REVIEW
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Efficacy of activating blood and resolving stasis therapy for IgA nephropathy: a systematic review and meta-analysis

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Author contributions

Qiu-Mei Lan and Jie Li were in charge of manuscript conception, design, and writing; Han-Qing Zhang, Zi-Jun Zhou, and Yun-Ze Xing were in charge of data collection and analysis, and quality evaluation; Ya-Xuan Fang was in charge of English revision; Bo Yang was in charge of supervision and proofreading.

Competing interests

The authors declare no conflicts of interest.

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Peer review information

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Abbreviations

IgAN, IgA nephropathy; TCM, traditional Chinese medicine; RCT, randomized controlled trial; OR, odds ratio; RR, risk ratio; CI, confidence interval; GD-IGA1, galactose-deficient IgA1.

Citation

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Abstract

Background: To systematically evaluate the efficacy and safety of activating blood and resolving stasis in patients with IgA nephropathy. **Methods:** From inception to May 2022, databases including PubMed, Embase, the Cochrane Library, Web of Science, WanFang database, Chinese Biomedical Database, VIP, and China National Knowledge Infrastructure were searched for randomized controlled trials about enhancing blood circulation and removing stasis for IgA nephropathy. For the articles that satisfied the requirements, quality assessment and meta-analysis were done. **Results:** Seventeen randomized controlled trials with a total of 1653 patients were included. Meta-analysis showed that activating blood and resolving stasis could increase therapeutic effectiveness (risk ratio (RR) = –0.47, 95% confidence interval (CI) (–0.37, –0.2), P = 0.0006) and decrease levels of serum creatinine (RR = –0.47, 95% CI (–0.37, –0.2), P = 0.0006), urea nitrogen (RR = 0.85, 95% CI (1.44, 0.26), P = 0.005), 24-hour urinary protein quantification (RR = 1.6, 95% CI (2.44, 0.95). P = 0.00001), and urine red blood cell count (RR = 1.7, 95% CI (2.57, 0.82), P = 0.0001). There was no significant difference between the two groups in terms of security (RR = 0.6, 95% CI (0.36, 1.01), P = 0.05). **Conclusion:** Western medicine combined activating blood and resolving stasis is more efficient than Western medicine therapy alone in treating IgA nephropathy, but it still needs to be supported by additional large-scale, multi-center randomized controlled clinical trials due to the poor quality of the included trials.

Keywords: IgA nephropathy; activating blood and resolving stasis; meta-analysis; randomized controlled trial; blood stasis

Background

IgA nephropathy (IgAN) is a glomerular disease caused by the abnormal deposition of immunoglobulin A in the mesangial area of the glomeruli. It is one of the most common primary glomerular diseases worldwide [1, 2]. The main clinical manifestation is hematuria, which may also be present to varying degrees along with proteinuria, hypertension, and decreased renal function [3]. Statistics show that end-stage renal disease, which is a major cause of renal failure in young people in China, progresses to end-stage in more than one-third of patients 20 years after its first episode [4]. The supportive therapy mode is still the preferred course of action for IgAN at the moment. Glucocorticoid therapy is taken into consideration for patients who continue to have proteinuria or develop progressive renal impairment despite receiving supportive care. However, patients experience numerous serious adverse reactions after hormone therapy, and there is still some argument internationally regarding the use of glucocorticoids for IgAN treatment. There is currently no adequate solution for the therapy of IgAN.

In recent years, the development of traditional Chinese medicine (TCM) has been strongly supported by the country, and the efficacy and safety of TCM in the treatment of IgAN have gradually been recognized by academia. IgAN can be classified as "blood syndromes," "edema," "consumptive disease" and "lumbago" in TCM based on its clinical manifestations. TCM holds that IgAN is a deficiency of the root and the tip, with a deficiency of the liver, spleen, kidney and Qi-Yin (Qi refers to the basic substance that constitutes the human body and maintains life activities, and is the unity of substance and function; in Chinese philosophy, Yin refers to the female, latent, passive principle, characterized by dark, cold, wetness, passivity, disintegration, etc.) as the root, and dampness-heat and blood stasis as the tip, activating blood and resolving stasis therapy throughout IgAN [5]. In order to provide useful information for clinical practice, the study's objective is to rigorously compare the efficacy and safety of activating blood and resolving stasis therapy with that of Western medicine in the treatment of IgAN.

Methods

We prospectively registered this study protocol on the International Prospective Register of Systematic Reviews (PROSPERO: CRD42022344795).

Criteria for inclusion

Studies. Publicly published randomized controlled trials using activating blood and resolving stasis therapy as the primary therapy, in both Chinese and English.

Participants. Patients with primary IgAN pathologically diagnosed on renal biopsy were included in the study, regardless of race, nationality and duration of disease.

Intervention. The use of TCM treatment that activating blood and resolving stasis therapy plays a major role, such as Chinese herbal decoction or Chinese patent medicine injection or single herbal medicine, the dose, usage and course of treatment are not limited, and the use of Western medicine alone or in combination.

Outcome. The overall effective rate (percentage of total cases minus invalid cases [6]), adverse event rate, and 24-hour urinary protein quantification, serum creatinine, urea nitrogen, urine red blood cell count before and after treatment in the experimental and control groups.

Criteria for exclusion

(1) Participants under the age of 18 and diagnosed with secondary IgAN; (2) patients with combined psychiatric, hematological, hepatic impairment, severe cardiovascular and cerebrovascular diseases; (3) incomplete or missing outcome data that will bias the result; (4) reviews, conference abstracts, dissertations, publications about animal experiments, articles that had already been published multiple times, and articles for which there was no full text; (5) sample size less than 10 cases; (6) the composition of the herbal decoction used in the intervention is unknown.

Method of search

To examine the efficacy and safety of the activating blood and resolving stasis therapy for IgAN, a comprehensive literature search was conducted in 8 electronic databases, including PubMed, Embase, The Cochrane Library, Web of Science, Wan Fang database, CBM, VIP, and CNKI, from their conception up to May 2022. The subject and free words were combined to perform the search. In order to expand the relevant data, the references of the included studies and associated reviews were manually retrieved. Specific terms include: glomerulonephile, IgA, Berger's diseases, Huoxue (a general term for promoting blood flow in the treatment of blood stasis), invigorating circulation of blood, activating blood, Huayu (a general term for resolving static blood in the treatment of blood stasis), dispersing blood stasis, oblood stasis, randomized controlled trial, randomized, piacebo, randomized controlled trial (RCT), etc. The specific search formula is shown in Figure 1.

Literature selection and data extraction

Two researchers independently screened, retrieved, and cross-checked the literature. If there is disagreement, it is resolved through discussion or consultation with a third party. When primary screening, duplicate literature was first excluded, and irrelevant literature was second excluded after reading the title. After the initial screening, the abstract and the full text were further read to determine whether they should be included. Data extraction includes: (1) basic information about the included studies, including title, first author, time of publication, type of study, etc; (2) basic participant information and baseline characteristics; (3) interventions and main outcomes; (4) key elements of evaluating bias risk.

Evaluation of the bias risk

Using the Cochrane Collaboration's approach, two researchers independently evaluated each trial's risk of bias. The bias risk assessment tool contained the following assessment tools: random sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other bias. Each study was given one of three labels after the risk of bias was evaluated: "low risk of bias," "unclear risk of bias," or "high risk of bias." Any disagreement was settled through consultation with the third researcher.

#1 "Glomerulonephritis, IGA"[Mesh]
#2 Berger's diseases OR Nephropathy 1, Iga OR IGA Glomerulonephritis OR Nephropathy, IGA OR Iga Nephropathy 1 OR Immunoglobulin A Nephropathy OR IgA OR Nephritis, IGA Typ[Title/Abstract]
#3 #1 OR #2
#4 Huoxue OR invigorating circulation of blood OR activating blood OR Huayu OR dispersing blood stasis OR oblood stasis[Title/Abstract]
#5 "randomized controlled trial"[Publication Type]
#6 randomized OR piacebo OR RCT[Title/Abstract]
#7 #5 OR #6
#8 #3 AND #4 AND #7

Figure 1 Search formula of PubMed. RCT, randomized controlled trial.

Data analysis

The included literature was evaluated and analyzed systematically using the statistical program Review Manager5.4. Different from measurement data that is expressed as a standardized mean difference, counting data is presented as an odds ratio (OR) or risk ratio (RR), both with a 95% confidence interval (CI). The Chi-square test and the *I*-square index were used in testing heterogeneity. When $I^2 \leq 50\%$, which indicated that there was no substantial heterogeneity in the studies, the fixed effect model was used, and when $I^2 > 50\%$, which indicated that there was significant heterogeneity among the studies, the random effect model was used. All tests were two-sided, and a statistically significant result was one with a *P* value of 0.05. In addition, we evaluated the possibility of publication bias using funnel plots.

Literature results

Search outcomes

After removing the redundant and animal-like items with NoteExpress software, 809 of the total 1361 articles were still available. There were 174 items remaining after reading the abstract and the title. The inclusion and exclusion criteria used to read the complete text led to the inclusion of 17 papers [7–23] with 1653 patients. According to every study, there was no statistical significance in the baseline data of each group, which were equal in terms of gender, age, condition before treatment, and other factors. The literature screening process is shown in Figure 2, and the basic information of the included studies is shown in Table 1. The specific composition of the prescription is shown in Table 2.

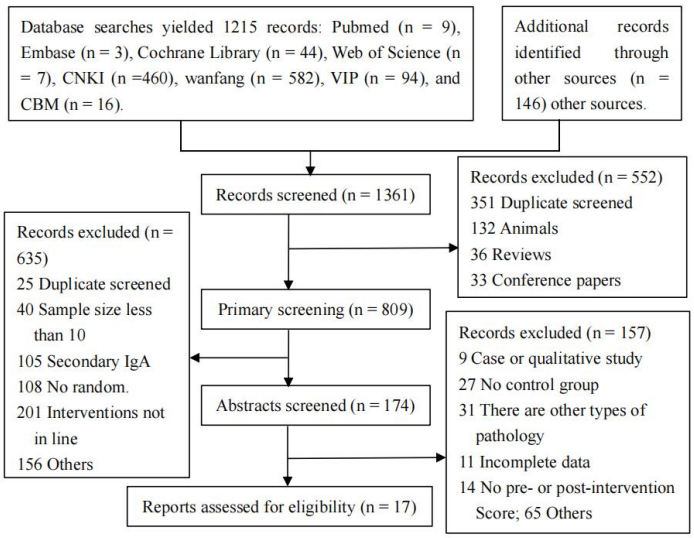

Figure 2 Flow chart of study identification and selection

Table 1 Basic information about the studies includes

Study	Sex (male)*	Sample size*	Intervention*	Outcome
Wang 2016 [7]	19/17	29/29	CG + Ligustrazine injection/Benazepril + Dipyridamole	abcde
Liu 2010 [8]	23/21	40/41	Ligustrazine injection/Benazepril	ace
Liu 2007 [9]	34/30 (M/F)	32/32	CG + Breviscapine injection/Fosinopril	abcdf
Chen 2017 [10]	30/29	49/49	CG + Breviscapine injection/Basic treatment + Metacortandracin	cdef
Chen 2008 [11]	-	29/28	CG + Fleabane injection/Conventional therapy	d
Shi 2006 [12]	30/15	60/30	CG + Fleabane injection/Conventional therapy	cd
Wang 2004 [13]	33/12	60/20	Compound danshen injection/Persantine + Vitamin C	acdf
Zheng 2016 [14]	14/15	26/26	CG + HXHY 1/Tacrolimus + Metacortandracin	adf
Zhao 2016 [15]	188/112 (M/F)	150/150	CG + HXHY 2/Dipyridamole	a
Shen 2011 [16]	9/10	20/20	Xuesaitong injection/Telmisartan	cde
Li 2019 [17]	18/20	34/34	CG + Activate blood and free collateral vessels prescription/Shenyan Kangfu tablet	cdef
Lu 2015 [18]	15/16	38/38	CG + HXHY 3/Basic treatment	abcdef
Zheng 2012 [19]	19/17	35/32	CG + Shuxuetong injection/Persantine + supportive treatment	cd
Li 2006 [20]	57/53 (M/F)	62/48	Basic treatment + Lotensin + Shuxuetong injection/Basic treatment + Lotensin + Vitamin C injection	abc
Li 2008 [21]	92/55	166/96	Hirudin capsules/Persantine	abcf
Guo 2016 [22]	17/12	30/26	CG + Centipede powder capsules/Telmisartan	abcdef
Ding 2010 [23]	33/32	48/46	Shenluotong decoction/Uremic clearance granule	abce

*, treatment group vs control group; M, male; F, female; CG, control group; a, effective rate; b, incidence of adverse reactions; c, serum creatinine; d, 24-hour urinary protein quantity; e, urea nitrogen; f, urine red blood cell count; HXHY, Huoxue Huayu, activating blood and resolving stasis.

Table 2 Specific prescription composition and efficacy

Study	Name	Main function	Composition
Zheng 2016 [14]	HXHY 1	Activate blood and resolve stasis	*Arecae Semen Tostum* 20 g, *Chuanxiong Rhizoma* 15 g, *Persicae Semen* 15 g, *Carthami Flos* 15 g, *Paeoniae Rubra Radix* 15 g, *Poria* 15 g, *Alismatis Rhizoma* 15 g, *Salviae Miltiorrhizae Radix et Rhizoma* 15 g, *Angelicae Sinensis Radix* 10 g, *Pheretima aspergillum* 10 g
Zhao 2016 [15]	HXHY 2	Activate blood and resolve stasis	*Salviae Miltiorrhizae Radix et Rhizoma*, *Astragali Radix*, *Poria*, *Imperatae Rhizoma*, *Eucommiae Cortex*, *Corni Fructus*, *Hirudo*, *Persicae Semen*, *Rubiae Radix et Rhizoma*, *Leonuri Herba*.
Li 2019 [17]	HXTL	Activate blood and free collateral vessels prescription	*Astragali Radix* 30 g, *Rehmanniae Radix* 15 g, *Paeoniae Rubra Radix* 15 g, *Ligustri Lucidi Fructus* 15 g, *Lycopi Herba* 15 g, *Angelicae Sinensis Radix* 10g, *Hirudo* 10 g, *Asari Radix et Rhizoma* 3 g
Lu 2015 [18]	HXHY 3	Eliminating blood stasis to promote regeneration of blood	Add *Rhei Radix et Rhizoma* 5 g, *Salviae Miltiorrhizae Radix et Rhizoma* 10 g, *Persicae Semen* 10 g, *Carthami Flos* 10 g on the basis of dialectical prescription
Ding 2010 [23]	SLT	Resolve stasis and free the collateral vessels	*Astragali Radix* 30 g, *Salviae Miltiorrhizae Radix et Rhizoma* 15 g, *Chinemys reevesii* 15 g, *Pheretima aspergillum* 12 g, *Chuanxiong Rhizoma* 10 g, *Cryptotympana pustulata* Fabricius 10 g, *Zaocys dhumnades* (Cantor) 10 g, *Bombyx mori* Linnaeus 10 g, *Poria* 10 g, *Rhei Radix et Rhizoma* 6–15 g

SLT, Shenluotong decoction; HXHY, Huoxue Huayu, activating blood and resolving stasis.

Assessment of risk bias

Four of the 17 RCTs [7, 16, 18, 19] described randomization processes, one of which used computer software for random assignment and the other three used a randomized control table; the rest mentioned "random" only and were evaluated as "low risk." None of the included trials made it clear whether or not blinding and allocation concealment were used, so they were rated as "unclear." Three studies [11, 18, 23] described the cases of loss and why they were dropped out, but they had no significant impact on the intervention effect because of the excluded cases just two or three, other studies had no cases falling out and were identified as "low risk." Five studies [8, 9, 12, 16, 19], which were categorized as "high risk" and the others as "low risk" did not fully provide their outcome indicators. All studies were marked as "unclear" because it was unable to tell whether there were any other sources of bias. Figure 3 displays the risk bias assessment.

Meta-analysis results

Rate of effectiveness

Eleven RCTs were reported on the clinical effectiveness rate of IgAN treated by activating blood and resolving stasis therapy. After the combination, there was no statistical heterogeneity among the studies (I^2 = 0, P < 0.00001), hence the fixed-effect model was employed for analysis. In accordance with the findings, the total effective rate of the experimental group was higher than that of the control group, and the difference was statistically significant (RR = 1.37, 95% CI (1.28, 1.47), P < 0.00001, Figure 4).

Serum creatinine

Fourteen RCTs provided data on serum creatinine, and the heterogeneity between the combined study groups was large (I^2 = 80%, P = 0.0006). Consequently, the random effect model was used for analysis. The results showed that the effect of serum creatinine reduction in the experimental group was better than that in the control group, and the difference was statistically significant (RR = –0.47, P = 0.0006). 95% CI (–0.37, –0.2), P = 0.0006, Figure 5).

Urea nitrogen

Eight RCTs reported the influence of activating blood and resolving stasis therapy on urea nitrogen in patients with IgAN, and data heterogeneity was found (I^2 = 91%, P = 0.005), so the random effect model was used for analysis. The results indicated that the impact of reducing urea nitrogen in the experimental group was greater than that in the control group (RR = –0.85, 95% CI (–1.44, –0.26), P = 0.005, Figure 6).

24-hour urinary protein quantification

Data from 12 RCTs on 24-hour urine protein quantification were provided, and the random effect model was chosen due to the high heterogeneity (I^2 = 93%, P < 0.00001). According to the findings, the experimental group's reduction in 24-hour urine protein quantification was more effective than that of the control group (RR = –1.6, 95% CI (–2.25, –0.95), P < 0.00001, Figure 7).

Red blood cell count in urine

Eight RCTs reported the data. After combining, we discovered that there was significant heterogeneity (I^2 = 96%, P = 0.0001). Therefor the random effect model was adopted for analysis. The outcomes demonstrated that the experimental group's effect of lowering urine red blood cell count was superior to that of the control group (RR = –1.7, 95% CI (–2.57, –0.82), P = 0.0001, Figure 8).

Adverse events

Six RCTs reported the data. After combination, a few significant heterogeneities were found (I^2 = 18%, P = 0.05), thereby the fixed-effect model was applied. The adverse event rate in the experimental group was lower than that in the control group, as demonstrated by the forest plot. The difference between them, however, was not statistically significant (RR = 0.6, 95% CI (0.36, 1.01), P = 0.05, Figure 9).

Publication bias

Based on the data of serum creatinine, the funnel plot was used to detect publication bias in our study. The funnel plot was largely symmetrical across all fourteen research, which suggests a minimal likelihood of publication bias. Despite the fact that studies involving serum creatinine were split into injection and non-injection groups for subgroup analysis, as well as the articles that may lead to high heterogeneity, such as the significant difference in sample size between the control group and the experimental group, were also tried to be eliminated, none of the sources of heterogeneity were found. Sensitivity analysis was not repeated due to the poor quality of the included studies. The funnel plot is displayed in Figure 10.

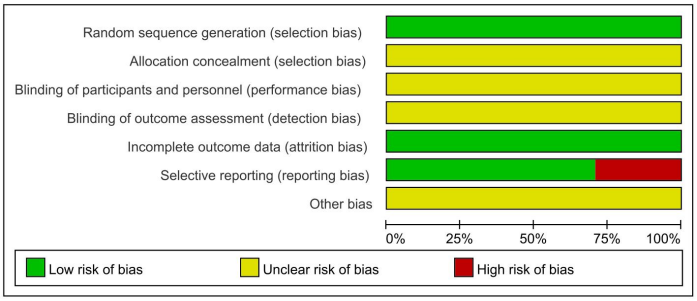

Figure 3 Assessment of risk bias

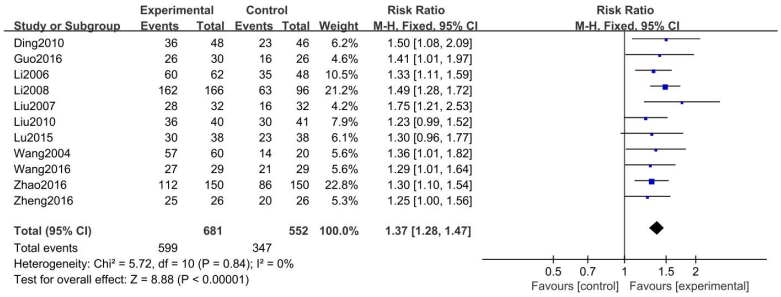

Figure 4 Forest plot of the clinical effective rate. CI, confidence interval.

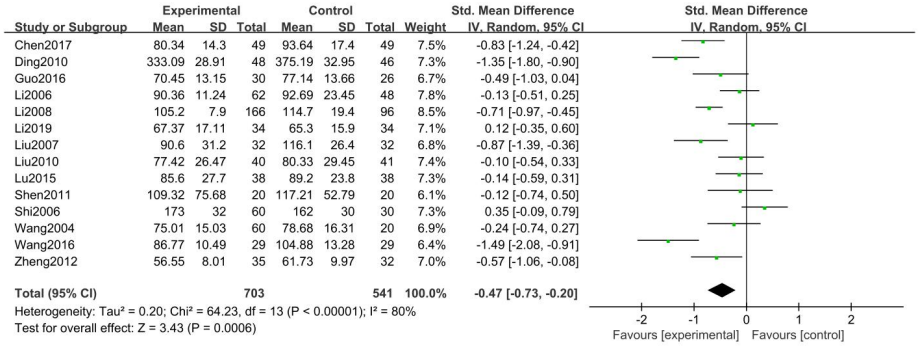

Figure 5 Forest plot of serum creatinine. CI, confidence interval; SD, standard deviation.

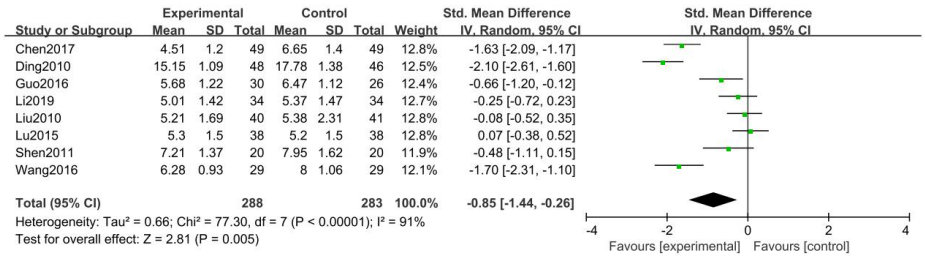

Figure 6 Forest plot of urea nitrogen. CI, confidence interval; SD, standard deviation.

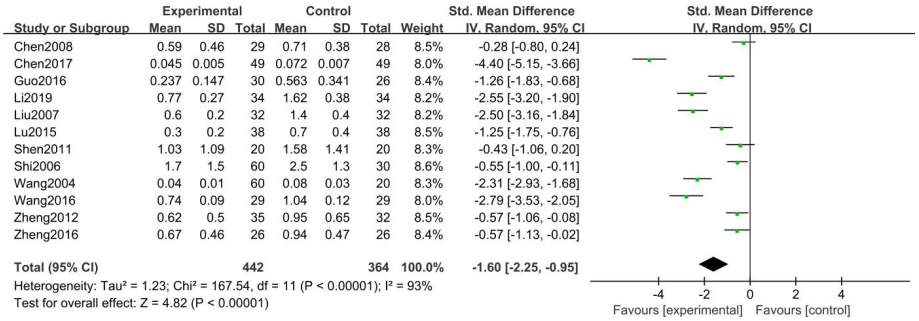

Figure 7 Forest plot of 24-hour urine protein quantification. CI, confidence interval; SD, standard deviation.

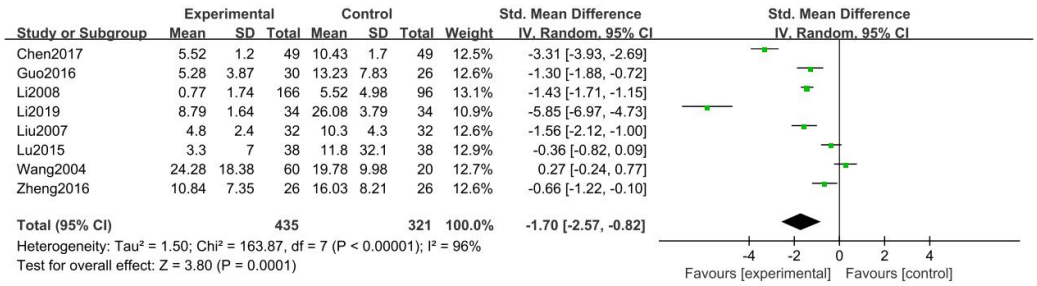

Figure 8 Forest plot of urine red blood cell count. CI, confidence interval; SD, standard deviation.

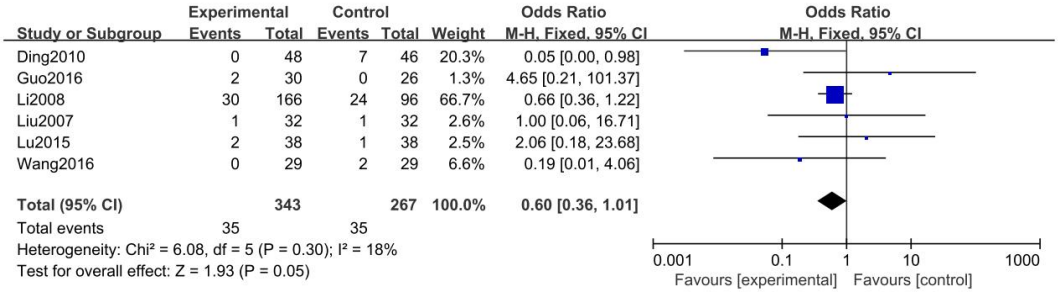

Figure 9 Forest plot of adverse event rate. CI, confidence interval.

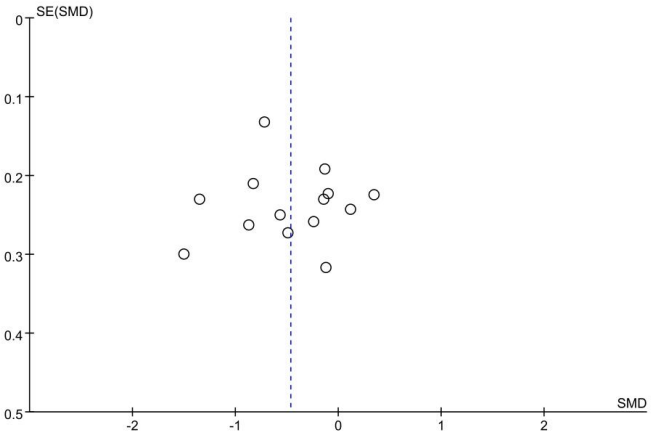

Figure 10 Funnel plot of serum creatinine. SE, standard error; SMD, standardized mean difference.

Discussion

The pathogenesis of IgAN is not yet clear, but the role of galactose-deficient IgA1 (GD-IGA1) in the pathogenesis of IgAN is well established, and the "multiple-hit theory" is widely accepted by academics [24]. The theory includes: (1) production of GD-IGA1; (2) production of IgG autoantibodies against GD-IGA1 molecules; (3) formation of immune complexes containing Gd-IgA1; and (4) the deposition of immune complexes into the mesangial region. As a result, pathological alterations in IgAN, such as cell proliferation in the mesangial matrix, endothelial cell proliferation, segmental sclerosis or adhesions, tubular atrophy, interstitial fibrosis, etc., are caused. Professor Wang argued that [25] intrarenal microscopic aggregation-accumulation is the basis for the microscopic syndrome differentiation of focal and segmental glomerular sclerosis, tubule atrophy, interstitial fibrosis, fibrous crescents, and periglomerular fibrosis that have the characteristics of being immobilized and unhealed for a long time. Accordingly, we should pay great attention to activating blood and resolving stasis therapy when treating IgAN.

According to the findings of the meta-analysis, combination therapy using activating blood and resolving stasis therapy is more effective in treating IgAN while also having good usability because it can lower levels of serum creatinine, urea nitrogen, urinary protein, and red blood cells in the urine. The blood-activating and stasis-resolving medicines can invigorate blood and disperse stasis, facilitate blood flow, unchoke fluid and humor, improve the pathological condition of blood stagnation and fluid-humor suffocation, and promote the improvement of microcirculatory disorders to help the full play of the function of warming Yang (in Chinese philosophy, the masculine, active and positive principle, characterized by light, warmth, dryness, activity, etc.) and nourishing Yin to tonify the kidney, which is conducive to the restoration of renal function. Modern studies have shown that the frequently-used blood-activating and stasis-resolving medications such as *Salviae Miltiorrhizae Radix et Rhizoma* can protect the kidney's tiny blood vessels, delay renal interstitial fibrosis, and prevent glomerular sclerosis [26]. Ligustrazine, an extract of *Chuanxiong Rhizoma*, can enhance renal circulation, inhibit fibrosis and improve hemorheology [27]. Hirudo can maintain renal function, lower IL-6 levels, decrease urine protein, and enhance whole blood and plasma viscosity in rats with IgAN blood stasis syndrome [28]. Through its antioxidant, anti-inflammatory, anti-fibrosis and anti-platelet aggregation effects, *Carthami Flos* can alleviate renal interstitial fibrosis, improve blood viscosity, coagulation and aggregation, increase renal blood flow perfusion, lessen blood viscosity in glomeruli, and prevent further deterioration of renal

disease [29].

Why is the IgAN characterized by blood stasis throughout? According to Wang et al. [30], there are some points to consider: the first one is deficiency. A long-term chronic illness can result in spleen and kidney deficiencies, which prevent the Qi and blood from being transformed and hinder the blood from moving through the meridians, causing stagnation. It should be treated with consolidating root and activating blood using *Astragali Radix*, *Atractylodis Macrocephalae Rhizoma*, *Poria*, *Codonopsis Radix*, *Angelicae Sinensis Radix*, *Spatholobi Caulis*, and other. The second one is heat. Patients with IgAN usually need to take glucocorticoids, which can easily harm their Yin and generate a deficient fire that can burn fluid and humor and induce blood stasis. As a result, Yin should be supplemented and heat should be cleansed first. *Moutan Cortex*, *Rehmanniae Radix Praeparata*, *Paeoniae Rubra Radix*, *Ophiopogonis Radix*, etc. are recommended for use. The third one is turbid toxin. As the illness worsens, kidney function declines gradually, and metabolites such as creatinine and urea nitrogen accumulate in the body. The buildup of turbid poison will block the flow of blood and cause blood stasis. This mutual development of stasis and toxin will intensify the disorder. This study showed that the activating blood and resolving stasis therapy reduced the levels of creatinine and urea nitrogen, this may be one of the reasons for the efficacy of the activating blood and resolving stasis therapy. To detoxicate, remove blood stasis, and get rid of the old to create the new, it should take *Lonicerae Japonicae Flos*, *Forsythiae Fructus*, *Smilacis Glabrae Rhizoma*, *Dioscoreae Spongiosae Rhizoma*, *Polygoni Cuspidati Rhizoma*, *Rhei Radix et Rhizoma*, etc.

The activating blood and resolving stasis therapy caused gastrointestinal discomfort and a little cough in six of the studies that showed adverse events. These side effects also went away when symptoms were treated symptomatically. There was a slight tendency for gastrointestinal bleeding in both the test and control groups, according to the report by Li et al. [21], but the incidence was low—3% and 7.3%, respectively. Neither group experienced any major adverse effects in all studies. As a result, while the study was unable to demonstrate that the combination of Western medicine and the activating blood and resolving stasis therapy is safer than Western medicine alone, it is evident from the reports of negative occurrences in the different studies that the risk associated with the activating blood and resolving stasis therapy is not high or even very low.

There are still several shortcomings in this study. First, it is uncertain if blinding will be used in the study due to a number of factors, including the poor quality of the included publications and the fact that the majority of them do not precisely describe the blinding method and allocation hiding. Second, specific prescriptions, usage and duration of treatment for the method of invigorating blood circulation and removing blood stasis were not all consistent, which may have skewered the results. Third, IgAN has a high rate of recurrence and a long course, so patients may experience spontaneous remission throughout a long treatment, which may exaggerate the therapeutic benefit. Follow-up and long-term observation ought to be necessary. The follow-up period for the RCTs included in this analysis, however, varies or is unclear.

In conclusion, the combined activating blood and resolving stasis therapy approach is superior to using only Western therapy to treat IgAN. However, more large-sample, multi-center, and high-quality RCTs are still required in order to verify the findings due to the low quality of the included publications.

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