antibiotic resistance, but also the components of NMT (Kadsura Pepper Stem, Barberry Root, Hairyvein Agrimonia Herband Bud) can also enhance the phagocytosis of macrophages, thereby improving the body’s nonspecific immune function and anti-infective ability to reduce the incidence of adverse reactions. In this study, 11 of the 29 RCTs reported the adverse events and there was no significant difference between NMT and antibiotics.

Figure 2. Egger graph was assessed for the effective rate.

Figure 3. Funnel plots were assessed for the effective rate.
group. In the single group, there were no adverse events reported. In the combined drugs group, the incidence of adverse events in NMT group was <5% and all the discomfort occurred during the treatment procedure was relieved and disappeared before the end of the treatment. However, for the NMT group were NMT combined with antibiotics, so it is not yet clear that the short moment of the adverse events was accounting of NMT or due to antibiotics. Nevertheless, only little information allowed for the adverse events in the limited researches about the treatment of CP by NMT so far. Therefore, the detail analysis of the adverse events was not allowed in this study.

5. Conclusion
In conclusion, NMT is effective and safety on the treatment of CP, especially when combined with antibiotics. However, since the quality of the clinical studies was in a comparatively lower lever and majority of the present researches were combined drugs, high quality and a good design of multicentered, randomized, parallel-controlled and blinding trials were needed in order to make further studies, and deserve further examination for the treatment of CP with NMT.

Author contributions
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