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Acupoint injection treatment for non-dialysis dependent chronic kidney disease

A meta-analysis of randomized controlled trials

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Abstract

Aim: To analyze the effects of acupoint injection in the treatment of non-dialysis dependent chronic kidney disease through a systematic review with meta-analysis.

Methods: This systematic review with meta-analysis was conducted following the recommendations of the declaration of PRISMA. Full-text literature of randomized controlled trial of acupoint injection therapy for non-dialysis chronic kidney disease was searched in PubMed, Embase, Cochrane Library, China National Knowledge Internet, the Chinese Scientific Journal Database, the Wanfang Database, China Biology Medicine database. The efficacy and safety of acupoint injection for non-dialysis chronic kidney disease were evaluated.

Results: Seventeen studies containing 1414 patients met the criteria. The results shows that acupoint injection combined with basic treatment can significantly improve the levels of Ccr (WMD = 4.81; 95% CI:2.54 to 7.08) and Hb (WMD = 4.56; 95% CI:1.72 to 7.39), reduce the levels of BUN (WMD = −0.90; 95% CI: −1.26 to −0.54)and Scr (WMD = −7.66; 95% CI: −12.39 to −2.93), and improve the effective rate (OR = 3.12; 95% CI: 2.29 to 4.26).

Conclusion: Our current analysis showed that combined acupoint injection therapy can reduce the levels of BUN and Scr, and increase Ccr and Hb in non-dialysis CKD patients. However, the existing evidence is still insufficient due to the high risk of included trial bias, and future research needs to improve methodological quality.

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Abbreviations: BUN = blood urea nitrogen, Ccr = endogenous creatinine clearance, CKD = chronic kidney disease, ESKD = end-stage kidney disease, GFR = glomerular filtration rate, Hb = Hemoglobin, KDIGO = kidney disease improving global outcomes, OR = odds ratio, RCT = randomized controlled trial, Scr = serum creatinine.

Keywords: acupoint injection, non-dialysis dependent chronic kidney disease (non-dialysis dependent CKD), meta-analysis, randomized controlled trial

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The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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All data generated or analyzed during this study are included in this published article [and its supplementary information files].

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1. Introduction

Chronic kidney disease (CKD) is a syndrome defined as persistent alterations in kidney structure, function, or both with implications for the health, Kidney Disease Improving Global Outcomes (KDIGO) describes a classification of severity, defining numerous stages of CKD based on glomerular filtration rate (GFR).[1] CKD has become a global public health problem with an incidence rate of 10% to 15%. The prevalence of CKD and health care costs continue to increase each year. Due to its variety of diseases and prolonged illness, it is often referred to as the "silent killer".[2] Many disease factors can cause CKD, including hypertension, diabetes, primary glomerulonephritis, renal vascular disease, hereditary kidney disease. When the patient's glomerular filtration rate (GFR) gradually decreases, it will enter End-Stage Kidney Disease (ESKD), an option for patients with ESKD is kidney replacement therapy.[3] As the disease progresses, renal hypertension, proteinuria, nerve damage, anemia, etc. are also becoming more and more serious. When CKD patients receive conventional treatment, major complications such as insomnia, fatigue, and uremia and pruritus cannot be effectively improved. Therefore, it is important to find new adjuvant therapies to enhance the efficacy and improve the quality of life.

In China, integrated Traditional Chinese and Western Medicine treatment also used for CKD treatment. For example,

oral administration of traditional Chinese medicine, Chinese medicine enema, and acupoint injection are added based on the conventional treatment of Western medicine.

Acupoint injection is the use of a syringe needle instead of acupuncture needle acupuncture points. After acupuncturist manipulates the needles to create a numb radiating sensation, called Deqi, a liquid is injected into the acupuncture points to treat the disease. Acupoint injection therapy, on the one hand, follows the basic theory of traditional Chinese medicine, uses TCM theory to conduct syndrome differentiation and treatment, to play the overall regulatory role of acupoints; on the other hand, it is combined with modern medicine to play the therapeutic role of drugs. In some countries, especially China, to achieve better results, acupoint injection based on traditional Chinese medicine theory is often used instead of intramuscular injection.[4,5] Modern research has found that the effect of acupoint injection is highly effective and quick-acting. That is, although the blood concentration of acupoint injection is much lower than that of intravenous injection, its efficacy can achieve the same or better effect than intravenous injection in a short time. The drug is slowly absorbed through the body at the injection site, prolonging the acupoint stimulation time, and the acupoint and drug action are superimposed.[6] Recent studies have found that acupoint injection can improve organ and nervous system functions by generating bioelectrical activity, and promote the body to restore normal metabolic functions.[7–9] More and more clinical studies have shown that acupoint injection therapy has definite advantages and reliable curative effects for CKD.[10,11] However, there is no high-quality clinical evidence yet. In this study, the efficacy of acupoint injection therapy for CKD was systematically evaluated by Meta-analysis, to provide a reference for clinical treatment.

2. Methods

The study protocol has been registered on international prospective register of systematic review (PROSPERO). The study registration number of PROSPERO is CRD42020168143.

2.1. Search strategy

In this study, the PubMed, Embase, Cochrane Library, China National Knowledge Internet (CNKI), the Chinese Scientific Journal Database (VIP), the Wanfang Database, and Chinese BioMedical Literature Database (CBM) were searched for original studies. Retrieval time was set from database building to December 2019. Besides, other relevant research papers were searched manually. The following search terms are used alone or in combination: "chronic renal" "chronic kidney" "chronic renal insufficiency" "chronic renal dysfunction" "acupoint injection" "randomized controlled trial". References to selected studies were also searched for other relevant studies. In addition, we use flowcharts to make the search process more detailed (Fig. 1).

2.2. Selection criteria

Literature type is a randomized controlled trial (RCT), with no restriction on whether to use blind method; All RCTs of patients following with the diagnosis of CKD and have not received dialysis. In the study, the control group and treatment group can receive the same basic treatment, including Western medicine treatment or Chinese medicine treatment. We allowed co-interventions in both experimental and control intervention groups only if the co-intervention was administered equally to all intervention groups. The control group can be a blank control or shame acupoint injection, while the treatment group was treated with acupoint injection. The outcome indicators are biochemical indicators: effective rate of clinical effect, Scr, Ccr, BUN, and Hb.

2.3. Literature screening and data extraction

Two researchers independently read the literature summary and the full text, then judged and cross-checked. The divergent literature was examined by the third researcher. The extracted data included baseline data (gender, age, course of the disease, primary disease), research design (randomization, control, blindness, treatment factors, course of treatment, treatment time, dose), sample size, evaluation index (mean, standard deviation, efficiency), adverse reactions, etc. The data were described and analyzed for incomplete patients.

2.4. Quality evaluation of literature

According to the methods described in the literature, Cochrane Assessment Manual was used to evaluate the methodological quality of the included studies, including selection bias, implementation bias, measurement bias, reporting bias, and others.

2.5. Statistical analysis

RevMan 5.3 software was used for statistical analysis of the collected data, $P < .05$ considered that there was statistical significance. The odds ratio (OR) and 95% confidence interval (95% CI) were used to measure the combined effect for enumeration data. The weighted mean difference (WMD) was used to measure the combined effect for a continuous variable. A heterogeneity test was performed first. If $I^2 > 50\%$, the random-effects model was used. Otherwise, the fixed-effects model was used. When $I^2 > 50\%$ or $P < .10$, it is considered that there is heterogeneity among the studies. Z-test was used to compare the effects, and the results were shown in forest maps. If significant heterogeneity is detected, a subgroup or sensitivity analysis is used to investigate the cause of heterogeneity. If the source of heterogeneity cannot be determined, a descriptive analysis will be used. The publication bias test was performed using the software Stata 12.0 for Egger detection.

3. Results

A total of 295 pieces of works of literature were retrieved (59 CNKI, 12 VIP, 74 Wanfang, 146 CBM, 1 PubMed, 3 Embase, and 0 Cochrane Library). After reading the title and abstract of the literature, 87 studies are excluded based on the topic and abstract, as they are irrelevant to our topic. After reading the full text, we re-screened and finally included 17 articles. The flow chart of literature screening is shown in Figure 1.

3.1. Study characteristics

All the included studies were in Chinese, published in 2003 and 2018 at the latest. A total of 1414 CKD patients (treatment group 712 people, control group 702 people) with non-dialysis were enrolled in 17 studies. The included studies were single-center

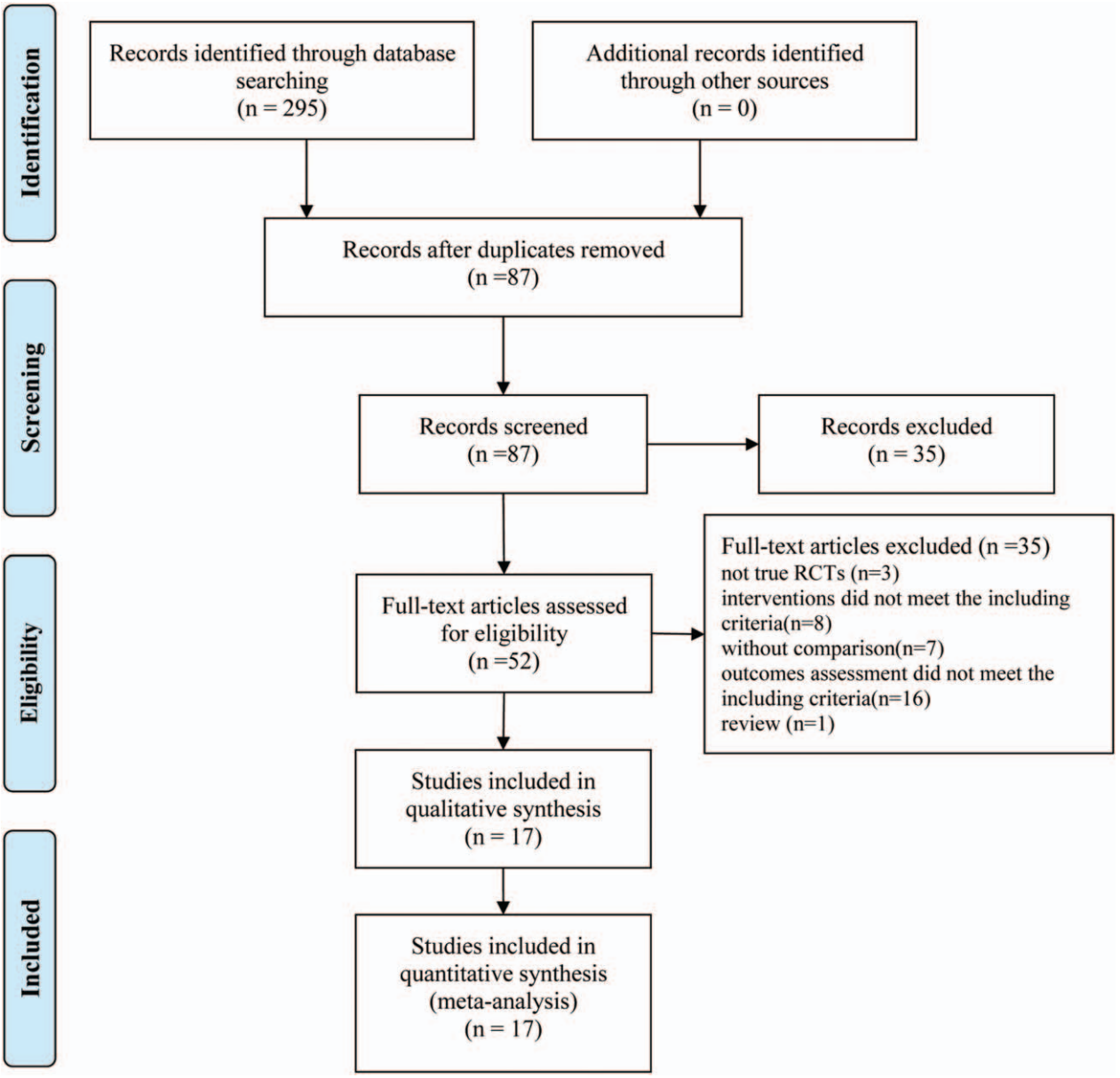

Figure 1. Flow chart of the search strategy used to identify trials for inclusion in the meta-analysis.

studies with a maximum sample size of 200 people. All studies were conducted in China and published in Chinese.

Sixteen studies used traditional Chinese medicine extracts (including Astragalus membranaceus, Houttuynia cordata, Salvia miltiorrhiza, Angelica, Chuanxiong, Ginseng, Aconite, Qingfeng rattan). Only one study used pancreatic kininogenase. The course of treatment ranged from 2 weeks to 12 weeks. In acupoint selection, ST36 was selected for 16 studies, BL23 was selected for 14 studies, BL20 was selected for 3 studies, and SP6 was selected for 2 studies. BL13, BL22, BL43, CV6, CV9 were selected by only one study. See Table 1.

3.2. Bias risk assessment for inclusion studies

Of the 17 studies included, 5 studies[12–14,26,29–31,35] provided specific random methods, while the remaining 12 studies only mentioned "random"; 2 studies[16,20] used single-blind method, and no one mentioned allocation concealment scheme. Because the included 15 studies did not mention blindness and 2 studies used single blindness, participants and researchers at the research center were at high risk of bias. Results were reported in all studies. The bias risk assessment included in the study is shown in Figure 2.

3.3. Meta-analysis of Outcome Indicators

3.3.1. Effective rate of clinical effect. Forteen studies reported the efficacy of acupoint injection in the treatment of non-dialysis chronic renal insufficiency. A total of 1216 patients were included, 609 in the treatment group and 607 in the control group. Combining 14 research results, the heterogeneity test ($\chi^2 = 4.19$, $P = .99$, $I^2 = 0\%$) between the treatment group and the control group showed that there was no statistical heterogeneity in the included study. Fixed-effect model was used. The combined effect, OR = 3.12, 95% CI (2.29, 4.26), $Z = 7.22$, $P < .00001$, showed that combined acupoint injection therapy could

Table 1

Basic features of the study.

Study	Sample size T/C	Acupoints	Injection drugs	Frequency	Duration	Outcome
Dai 2015[12]	37/38	BL23, ST36	Radix Astragali injection and Ligustrazine injection	qd	4 weeks	(2)(4)(5)
Fan 2016[13]	30/30	BL20,BL23,SP6,ST36	Zheng Qing Feng Tong Ning injection	qd	12 weeks	(1)(2)(3)(4)
Li 2012[14]	25/25	ST36	Radix Astragali injection	3 times/week	8 weeks	(1)(2)(3)(4)(5)
Li 2015[15]	30/30	ST36	Radix Astragali injection	qod	12 weeks	(1)(2)(4)
Li 2016[16]	43/43	BL23, ST36	Radix Astragali injection	not available	4 weeks	(1)(2)(3)(4)
Liu 2014[17]	76/74	BL23, ST36	Pancreatic kallikrein injection	qod	3 weeks	(1)(2)(4)
Tan 2015[18]	60/60	BL20,BL23,SP6,ST36	Radix Astragali injection	3 times/week	8 weeks	(1)(5)
Wang 2009[19]	33/34	BL23, ST36	Shenfu injection	qod	4 weeks	(1)(2)(3)(4)
Wang 2012[20]	57/56	BL13,BL20,BL22,BL23,BL43,CV6,CV9	Angelica Sinensis injection	qod	4 weeks	(1)(2)(3)(4)
Wang 2015[21]	30/29	BL23, ST36	Radix Astragali injection and Salvia miltiorrhiza injection	qod	8 weeks	(1)(2)(3)(4)
Xiong 2006[22]	23/20	BL23, ST36	Houttuynia injection	qod	12 weeks	(2)(4)(5)
Yang 2018[23]	29/30	BL23, ST36	Zheng Qing Feng Tong Ning injection	qd	2 weeks	(1)(2)(4)
Ye 2013[24]	28/28	BL23, ST36	Radix Astragali injection	qod	12 weeks	(1)(2)
Zeng 2009[25]	30/30	BL23, ST36	Radix Astragali injection	qd	3 weeks	(1)(2)(3)(4)
Zhang 2003[26]	43/37	BL23, ST36	Radix Astragali injection	qd	4 weeks	(2)(3)(4)(5)
Zhang 2014[27]	100/100	BL23, ST36	Houttuynia injection	qd	8 weeks	(1)(2)(3)(4)(5)
Zou 2015[28]	38/38	ST36	Chuankezhi injection	qd	4 weeks	(1)(2)

T = treatment group; C = control group. qd once a day, qod every other day; BL13 Feishu, BL20 Pishu, BL22 Sanjiaoshu, BL23 Shenshu, BL43 Gaohuangshu, CV6 Qihai, CV9 Shuifen, SP6 Sanyinjiao, ST36 Zusanli; (1) Effective rate of clinical effect (2) Serum creatinine (Scr); (3) Endogenous creatinine clearance (Ccr); (4) Blood urea nitrogen (BUN); (5) Hemoglobin (Hb).

significantly improve the curative effect of non-dialysis dependent CKD, as shown in Figure 3.

3.3.2. Scr. Combined with 16 studies, the heterogeneity test ($\chi^2=45.43$, $P<.0001$, $I^2=67\%$) between the treatment group and the control group showed that there was statistical heterogeneity in the included studies. A random-effect model was used. The combined effect, WMD = 7.66, 95% CI (−12.39, −2.93), $Z=3.18$, $P=.001$, the difference was statistically significant, indicating that acupoint injection therapy can significantly reduce the Scr level in non-dialysis dependent CKD patients, as shown in Figure 4.

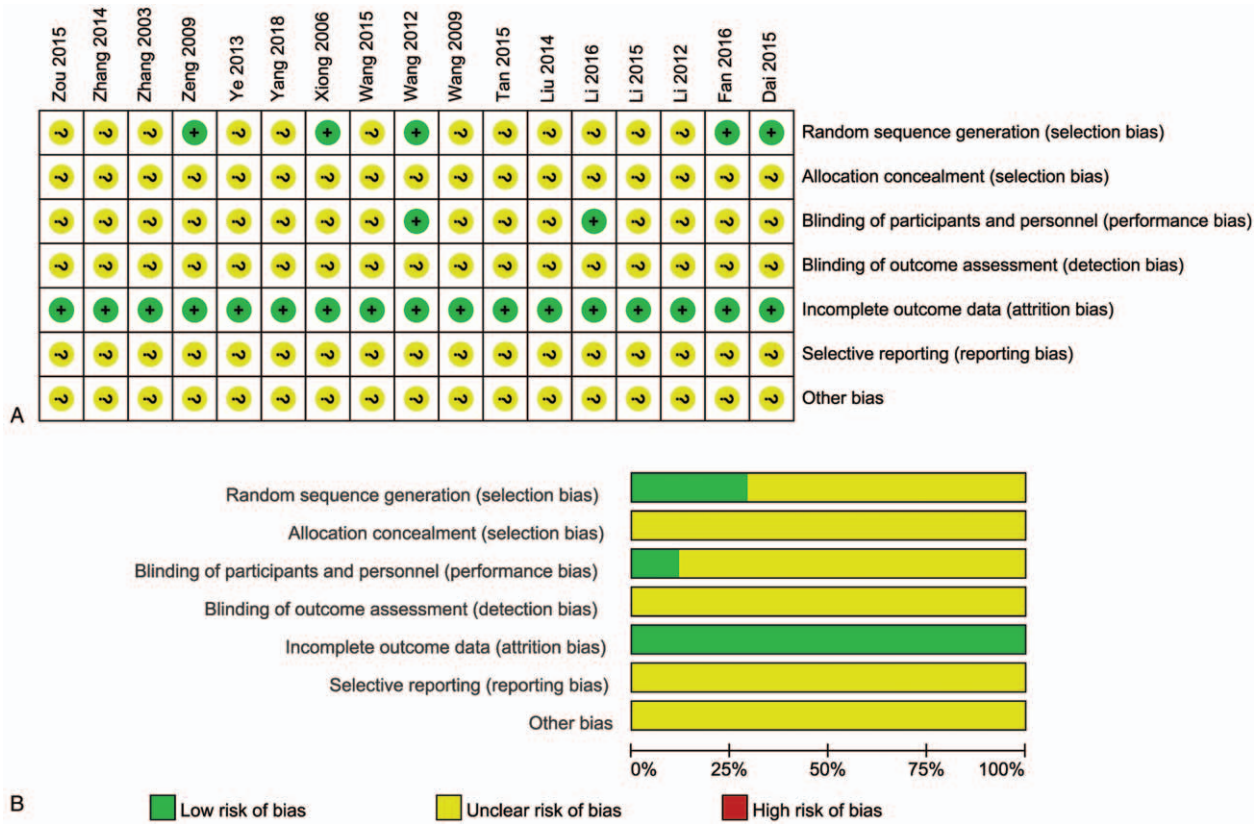

Figure 2. Quality assessment of included studies in this review: (A) Risk of bias summary; (B) Risk of bias graph.

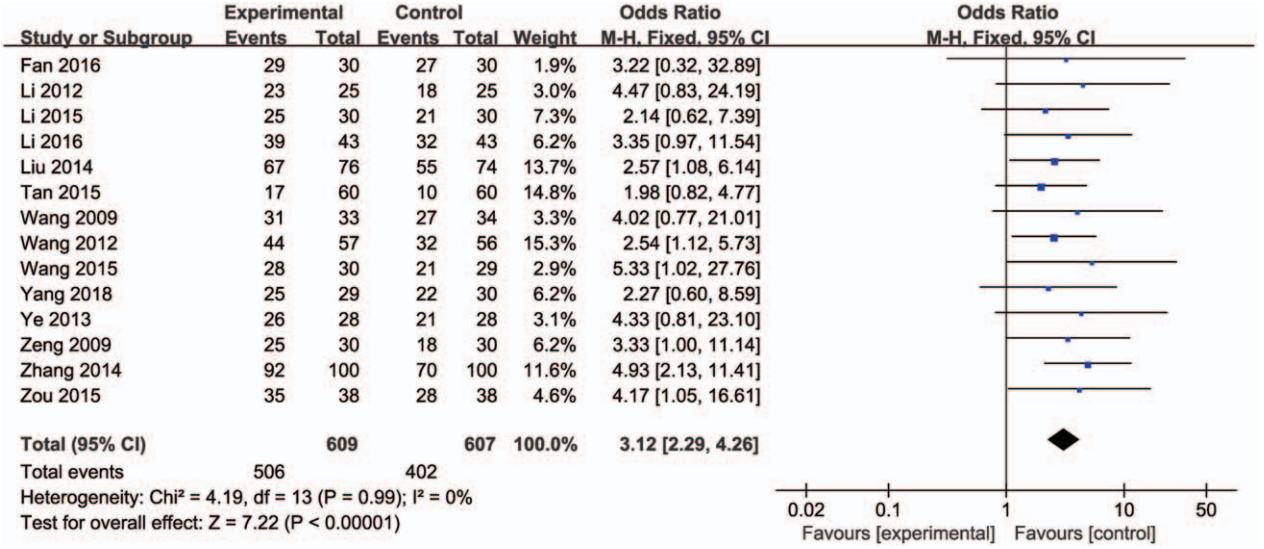

Figure 3. Clinical efficacy of acupoint injection in the treatment of CKD.

3.3.3. Ccr. Combining with 9 studies, the heterogeneity test ($\chi^2=20.10$, $P=.01$, $I^2=60\%$) was compared between the 2 groups showed that there was statistical heterogeneity in the included studies. The random-effect model was used. The combined effect, WMD=4.81, 95% CI (2.54,7.08), $Z=4.15$, $P<.0001$, the difference between the 2 groups was significant, indicating that acupoint injection can significantly increase the level of Ccr in CKD patients with non-dialysis therapy, as shown in Figure 5.

3.3.4. BUN. Combined with 14 studies, the heterogeneity test ($\chi^2=36.86$, $P=.0004$, $I^2=65\%$) between the 2 groups showed that there was statistical heterogeneity in the included studies. The random-effects model is used. The combined effect, WMD =−0.90, 95% CI (−1.26, −0.54), $Z=4.91$, $P<.00001$, the difference between the two groups was statistically significant, indicating that acupoint injection therapy can significantly reduce BUN level in CKD patients with non-dialysis therapy, as shown in Figure 6.

3.3.5. Hb. Combining with 5 studies, the heterogeneity test ($\chi^2=4.09$, $P=.54$, $I^2=0\%$) was compared between the 2 groups showed that there was no statistical heterogeneity in the included studies. The fixed-effect model was used. The combined effect, WMD=4.56, 95% CI (1.72,7.39), $Z=3.15$, $P=.002$, the difference between the 2 groups was significant, indicating that acupoint injection therapy can significantly increase the level of Hb in non-dialysis dependent CKD patients, as shown in Figure 7.

3.3.6. Adverse event. Six studies provided safety-related information, 4 of which reported no adverse events.[12,20,23,25] In one study,[13] there were 3 cases of erythema, itching, and numbness in the injection site, scalp, and sole. They stopped injecting and quit the study. The symptoms disappeared 2 days

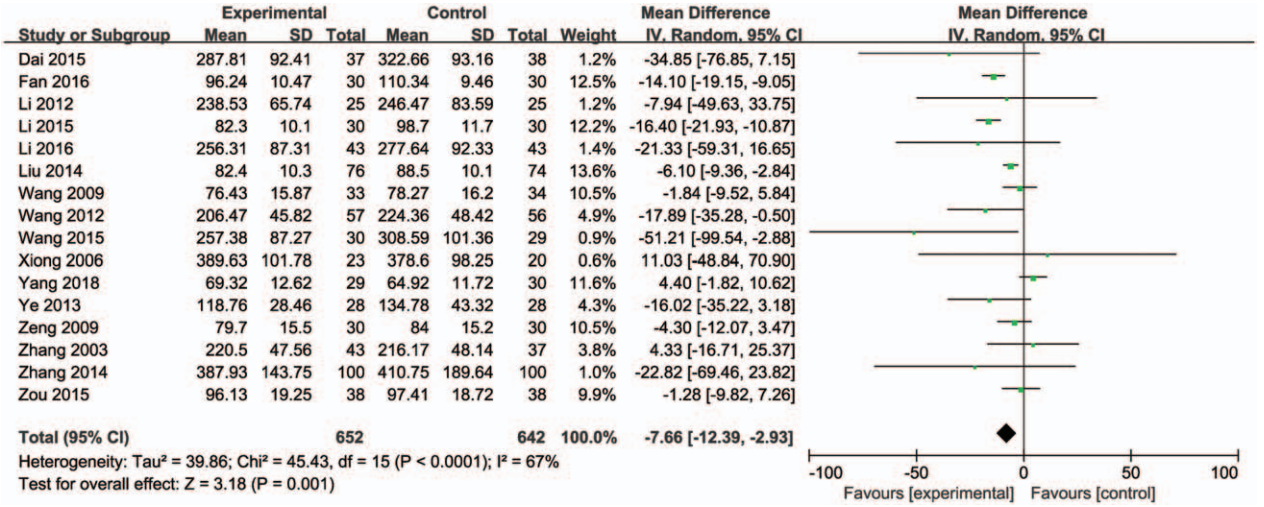

Figure 4. Effect of acupoint injection on Scr.

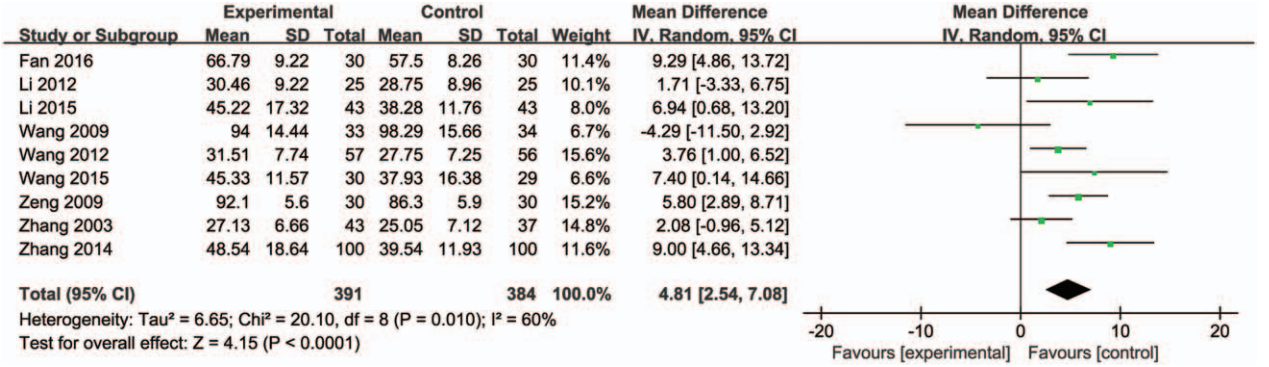

Figure 5. Effect of acupoint injection on Ccr.

after taking loratadine orally. In another study,[14] there were 3 cases of swelling and pain at the injection point, which may be caused by poor absorption of drugs and dissipated after hot compress. Acupoint injection therapy may cause local discomfort and allergic reaction, and no other adverse events were found.

3.4. Publication bias

We used the Stata software to assess publication bias. The funnel plot of publication bias (Fig. 8A) shows that all studies are equally distributed on both sides. Egger test ($P = .56$) also shows the publication bias was not evident in our meta-analysis (Fig. 8B). However, since most of the literature was in Chinese and the sample size was not large, we hypothesized a potential publication bias.

4. Discussion

Traditional Chinese medicine is widely used in China, nearly half (45.3%) of the patients with CKD in Taiwan had been prescribed and used Chinese herbal medicine after diagnosis.[29] At present, the treatment of CKD is mainly to control the primary disease and delay the progress of the disease. In recent years, the combination of traditional Chinese and Western medicine, a variety of means, and comprehensive treatment of CKD has achieved certain effects. Many studies have proved that traditional Chinese medicine characteristic therapy has certain advantages and characteristics in improving the quality of life and delaying the progression of chronic disease.[30,31] Acupoint injection therapy first appeared in China in the 1950s and is an improved technique for acupuncture therapy.[32] The injected liquid can be a solution to western medicine, vitamins, Chinese medicine extract, saline, and the like.[33,34] Acupoint injection therapy can not only play a role through the drug itself but also exert a role in the stimulation of acupoints and meridians by the pressure exerted by the drug in the acupoints. After acupoint injection, the drug exerts a certain pressure on acupoints, prolongs the time for acupoints to acquire Qi, and strengthens the stimulation of acupoints.[35,36] Because of its convenience, safety, and effectiveness in clinical application, it is used as adjuvant therapy for many diseases.[4,37]

Acupoint injection therapy has begun to receive attention in the clinic because of its efficacy and ease of operation. There are more and more clinical studies on acupoint injection therapy for CKD. This study evaluated four aspects of biochemical indicators (Scr, Ccr, BUN, Hb). To the best of our knowledge, this is the first meta-analysis of acupoint injection therapy for CKD.

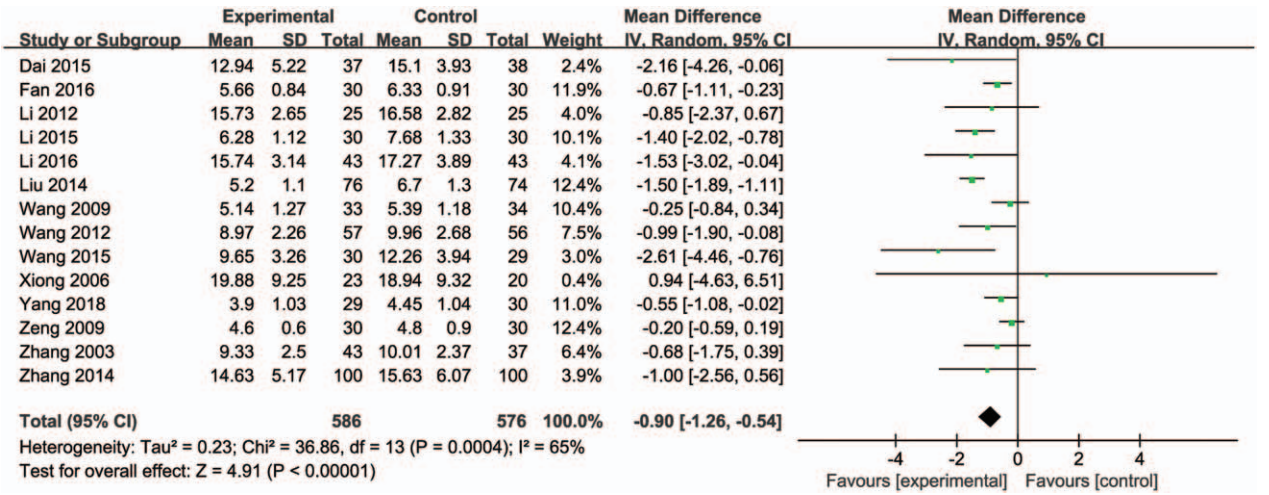

Figure 6. Effect of acupoint injection on BUN.

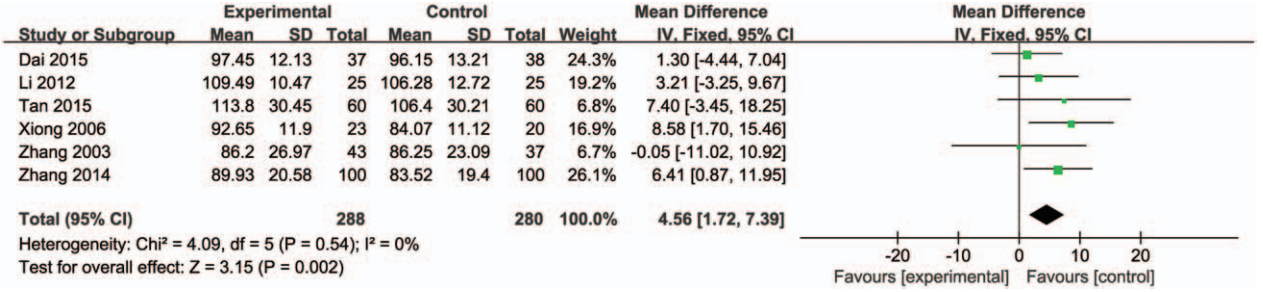

Figure 7. Effect of acupoint injection on Hb.

Our review included 17 studies and 1414 patients with CKD. In the 16 studies included, the acupoint-injected drugs were used Chinese herbal extracts, including Astragalus membranaceus, Houttuynia cordata, Salvia miltiorrhiza, Angelica, Chuanxiong, Ginseng, Aconite, Qingfeng rattan. These drugs have the effect of diuresis, swelling, qi and blood circulation, and have a good effect on the treatment of chronic renal insufficiency. The acupoints selected by the institute include Zusanli (ST36), Shenshu (BL23), Pishu (BL20), Sanyinjiao (SP6), Feishu (BL13), Gaohuangshu (BL43), Sanjiaoshu (BL22), Qihai (CV6), Shuifen (CV9) and the stimulation of these acupoints can play a role in reducing water swelling. The most frequently used acupoints are Zusanli (16 studies) and Shenshu (14 studies). Shenshu is the back-shu acupoint of the kidney, and Zusanli is the acupoint of the stomach meridian of Zuyangming. Traditional Chinese medicine theory believes that the initial cause of chronic kidney disease is in the kidney and spleen. Choosing Zusanli and Shenshu points can strengthen the spleen and kidney to improve the symptoms of the disease. Astragalus injection is the most commonly used drug in meta-analysis. It is an extract of traditional Chinese medicine Astragalus. The main components are astragalus saponin, isoflavones, polysaccharides, and trace elements. Traditional Chinese medicine believes that it has the effects of replenishing qi, replenishing qi, and reducing swelling. It can be seen that in the clinical treatment of CKD in China, acupoint injection can be a treatment method combining traditional Chinese medicine and meridian theory with traditional Chinese medicine. According to the statistics of the 17 studies included, the acupuncture injection for the treatment of chronic renal insufficiency has the exact curative effect of the drugs and acupoints with the effect of diuresis, qi and blood circulation.

We suggest future studies to evaluate the efficacy and safety of acupoint injection for non-dialysis CKD in different populations or regions. In this Meta-analysis, all included clinical trials of acupoint injection for non-dialysis CKD were conducted and published in China. The reason may be that acupoint injection is one of the methods of acupuncture and moxibustion in Traditional Chinese medicine. It is based on the theory of meridians and collaterals. However, acupuncture has been applied in a variety of comorbidities in CKD patients and the efficacy is gradually recognized and accepted worldwide.[38] We also suggest that reporting for these trials should follow the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) to explicitly and transparently explain the therapeutic processes involved.[39]

Future research needs to expand the sample size while ensuring methodological quality. Due to the lack of a sufficient number of high-level clinical studies now, future studies may have an impact on the effectiveness and safety of acupoint injection for non-dialysis CKD. Clinical trial registration, protocol publication, sample size calculation were not mentioned in the included clinical trials, so we are unable to analyze whether the trials have selective reporting and/or incomplete outcome reporting. Besides, the follow-up time of all the trials was short.

Acupoint injection for non-dialysis CKD as a new supplement and replacement therapy, its safety needs to be further elucidated. In all included clinical trials, there were 3 cases of erythema, itching, and numbness in the injection site, scalp and sole.[13]

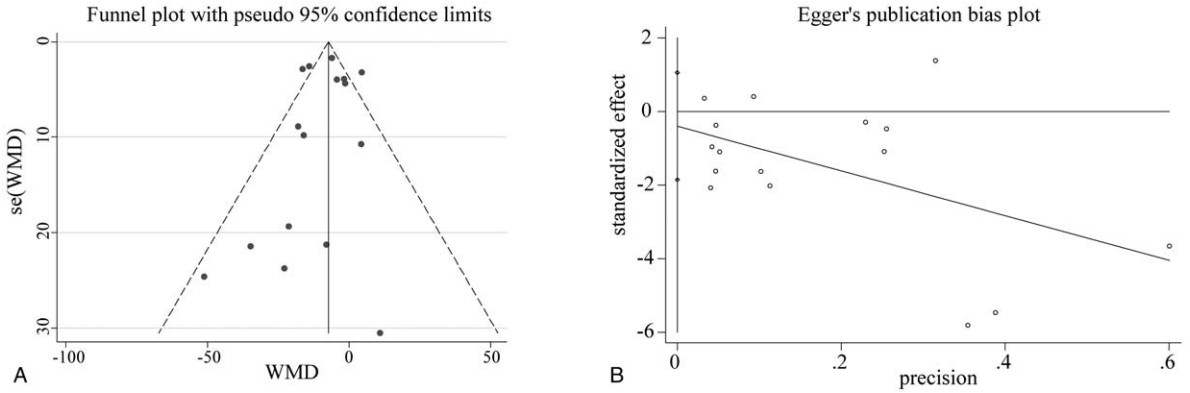

Figure 8. Publication bias: (A)The funnel plot of publication bias;(B)Eegg's test of publication bias.

They stopped injecting and quit the study, and the symptoms disappeared 2 days after taking loratadine orally. Besides, there were 3 cases of swelling and pain at the injection point.[14] In summary, acupoint injection may cause local discomfort and allergic reaction, and no other adverse events were found.

This meta-analysis is the first meta-analysis focuses on the efficacy and safety of acupoint injection for chronic non-dialysis dependent CKD. However, this meta-analysis also had some deficiencies. First, the database we selected is in English and Chinese, and it may miss some articles published in other languages. Second, most of the studies have great differences in RCT design, treatment plan, efficacy evaluation, etc., which lead to high heterogeneity after data merge analysis. Finally, all trials were conducted and published in China, it may affect the applicability of the results in other regions and ethnic groups. These deficiencies and methodological defects make it difficult for us to draw clear conclusions.

5. Conclusion

In conclusion, although there are still some deficiencies in the literature, the results suggest that combined acupoint injection therapy can reduce the levels of BUN and Scr, and increase Ccr and Hb in non-dialysis CKD patients, which has certain guiding significance for clinical treatment. Future studies also need to expand the sample size and improve the quality of reporting.

Author contributions

Conceptualization: Tiantian Yang, Guomin Si
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Resources: Tiantian Yang, Junnan Zhao, Qi Guo
Software: Yanfang Wang
Supervision: Tiantian Yang
Writing – original draft: Tiantian Yang
Writing – review & editing: Guomin Si

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