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Efficacy and safety of Shenfu injection on bradyarrhythmia

A systematic review and meta-analysis

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Abstract

Background: Bradyarrhythmia is a form of arrhythmia commonly seen in clinical settings. This study aims to investigate the efficacy and safety of the Shenfu injection (SFI) in the treatment of bradyarrhythmia.

Methods: A comprehensive search was conducted in seven databases for randomized controlled trials (RCTs) related to SFI and the treatment of bradyarrhythmia. Primary outcome in this meta-analysis included the overall response rate in clinical symptom improvement. The risk of bias was evaluated utilizing the Cochrane Collaboration's tool.

Results: A total of 28 studies, involving 2143 patients with bradyarrhythmia, were included. The meta-analysis results suggest that SFI treatment is superior to conventional medication alone. Further sensitivity analysis demonstrated that the total response rate in the SFI group was significantly higher than that in the conventional medication group (RR = 1.29; 95% CI: 1.22–1.37; $P < .00001$). Moreover, the improvement in heart rate in the SFI group was significantly better than that in the conventional medication group (MD = 5.17; 95% CI: 3.77–6.58; $P < .00001$). In terms of safety, the incidence of adverse events was lower in the SFI treatment group (5.25%, 19/362) compared to the conventional medication alone group (34.04%, 113/332) (RR = 0.20; 95% CI: 0.08–0.51; $P < .001$).

Conclusion: SFI demonstrates significant improvement in the overall response rate and safety for patients with bradyarrhythmia compared to conventional basic therapy. However, due to the presence of potential bias in the included studies, well-designed RCT trials are needed to confirm the efficacy and safety of adjuvant SFI therapy for the treatment of bradyarrhythmia.

Abbreviations: AV = atrioventricular, CBM = Chinese Biomedical Literature Database, CI = confidence interval, CNKI = China National Knowledge Infrastructure, Embase = Excerpta Medica Database, MD = mean difference, NT-proBNP = N-terminal pro-B-type natriuretic peptide, *P* = *P* value, PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCTs = randomized controlled trials, RR = relative risk, SFI = Shenfu Injection, TCM = traditional Chinese medicine, VIP = China Science and Technology Journal Database.

Keywords: bradyarrhythmia, meta-analysis, Shenfu injection, systematic review, traditional Chinese medicine

YW, MY, and RC contributed to this article equally.

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

The need for ethical review in this study was considered unnecessary, as it involved a secondary analysis of previously conducted RCTs, all of which underwent and received prior approval through an ethical review process.

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1. Introduction

Arrhythmia includes different types and can develop as a result of various heart diseases.[1–5] Bradyarrhythmia is a type of serious arrhythmia that is frequently observed in clinical settings. It is characterized by a slow heart rate, normally lower than 60 beats per minute. This can result in reduced cardiac output, leading to symptoms such as dizziness, fatigue, syncope, and even death. The incidence of bradyarrhythmia typically continues to rise with increasing age.[6] Drug therapy and pacing therapy are the mainstays of bradyarrhythmia treatment.[7–13] Common drugs used include atropine, isoproterenol, and aminophylline.[14,15] However, their efficacy is limited by the difficulty in regulating the dosage and the frequent occurrence of adverse reactions, making them unsuitable for long-term use.[16] Moreover, complications after surgery, the expensive nature of the procedure, and the requirement for ongoing follow-up throughout one's life contribute to the reluctance or inability of many patients to undergo pacemaker implantation.[17–20] This population is at a greater risk of serious complications and accidents, underlining the urgent need to identify alternative treatment options.

In China, Traditional Chinese Medicine (TCM) herbs and their extracts are commonly utilized for the treatment and management of a wide range of diseases and conditions.[21–27] Shenfu injection (SFI) is a TCM injection composed of *Red ginseng* and *Aconiti Lateralis Radix Praeparata*. It has been proven effective in treating sepsis, shock, heart failure, and other critical illnesses, while possessing the benefits of high safety and efficacy.[28] In a previous data mining study, *Aconiti Lateralis Radix Praeparata* and *Red ginseng* were recognized as common TCM for managing bradyarrhythmia,[29] while several animal experiments confirmed SFI's ability to improve bradyarrhythmia.[30,31] However, there remains a dearth of research concerning the comprehensive assessment of the clinical effectiveness and safety of SFI in the management of bradyarrhythmia.

It is worth noting that previous meta-analyses on the same topic, conducted in 2010[32] and 2016,[33] have been reported. In this study, our objective was to perform an updated meta-analysis and systematic review using the rigorous and up-to-date methods outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[34–36] This approach was intended to enhance the accuracy and reliability of their results, aiming for clear and objective outcomes.

2. Methods

2.1. Inclusion criteria

2.1.1. Participants. Patients exhibited a heart rate of less than 60 beats per minute and/or had electrocardiogram results indicative of bradyarrhythmia, such as sinus bradycardia, sick sinus syndrome, and atrioventricular (AV) block. It is important to note that there were no limitations based on the subject's age, gender, or dialectical type.

2.1.2. Interventions. SFI was compared with conventional therapy, Western medicine, and other traditional Chinese medicines; additionally, the combination of SFI and Western medicine was compared with the same Western medicine alone. Conventional therapy included anticoagulation, vasodilation, and treatment of underlying diseases, but did not involve the use of antiarrhythmic drugs.

2.1.3. Outcomes. Outcomes: total response rate of clinical symptoms, changes in mean heart rates; safety outcome: adverse events.

2.1.4. Studies. The studies were randomized controlled trials (RCTs) that had been conducted with or without blinding, depending on the specific protocol and methodology employed. Notably, both Chinese and English literature were included in this study.

2.2. Exclusion criteria

The following studies were excluded from the analysis:

1. Animal or cell experiments, conference reports, article comments or responses, repeatedly published studies, studies with incomplete data, the unavailability of full text, and other literature that did not meet the necessary qualifications.
2. Subjects with tachyarrhythmia or bradyarrhythmia, with other comorbidities, were excluded.
3. Subjects diagnosed solely based on the TCM disease name or syndrome type for this disease and other Western medicine diseases were also excluded.
4. Studies involving interventions that combined multiple Chinese patent medicines were also excluded.
5. Lastly, studies focusing solely on examining the comprehensive efficacy of SFI at different doses were also excluded.

2.3. Search strategy

A comprehensive search was conducted using seven databases, namely China National Knowledge Infrastructure (CNKI), Wanfang Database, China Science and Technology Journal Database (VIP), Chinese Biomedical Literature Database (CBM), PubMed, Excerpta Medica Database (Embase), and Cochrane Library. The computer-based search was performed until December 31, 2022. To identify relevant studies, a combination of subject words and free words were used alongside the following keywords: "Shenfu," "Shenfu injection," "arrhythmia," "bradycardia," "bradyarrhythmia," "sick sinus syndrome," and "conduction block." Each database was searched according to its unique characteristics.

2.4. Study selection and data extraction

Two researchers independently conducted searches using the specified keywords. They selected relevant literature on the treatment of bradyarrhythmia with SFI by reviewing titles and manually removing duplicate studies. Subsequently, the full texts of potentially eligible studies were retrieved and evaluated based on predetermined inclusion and exclusion criteria. Two reviewers independently conducted data extraction from the trials that were included in the analysis. Various data points, such as literature title, first author, year of publication, diagnostic criteria, sample size, gender distribution, mean age of participants, intervention measures, treatment duration, main outcome measures (total response rate), as well as information regarding the type and frequency of adverse reactions, were included in the study. Any discrepancies that arose during data extraction were resolved through discussion involving a third reviewer, as previously suggested.[37–41]

2.5. Methodological quality assessment

To evaluate the quality of the studies that were incorporated, a recommended evaluation approach from the Cochrane Handbook for Systematic Reviews of Interventions was employed. This assessment covers several aspects, including the randomization method, allocation concealment during the randomization process, subject blindness, outcome assessment blindness, data integrity, selective reporting bias, and other potential sources of bias (e.g., reporting funding sources or conflicts of interest). Each aspect is categorized as "low risk" (A) if it meets all requirements; "unclear risk" (B) if there is uncertainty

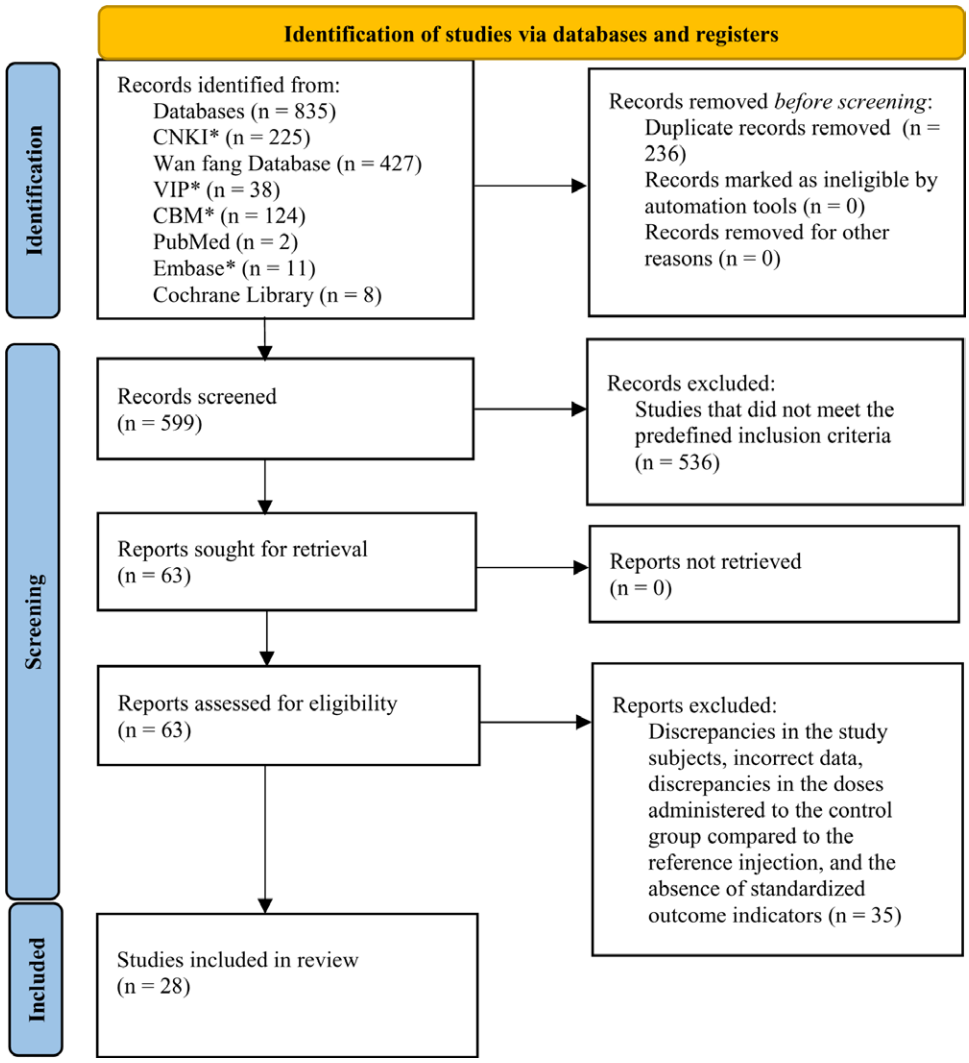

Figure 1. PRISMA diagram for the search strategy and selected studies. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CNKI*-China National Knowledge Infrastructure; VIP*-China Science and Technology Journal Database; CBM*-Chinese Biomedical Literature Database; Embase*-Excerpta Medica Database; n, number.

or insufficient information; or "high risk" (C) if it does not meet requirements, as previously described.[42,43] Studies that received an A rating in all aspects were considered Grade A. Studies with one or more B ratings but no C ratings were classified as Grade B. Studies with one or more C ratings were designated as Grade C. The results obtained from both researchers' assessments were cross-checked for agreement. In cases where disagreements arose between them, discussions or consultations with a third party helped resolve any discrepancies encountered during the evaluation process.

2.6. Data synthesis and analysis

This meta-analysis was conducted using Review Manager 5.4, a widely-used software provided by the Cochrane Collaboration.[44–46] Outcome data analysis used relative risk (RR) with a 95% confidence interval (CI) for categorical variables, and mean difference (MD) for continuous variables. Study heterogeneity was assessed with the I^2 statistic, as reported.[47–50] If substantial heterogeneity was observed ($I^2 > 50\%$ or $P < .05$), a sensitivity analysis was conducted to identify possible sources, and a random-effects model was applied. In cases of minimal heterogeneity, a fixed-effect model was employed. Funnel plots were used to assess publication bias for outcome measures based on more than 10 studies. To address the limitations of funnel plots, Egger's test and Begg's test were conducted using R software, with a significance threshold set at $P < .05$.[51–53] Additionally, the trim-and-fill method was applied to calculate the new effect size, further validating the robustness of the results.[54]

3. Results

3.1. Study identification

We retrieved a total of 835 documents from seven databases: CNKI (225), Wanfang database (427), VIP (38), CBM (124), PubMed (2), Embase (11), and Cochrane Library (8). Initially, we removed duplicate literature, resulting in the exclusion of 236 articles. Then, 2 researchers independently reviewed the titles and abstracts of the remaining articles. 536 articles were excluded because they did not meet the criteria for inclusion. Next, the full texts of the remaining articles were carefully examined. We further removed studies that involved inconsistent study subjects, data errors, different doses of SFI in control groups, and inconsistent outcome indicators. This process led to the removal of an additional 35 articles. Finally, after these rigorous selection steps, we included a total of 28 studies for

Table 1

Basic characteristics of the included studies.

Author	Year	Sample size		Effective event		Sex		Age (years)		Intervention measures		Duration	Outcome
		I	C	I	C	M	F	I	C	I	C		
Liu Desheng[55]	2000	112	100	106	90	–	–	–	–	SFI (30 mL) + Atuopin (0.005 mg/kg)	Atuopin (0.01 mg/kg)	Intraoperative transient medication	①
Lu Saijun[56]	2000	31	25	26	5	35	21	16–75	18–67	SFI (60-100 mL)	Danshen injection (20 mL) + Energy admixture (ATP, Coenzyme A, Vitamin C, Vitamin B6, KCl, etc.)	7 d	①
Chen Xiexing[57]	2001	63	62	55	25	77	48	45 ± 20.1	46 ± 23.1	SFI (50 mL) + Basic treatment	Polarized solution (Insulin 4 IU + 10% KCl 5 mL + 10% Glucose 250 mL) + Basic treatment	14 d	①②③④
Liu Guohua[58]	2001	32	30	29	22	42	20	46 ± 3.7		SFI (50 mL) + Isoproterenol + Atuopin	Isoproterenol (1-2mg) + Atuopin	Not described	①④
Liu Ming[59]	2001	43	30	39	19	46	27	56.7	57.3	SFI (100 mL) + Basic treatment	Xinbao pill + Basic treatment	10 d	①
Miao Yingnian[60]	2001	30	26	25	15	35	21	59.6	58.3	SFI (60 mL) + Basic treatment	Atuopin (0.3 mg po tid) + Basic treatment	6 wk	①④
Ji Gaorong[61]	2002	22	10	18	4	–	–	–	–	SFI (100 mL)	Atuopin (1 mg)	2 wk	①②④
Fang Juzheng[62]	2003	35	35	31	29	54	16	20–73		SFI (40 mL) + Polarized solution	654–2 injections (40 mg) + Polarized solution	20 d	①③
Huang Shien[63]	2003	30	28	25	16	29	29	66	67	SFI (50 mL)	Atuopin (0.6 mg po tid)	2 wk	①②
Zhu Hongming[64]	2004	35	32	31	24	41	26	56		SFI (50 mL) + Basic treatment	Compound Danshen injections (30 mL) + Basic treatment	15 d	
Huang Aijun[65]	2005	30	15	23	8	26	19	34–68		SFI (60 mL) + Xinbao pill + Basic treatment	Xinbao pill + Basic treatment	10 d	①③
DongBingqiang[66]	2006	23	22	20	12	28	17	48.6	47.9	SFI (80 mL) + Basic treatment	Basic treatment	14 d	①
Su Dayu[67]	2006	32	30	28	11	29	33	66.8	65.2	SFI (60 mL) + Vascular anticoagulant	Vascular anticoagulant	3–4 wk	①②
Xie Yangming[68]	2007	28	18	23	11	29	17	58 ± 31	56 ± 34	SFI (20 mL)	Atuopin (1 mg)	14 d	①②④
Lin Dechao[69]	2009	60	48	60	36	65	33	75.2	76.5	SFI (40 mL)	Polarized solution	15 d	①③
Liu Sumei[70]	2010	42	46	39	31	56	32	54.3 ± 11.5	56.8 ± 9.7	SFI (40 mL)	Anisodamine (20 mg)	14 d	①
Guan Jian[71]	2011	52	50	49	42	63	39	45.3 ± 10.2		SFI (30 mL) + Atuopin (0.5–1 mg) + Isoproterenol (0.5–1 mg)	Atuopin (0.5–1 mg) + Isoproterenol (0.5–1 mg)	7 d	①④
WangShenglin[72]	2011	30	30	28	20	33	27	73.31	74.11	SFI (60 mL) + Basic treatment	Atuopin (1 mg) + Basic treatment	14 d	
Li Aijie[73]	2012	47	45	43	34	56	36	45.6 ± 9.5	46.2 ± 10.2	SFI (80 mL) + Basic treatment	Atuopin (0.3 mg po tid) + Basic treatment	28 d	①
Shen Yuntao[74]	2012	26	21	22	18	27	20	39–78	33–81	SFI (60mL) + Basic treatment	Isoproterenol + Atuopin + Basic treatment	14 d	①
Tian Jun[75]	2012	40	40	37	30	51	29	69.1	68.4	SFI (60 mL) + Basic treatment	Atuopin (1 mg) + Basic treatment	14 d	①
Wu Yueping[76]	2012	40	40	34	20	–	–	55.8 ± 8.7	56.2 ± 10.1	SFI (40 mL) + Vascular anticoagulant	Vascular anticoagulant	15 d	①
Zhao Lizhi[77]	2012	40	40	37	28	39	41	52 ± 18		SFI (50 mL) + Basic treatment	Basic treatment	14 d	①③④
Han Lili[78]	2014	23	22	19	13	26	19	71.3	73.7	SFI	Polarized solution (Insulin 6 IU + 10% KCl 5 mL + 10% Glucose 250 mL)	14 d	①③
Lin Huichuan[79]	2019	60	60	59	49	77	43	54.3 ± 9.1	55.9 ± 9.3	SFI (80 mL) + Atuopin (0.3 mg po tid) + Basic treatment	Atuopin (0.3 mg po tid) + Basic treatment	7 d	②
Wu Yuankui[80]	2015	42	42	37	23	43	41	35–72		SFI (50 mL) + Vascular anticoagulant	Vascular anticoagulant	45 d	①
Liu Feng[81]	2015	26	26	23	16	29	23	58.6 ± 6	56.4 ± 5.6	SFI (40–60 mL)	Atuopin (1mg)	10–14 d	①
Guan Shuying[82]	2017	48	48	46	36	41	55	61.3 ± 1.2	62.4 ± 2.5	SFI (40 mL) + Wenxin granules (9 mg po tid)	Wenxin granules (9 mg po tid)	28 d	②

①Total response rate of clinical symptoms; ②Mean heart rate change; ③electrocardiogram; ④others.

C = control group, F = Female, I = intervention group, M = Male, po = peros, SFI = shenfu Injection, tid = three times a day.

analysis. Please refer to Figure 1 for the comprehensive depiction of this process, as outlined in the PRISMA diagram.

3.2. Characteristics of included studies

The analysis included a total of 28 studies, comprising 2143 cases in both the test and control groups. Among these, there were 1122 cases in the test group and 1021 cases in the control group. For more specific information regarding the characteristics of these studies, please refer to Table 1.

3.3. Assessment of methodological quality

All the included studies in this analysis reported on the randomization of patients. However, only four articles provided information on the methods used for random sequence generation.[68,72,73,75] In one study,[62] drug solutions were filled and wrapped by specialized nurses to ensure blinding. The 28 studies included in the analysis provided complete-case data, and there were no inconsistencies found in the methodology and results sections of each study. However, due to ambiguities present in some of the included studies, their overall quality remains unclear. Among these studies, 19 were graded as B (unclear risk) and 9 as grade C (high risk) according to the Cochrane grading system for quality evaluation. A summary of the Cochrane bias risk assessment results can be found in Figure 2. Additionally, the percentages for each risk of bias are displayed in Figure S1, Supplemental Digital Content, https://links.lww.com/MD/O785.

3.4. Evaluation of outcome indicators

3.4.1. Total response to treatment. All studies included in the analysis reported the overall response rate for the improvement of clinical symptoms. The results of the meta-analysis, as shown in Figure 3, were obtained using a random effects model due to the high heterogeneity observed across the studies ($P < .00001$, $I^2 = 70\%$). The findings revealed that the total response rate in the test group was significantly higher than that in the control group (RR = 1.34, 95% CI: 1.23–1.46, $P < .00001$). This indicates that SFI has a positive effect on improving the overall response rate for the clinical treatment of bradyarrhythmia.

Through the sensitivity analysis, we conducted a step-by-step removal of the literature and analyzed the sources of heterogeneity. Upon excluding the studies by Chen et al,[57] Lu et al,[56] and Liu et al,[55] the heterogeneity was significantly reduced with $P = .07$ and $I^2 = 31\%$. This suggests that these three studies may be the main sources of heterogeneity within the meta-analysis. After removing these three studies, a combined analysis showed no change in direction (RR = 1.29, 95% CI: 1.22–1.37, $P < .00001$), indicating stable results even without their inclusion. It is worth noting that these three studies could potentially contribute to heterogeneity due to various reasons: the study by Liu et al involved intraoperative instantaneous administration as a medication method,[55] which differed from other included studies. In Chen's study, the control group's interventions only consisted of polarizing fluid, leading to significant differences in treatment effects compared to other groups.[57]

Due to the presence of certain biases in this study, such as the lack of randomization and blinding, subgroup analyses were further conducted based on the risk of bias from randomization, allocation concealment, and blinding. As shown in Figures S2–S4, Supplemental Digital Content, https://links.lww.com/MD/O786, significant differences were observed only between different subgroups in relation to allocation concealment (i.e., subgroup A without allocation concealment, subgroup B with allocation concealment, and subgroup C with unclear allocation concealment), with a P value of .003 and high heterogeneity among subgroups ($I^2 = 82.4\%$). Additionally, a subgroup analysis was conducted based on the type of intervention in the experimental groups (SFI alone, SFI combined with one additional treatment, and SFI combined with two additional treatments). As shown in Figure S5, Supplemental Digital Content, https://links.lww.com/MD/O787, although the P value for subgroup differences did not reach statistical significance, the high I^2 value (64.1%) indicates that the intervention type (i.e., whether SFI is combined with other treatments) may contribute to heterogeneity.

3.5. Publication bias

In Figure S6, Supplemental Digital Content, https://links.lww.com/MD/O788, the funnel plot shows an asymmetric distribution of studies, indicating a high risk of publication bias. This potential bias is further supported by both Egger's ($t = 4.32$, $P = .0003$) and Begg's tests ($z = 3.13$, $P = .0018$). However, after adjustment with the trim-and-fill method (RR = 1.23, 95% CI: 1.17–1.29, $P < .0001$), the association between the exposure factor and the outcome remained significant, suggesting that although bias may be present, it is unlikely to fully account for this association.

3.6. Mean heart rate after medication

A total of 7 studies provided data on changes in mean heart rate over 24 hours.[57,61,63,67,68,79,82] However, the study by Su et al was excluded from the analysis as it only reported mean heart rate data for the test group.[67] Before treatment initiation, there were no significant differences in mean heart rate (<60 beats per minute) between the test and control groups. Following treatment administration, both the test and control groups showed improvements in mean heart rate compared to baseline measurements. Moreover, the test group exhibited greater improvement in mean heart rate compared to the control group (MD = 7.48; 95% CI: 2.99–11.97; $P = .001$), as shown in Figure S7, Supplemental Digital Content, https://links.lww.com/MD/O789 However, the meta-analysis revealed high heterogeneity among these studies ($P < .00001$, $I^2 = 92\%$). Sensitivity analysis demonstrated that excluding Chen's study[57] resulted in a significant decrease in heterogeneity ($P = .46$, $I^2 = 0\%$), but did not change the overall direction of results (MD = 5.17; 95% CI: 3.77–6.58, $P < .00001$). The observed difference could be attributed to variations in interventions across studies. It is crucial to acknowledge that, in addition to differences in interventions, there might be other potential sources of heterogeneity impacting the outcomes observed within this analysis.

3.7. Efficacy as compared with atropine

A total of four studies included in this analysis utilized the SFI group and the atropine group for comparison.[61,63,68,81] These studies exhibited low inter-study heterogeneity ($P = .82$, $I^2 = 0\%$). Using a fixed-effect model, the meta-analysis (Figure S8, Supplemental Digital Content, https://links.lww.com/MD/O790) demonstrated that the overall efficacy of SFI for bradyarrhythmia was significantly better compared to atropine (RR = 1.48, 95% CI: 1.21–1.83, $P = .0002$).

3.8. Adverse reactions and safety evaluation

A total of 10 studies reported the adverse events in their respective interventions.[56,58,59,62,63,72–75,82] Out of these studies, a total of 19 cases were reported in the test group and 113 cases were reported in the control group. However, it is important to note that the remaining 18 studies did not provide information on adverse effects. Based on these results (Figure S9, Supplemental Digital Content, https://links.lww.com/MD/O791), it appears

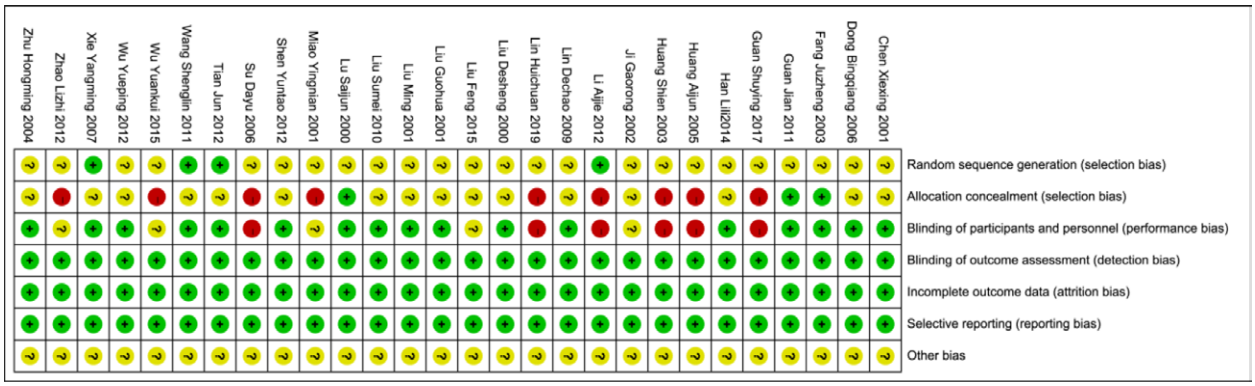

Figure 2. A summary of risk of bias. +, Low risk; ?, Unclear risk; -, High risk.

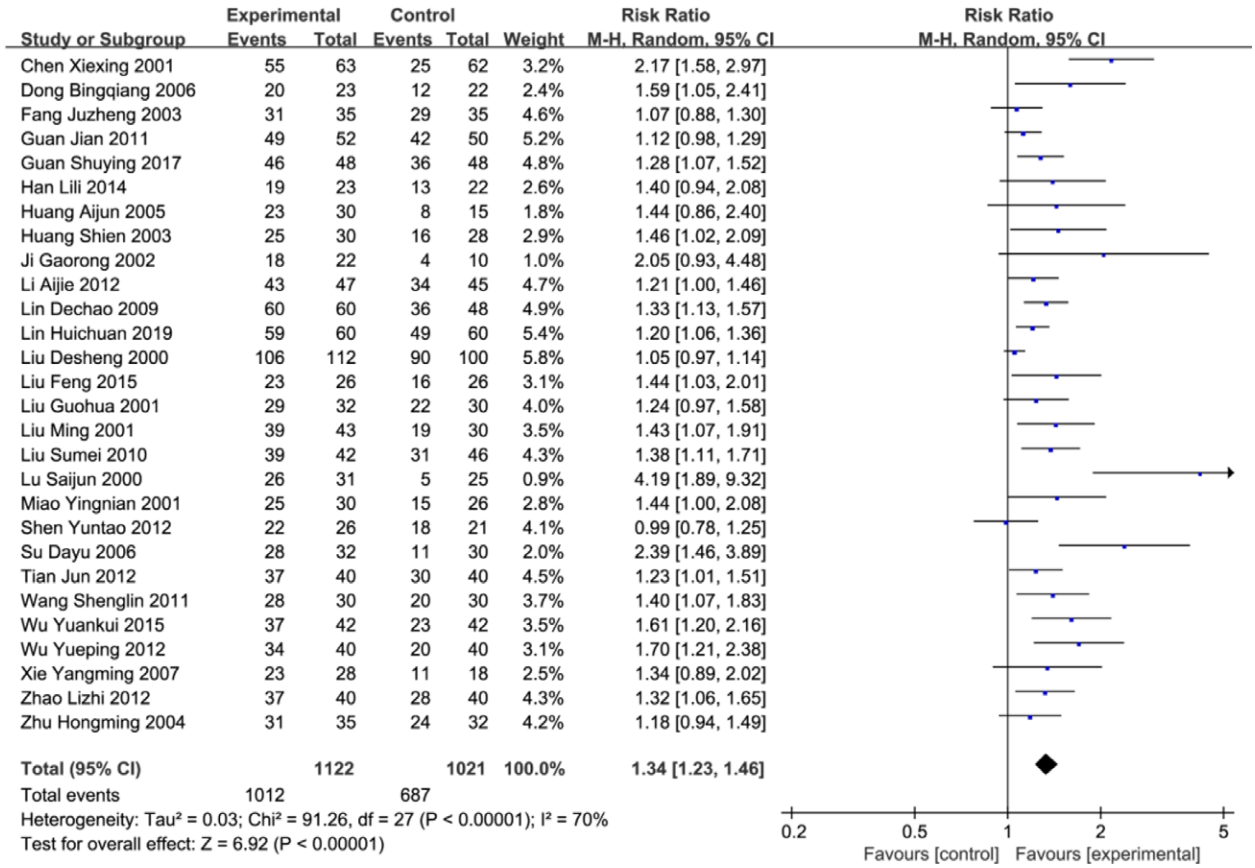

Figure 3. Forest plot of total efficacy. CI = confidence intervals, M-H = Mantel-Haenszel.

that the SFI may have a higher safety profile for treating bradycardia. However, caution must be exercised when interpreting these findings due to the significant heterogeneity observed among the included studies ($P = .002$, $I^2 = 65\%$). Upon conducting sensitivity analysis by eliminating each study one by one, it was found that the exclusion of Guan's study[82] resulted in reduced heterogeneity ($P = .05$, $I^2 = 49\%$). This study may contribute to increased heterogeneity, potentially due to its longer duration (28 days) and intervention programs involving Chinese patent medicines for both experimental and control groups.

4. Discussion

The systematic evaluation and meta-analysis of 28 RCTs yields robust evidence supporting the efficacy of SFI for treating bradyarrhythmia. The results indicate that SFI outperforms conventional treatment in terms of both overall response rate and heart rate improvement. Notably, the analysis also reveals a lower incidence of adverse events associated with SFI compared to conventional therapy alone.

4.1. The effect of SFI in treating bradyarrhythmia

This study's findings indicate that SFI effectively improves the overall clinical efficacy rate in treating bradyarrhythmia and increases the average heart rate after administration, demonstrating superior clinical efficacy. Additionally, SFI improves factors such as mean heart rate, sinus node function[68] and NT-proBNP levels[77] consistent with prior clinical studies.[33] SFI's use in cardiovascular diseases, including bradyarrhythmia, has thus

gained widespread acceptance.[83–96] Bradyarrhythmia is characterized by dysfunction in the sinus node, AV node, atrial tissue, and specialized conduction systems.[97–100] Components of SFI, such as ginsenosides, have been shown to significantly improve cardiac function, while aconitine enhances AV node excitability and AV conduction[101] and supports pacing in the sinus node.[30] The effectiveness of TCM is derived not only from the individual contributions of its components but also from the synergistic interactions among various active compounds.[102–104] For example, systemic pharmacological studies have demonstrated the synergistic effects of combining *Panax ginseng C.A.Mey* and *Aconiti Lateralis Preparata* in treating sick sinus syndrome. This combination influences neuroactive ligand-receptor interactions and key cellular signaling pathways, including cAMP, calcium, and PI3K-Akt.[105] Animal studies on guinea pig ventricular myocytes also indicate that SFI has antiarrhythmic effects, selectively blocking cardiomyocyte sodium channels.[106] These findings suggest SFI's therapeutic efficacy in bradyarrhythmia may be due to its regulatory influence on ion signaling pathways and enhancement of signal transduction processes. Nonetheless, further research, including rigorously designed RCTs, is required to confirm SFI's efficacy and safety in bradyarrhythmia treatment.

4.2. The safety of SFI in treating bradyarrhythmia

A total of 10 studies reported adverse events.[56,58,59,62,63,72–75,82] In the SFI treatment group, common adverse reactions included facial flushing, dry mouth, sweating, and mild nausea, with no serious adverse events recorded. In contrast, the control group experienced side effects more frequently associated with cholinergic receptor blockade, such as dry mouth, palpitations/tachycardia/arrhythmia, skin flushing, hot flashes, and urinary retention. Our findings suggest that combination therapy with SFI for bradyarrhythmia may present a lower risk profile compared to traditional medication alone. However, in studies where SFI was used in conjunction with other medications, identifying the precise source of observed adverse reactions is challenging. Moreover, none of the reported adverse events provided a clear process for causal determination. Thus, while SFI appears promising, further high-quality studies with rigorous designs are needed to validate its safety profile in managing bradyarrhythmia.

4.3. Advantages and limitations

This study represents the largest systematic review and meta-analysis conducted thus far to summarize and evaluate the efficacy and safety of SFI in patients with bradyarrhythmia. The researchers followed the high standards set by the PRISMA methodology, which ensures transparency, minimizes bias, and facilitates a rigorous assessment of the available evidence pertaining to SFI treatment for bradyarrhythmia.

Our study has several limitations. Firstly, only a small proportion (14.3%) of the included studies correctly implemented random sequence generation, and just one study used single-blind methodology. Secondly, only 10.7% of studies adequately addressed the allocation concealment issue, while 32.1% of studies may have introduced selection bias, as participants could predict their allocation based on the drug formulation. These limitations resulted in a low overall quality rating for the included studies, which significantly limits the generalizability of the conclusions drawn from this research. Thirdly, inconsistencies in treatment duration and age distribution among control groups likely affected comparability, and many studies lacked essential information, such as consistent diagnostic criteria or intervention details (e.g., manufacturer and batch numbers). Future research should address these issues by rigorously implementing randomization, allocation concealment, and blinding, and by increasing sample sizes. Fourthly, missing data were not consistently handled across studies, which may have introduced bias in certain outcomes. Fifthly, the efficacy indicators in this study lack objectivity, with symptom improvement categorized as markedly effective, effective, or ineffective. This subjective grading system, lacking standardized criteria, may introduce bias and compromise the study's credibility. Future research should prioritize the use of more objective and standardized indicators. Sixthly, the incomplete reporting of adverse events in the included studies hampers the ability to draw definitive conclusions about the safety profile of SFI.

5. Conclusion

Combining SFI with conventional therapy seems to be a potentially safer approach for improving the total effective rate in patients with bradyarrhythmia. However, given the limitations identified in the included studies, more robust research is needed to strengthen these conclusions. High-quality RCTs will provide additional confirmation regarding the effectiveness and safety of SFI treatment for bradyarrhythmia.

Author contributions

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