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Paper Accepted*

ISSN Online 2406-0895

Original Article / Оригинални рад

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Efficacy of combined use of *Tetradium ruticarpum* (A. Juss.) patch and Chinese massage (Tuina) for the treatment of insomnia in elderly chronic heart failure patients

Ефикасност комбиноване употребе фластера *Tetradium ruticarpum* (*A. Juss.*) и кинеске масаже (туина) за лечење несанице код старијих болесника са хроничном срчаном инсуфицијенцијом

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Received: January 3, 2024
Revised: August 22, 2024
Accepted: August 25, 2024
Online First: August 29, 2024
DOI: https://doi.org/10.2298/SARH240103068L

*__Accepted papers__ are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.

Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.

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SUMMARY

Introduction/Objective The objective of the paper was to evaluate the efficacy of *Tetradium ruticarpum* (A. Juss.) patch (TRP) in combination with Chinese massage (Tuina) for the treatment of insomnia in elderly patients with chronic heart failure (CHF).

Methods A cohort of 320 elderly CHF patients with comorbid insomnia, treated at the Zhejiang University of Traditional Chinese Medicine Affiliated Wenzhou Hospital from January 2019 to July 2022, were enrolled and equally divided into 4 groups (n = 80 per group). The control group received standard pharmacological intervention with eszopiclone. Patients in TRP group received TRP alone, while those in Tuina group received Tuina therapy alone. Patients in the combined treatment group received both TRP and tuina therapy. All treatments lasted for 14 days. Sleep quality was assessed at baseline and then on days 7 and 14 after treatment using the Pittsburgh Sleep Quality Index Scale (PSQI).

Results There were significant reductions in total PSQI scores in all groups on day 7 compared to baseline ($p < 0.05$). On day 14, the combined treatment, Tuina, and TRP groups showed significantly reduced total PSQI scores relative to baseline, while a reversal of this trend was seen in the control group ($p < 0.05$). The combined treatment group had the lowest total PSQI scores at both days 7 and 14.

Conclusion The combined use of Tuina and TRP may be effective in alleviating insomnia in elderly CHF patients. It resulted in consistent and sustained efficacy, potentially reducing the likelihood of drug resistance.

Keywords: Chinese massage (Tuina); *Tetradium ruticarpum* (A. Juss.) patch; chronic heart failure; insomnia

САЖЕТАК

Увод/Циљ Циљ рада била је процена ефикасности фластера *Tetradium ruticarpum (A. Juss.)* (ТРП) када се користи у комбинацији са кинеском масажом (туина) за лечење несанице код старијих болесника са хроничном срчаном инсуфицијенцијом (ХСИ).

Методе Кохорта од 320 старијих болесника са ХСИ са коморбидном несаницом који су били на лечењу у болници Венцоу, придруженој болници Универзитета Цеђанг у оквиру Универзитета традиционалне кинеске медицине (ТКМ) од јануара 2019. до јула 2022. године, била је уписана и додељена једнако у четири групе (n = 80 у свакој од четири групе). Контролна група је примила стандардну фармаколошку интервенцију са есзопиклоном. Болесници у ТРП групи су примали само ТРП, док су они у групи туина примали само терапију туина. Болесницима у групи комбинованог третмана дате су и ТРП и туина терапије. Сви третмани су трајали 14 дана. Квалитет спавања је процењен на почетку, а затим седмог и 14. дана након третмана коришћењем Питсбуршке скале индекса квалитета сна (ПСКС).

Резултати: Било је значајног смањења укупних ПСКС резултата у свим групама 7. дана, у односу на почетну линију ($p < 0,05$). Дана 14, комбиновани третман, туина и ТРП групе су показале значајно смањене укупне ПСКС резултате, у односу на почетне вредности, док је преокрет овог тренда примећен у контролној групи ($p < 0,05$). Група комбинованог третмана је имала најниже укупне ПСКС резултате и седмог и 14. дана. **Закључак** Комбинована употреба туина и ТРП-а може бити ефикасна у ублажавању несанице код старијих пацијената са ХСИ. То је резултирало доследном и трајном ефикасношћу, чиме је потенцијално смањена вероватноћа резистенције на лекове.

Кључне речи: кинеска масажа (туина); фластер *Tetradium ruticarpum (A. Juss.)*; хронична срчана инсуфицијенција; несаница

INTRODUCTION

The prevalence of chronic heart failure (CHF) among the elderly population in China exceeds 4 million [1]. The combination of advanced age and CHF precipitates a marked decline in sleep quality [2]. CHF contributes to sleep disturbances through symptoms such as chest tightness

and breathlessness which interfere with the ability to lie down comfortably, leading to nocturnal discomfort and sedentary breathing [3]. Additionally, the reduced mobility associated with CHF exacerbates psychological distress which often manifests as anxiety and depression, leading to further deterioration in sleep quality [4]. During the protracted course of CHD, these physiological and psychological factors become compounded, thereby exacerbating insomnia and significantly decreasing the quality of life of the patient. Notwithstanding its negative impact, insomnia often receives less attention than the primary cardiac condition. This has resulted in paucity of diverse and effective therapeutic options for management of insomnia.

Traditional Chinese Medicine (TCM) emphasizes holistic regulation of bodily functions and seeks to re-establish equilibrium within the internal environment. This systemic approach offers potential benefits for managing insomnia, particularly in the elderly population. Recent empirical studies have highlighted the efficacy of Tuina in combination with other treatments in improving sleep quality, alleviating depressive symptoms, reducing TCM symptom scores, and enhancing overall quality of life in patients with insomnia [5, 6]. Furthermore, evidence suggests that TRP, a traditional *warm-natured* TCM modality, may be applied to *Yongquan* acupoints in the treatment of insomnia in the elderly, and it results in markedly fewer side effects than Western medications [7, 8]. However, there is a discernible gap in clinical research regarding the effectiveness of combined application of Tuina and TRP in the treatment of insomnia in elderly CHF patients.

Therefore, the current study was aimed at investigating the clinical efficacy of an integrated intervention with Tuina and TRP in a cohort of elderly CHF patients afflicted with insomnia, with eszopiclone as a pharmacological benchmark. The study was an attempt to carry out a comprehensive evaluation of the therapeutic impact of TCM modalities on sleep disturbances in elderly CHF patients with insomnia.

METHODS

Clinical participants and ethics

This study enrolled 320 CHD patients with concomitant insomnia who were seen at the Zhejiang University of TCM Affiliated Wenzhou Hospital between January 1, 2019 and July 13, 2022. All subjects provided informed consent and agreed to participate in the study after

being informed of its nature, potential risks, and benefits. This study was approved by the Medical Ethics Committee of our hospital (approval number: WZY-2-23-KT-022-01). A strict selection process was designed to ensure the homogeneity of the study population in order to accurately assess the effects of the proposed TCM intervention on sleep quality in elderly CHD patients.

Inclusion criteria

All participants were confirmed to have CHD as per the criteria set out in the 2018 edition of Chinese Guidelines for the Diagnosis and Treatment of Heart Failure, as published by the Cardiovascular Disease Branch of the Chinese Medical Association [9]. Insomnia diagnosis was established in accordance with the parameters stipulated in the 2017 edition of the Chinese Guidelines for the Diagnosis and Treatment of Insomnia in Adults, as authorized by the Neurology Section of the Chinese Medical Association [10]. Eligible participants were those who exhibited a New York Heart Association (NYHA) functional classification of I-III, thereby indicating acceptable cardiac function.

Exclusion criteria

All patients with cardiac function class IV were excluded from this study. Moreover, patients with a history of malignancy, psychiatric disorders, and poorly-controlled common chronic diseases (e.g., type 2 diabetes mellitus, hypertension, etc.), were excluded from the study.

Grouping and treatment

Grouping

A cohort of 320 patients diagnosed with CHD and comorbid insomnia was assigned to 4 groups: combined treatment group, Tuina group, TRP group, and control group, with 80 subjects in each group.

Treatments

Patients in the control group received pharmacological intervention for insomnia in the form of estazolam (License: H11020891). The administration protocol involved an oral dose of 1 mg of eszopiclone given at bedtime. In the TRP group, a traditional acupoint application method was utilized to address insomnia symptoms. Specifically, 9 g of TRP was finely ground with an adequate volume of white vinegar to produce a paste which was uniformly spread out on oil paper to a thickness of approximately 1 cm. This preparation was applied bilaterally to the *Yongquan* acupoints at 20:00 h, and it was allowed to remain in place for a duration of 12 h each night. The Tuina group underwent therapeutic Chinese massage which was carried out daily for 20 min.

The acupoints and meridian areas for Chinese massage (Tuina) were: (a) the temples, along with the *Feng chi* and sleeping acupoints; (b) the area along the arch of the eyebrow from the *yin-tang* to the temples; (c) the area along the sides of the nose from the *yin-tang* down through the *yangbai* acupoints and back to the temples; (d) the area from the *yin-tang* to the *bai-hui* acupoints on the scalp, and (e) the areas around the eyes, forehead and cheeks, and the sides of the ears in the hairline zone. The other acupoints used were the abdominal *Zhong wan, Oihai* and *Guan yuan* acupoints, as well as the bladder meridian, the governing vessel, and the heart *shu*, liver *shu*, gallbladder *shu*, spleen *shu*, stomach *shu*, and kidney *shu* acupoints.

The combined treatment group received a synergistic intervention comprising the TRP acupoint application and Tuina as detailed above. The intervention period for all groups was set at 14 days. The study meticulously outlined the treatment modalities to ensure a standardized approach across all participants, in order to allow for reliability in the evaluation of the efficacy of the TCM interventions for insomnia in patients with CHD.

Data collection and follow-up

Cardiac function

Pre-developed questionnaires were applied for collection of clinical data from medical records. The data comprised gender, age, height, weight, history of chronic diseases, and cardiac function indicators. The height and weight of each of the subjects were used to calculate the body mass index (BMI) by dividing body weight (in kg) with the square of height in meters (m^2).

The histories of previous chronic diseases such as hyperlipidemia, myocardial infarction, cardiac arrhythmia, type 2 diabetes mellitus (DM), primary hypertension and stroke, were determined based on the diagnostic certificates in medical records and the history of previous medications and treatments taken. If these could not be determined, the patient's primary healthcare physician was consulted for clarification. Cardiac function was assessed using NYHA classification, six-minute walk distance test (6MWD), left ventricular ejection fraction (LVEF) measured using cardiac ultrasound, and calculated metabolic equivalents (MET) [11, 12].

Sleep quality

Sleep quality was quantitatively assessed at baseline, on 7th day, and at the culmination of the 14-day treatment period, using the PSQI. This self-administered assessment measures seven components of sleep: latency, use of sleep medication, sleep quality, efficiency, disturbances, duration, and daytime dysfunction. Each component was scored on a scale in which scores ranged from 0 (no sleep difficulty) to 3 (severe sleep difficulty), yielding a composite score between 0 and 21. The higher the score, the poorer the sleep quality [13].

Statistical analysis

All analyses were performed using the SPSS software version 23.0. Continuous variables consistent with normal distribution are presented as mean ± standard deviation (SD). Inter-group comparisons for the variables across the 4 groups were conducted using ANOVA, with post-hoc pairwise comparisons performed via the Least Significant Difference (LSD) method. Categorical variables are depicted as frequencies, and were compared amongst groups using the chi-square test; inter-group differences were assessed by comparing the categories with the highest and lowest frequencies. The χ^2test yielded values and p values. Multifactorial logistic regression was employed for determination of the association between the treatment regimen and sleep improvement. This yielded odds ratios (ORs), 95% confidence intervals (CIs), and p-values. Statistical significance was inferred at $p < 0.05$.

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

RESULTS

Comparison of baseline characteristics amongst the four groups of patients

Results of comparison of baseline characteristics of patients amongst the four groups are presented in Table 1. There were no significant differences in gender, age, ethnic distribution, BMI levels, and the history of various chronic conditions such as hyperlipidemia (HTG), previous myocardial infarction (MI), arrhythmia, type 2 diabetes mellitus (DM), and essential hypertension, amongst the 4 groups ($p > 0.05$). However, the frequency of stroke history, a factor closely linked to insomnia, was significantly higher in the control group than in the TRP group ($p = 0.027$). No significant differences were observed in stroke history among the other groups ($p > 0.05$). This uneven distribution of stroke history may potentially influence the validity of the outcomes of this study.

Comparison of baseline cardiac function among the four groups of patients

As shown in Table 2, there were no significant differences in NYHA classification, 6MWD results, LVEF, and MET levels among the four groups. These findings indicate that cardiac function, a critical factor that affects sleep, was comparably distributed across the study groups, which shows that the results of this study are reliable. Furthermore, all subjects had adequate cardiac function which helps minimize risks when implementing sleep improvement interventions.

Comparison of PSQI scores among the four groups of patients

Table 3 shows that there were no significant differences in total PSQI scores and sub-scores in the seven dimensions among the four groups at baseline ($p > 0.05$). This indicates that the initial sleep conditions were similar across all groups, thereby enhancing the comparability of outcomes in subsequent studies on mitigation of insomnia using TCM.

On the 7th day of treatment, significant variations were observed in the total PSQI scale scores and sub-scores in the seven dimensions among the 4 groups, with the combined treatment group

having the lowest total score and sub-scores ($p < 0.05$). These results indicate differences in efficacies of the various treatment regimens, with the combined treatment group exhibiting the highest efficacy.

On the 14th day of treatment, the differences in total PSQI scale scores and sub-scores in the seven PSQI dimensions amongst the groups were further amplified ($p < 0.05$). The combined treatment group maintained the lowest total score and sub-scores, while the score of the control group rebounded to baseline levels, with total score and sub-scores being the highest amongst the 4 groups ($p < 0.05$). These findings suggest that the efficacy of treatment was least in the control group on the 14th day of treatment.

Comparison of PSQI total scores at the three time points among the four groups

There were distinct changes in total scores on the PSQI for each study group during the treatment course. All the four groups had significantly lower PSQI total scores on the seventh day of treatment, when compared to baseline, indicating the effectiveness of the various therapies administered ($p < 0.05$). However, on the 14th day of treatment, the total PSQI score of the control group was significantly rebounded to the baseline level. In contrast, the total PSQI scores for the combined therapy group, the Chinese massage (Tuina) group, and the TRP group were significantly reduced on day 14, relative to the respective baseline levels ($p < 0.05$). These findings suggest that therapeutic efficacy in control group was significantly attenuated on day 14, while the other three groups sustained their levels of efficacy. As shown in Table 4.

Multifactorial logistic analysis of the total PSQI scores of the four groups after treatment

As depicted in Table 5, after adjusting for gender, age, ethnicity, body mass index, history of previous diseases, and cardiac function indices, multifactorial analysis revealed that the combined treatment group had significantly lower total PSQI scores than the control group on day 7 of treatment ($p < 0.05$). In contrast, the Tuina and TRP groups did not exhibit statistically significant differences in total PSQI scores, when compared to control group ($p > 0.05$). These findings suggest that the combined treatment group outperformed, while the Tuina and TRP groups showed comparable efficacy to the control group. Furthermore, multifactorial analysis indicated that on day 14 of treatment, the PSQI total scores were significantly lower in the

combination therapy group, the Tuina group, and the TRP group than in the control group ($p < 0.05$). These findings, in addition to the preceding results, suggest that sleep improvement efficacy remained satisfactory in the combined treatment group, the Tuina group, and the TRP group at day 14. In contrast, therapeutic efficacy was markedly decreased in control group.

Side effects of the four groups after treatment

During the treatment period of all subjects, only 1 patient in the TRP group developed a mild rash, while 2 patients in the control group were accompanied by drowsiness and 1 patient developed dizziness. Patients in the combination therapy group and Tuina group did not experience any adverse effects.

DISCUSSION

CHF a prevalent disease in the elderly population, is a common cardiac insufficiency condition due to several factors such as coronary artery disease, arrhythmia, and heart valve disease [3]. Although insomnia is not a symptom of CHF, it may be a resultant condition which further exacerbates the physiological and psychological states of CHF patients. This negative impact on CHF treatment and quality of life of patients underscores the need for effective treatment for insomnia. Modern medications such as eszopiclone and zolpidem offer reliable sedative effects. However, these drugs are associated with risks such as respiratory depression, particularly in CHF patients, in addition to the likelihood of increased drug resistance after long-term use [14]. In contrast, TCM offers benefits in the treatment of insomnia due to its unique properties [15].

The present study has demonstrated that the combined use of Chinese massage (Tuina) and TCM-based relaxation practices (TRP) significantly mitigated insomnia, when compared to eszopiclone. Furthermore, with extended regular use, Tuina and TRP, individually and in combination, maintained their effectiveness, unlike eszopiclone which showed waning response over time. These findings are consistent with published data [5–8], an indication of the potential benefits of TCM in the management of insomnia in CHF patients.

Advancements in contemporary medicine have resulted in the extraction of evodiamine, the bioactive constituent of TRP. Subsequent research revealed its diverse biological potential: it was shown to effectively mitigate inflammation, malignant tumors, metabolic disorders, and cognitive impairments, and some preliminary data on the underlying molecular mechanisms are also available [16, 17, 18]. However, the specific mechanism behind anti-insomnia effect of TRP was unknown, thereby highlighting an area of focus in future basic medical investigations. It has been reported that dehydroevodiamine (DHE) and hortiamine, extracts from TRP, are able to potentially inhibit potassium channels in the myocardium in cellular and animal experiments, resulting in altered excitatory processes in the myocardium, which induces severe arrhythmias including tip-twisting ventricular tachycardia and ventricular fibrillation [19]. In contrast, another study showed that Rutaecarpine(another TRP extract) is A promising cardiovascular protective alkaloid [20].In present study, only 1 patient was found to have a mild rash with the application of TRP and no patients with arrhythmia or blood pressure abnormalities were seen. The appearance of the rash may be related to the topical application of TRP, which also resulted in a very low intake of DHE and hortiamine, which avoided cardiac arrhythmia. The safety of the topical application of TRP has also been supported by another clinical study [21].

Chinese massage (Tuina), an integral part of external treatments in TCM, employs a plethora of techniques on various human acupoints to facilitate meridian flow and enhance internal organ functions, thereby aiding the treatment of diseases [22]. Tuina exhibits a broader spectrum of application, when compared to TR, which accounts for its benefits in diverse conditions affecting the motor, respiratory, neurological, digestive, and urinary systems [23]. This study not only confirmed the therapeutic effect of Tuina in insomnia, but also underscored the enhanced efficacy of combining Tuina with TRP in the management of insomnia. Furthermore, the research team exploited the application of Tuina and TRP to abdominal acupuncture points and meridians associated with gastrointestinal function post-surgery [24, 25]. Thus, these findings may potentially expand the clinical application of combined therapy involving Tuina and TRP.

Limitations of the study

A major limitation of this study is its small sample size, primarily due to limitations such as lack of funding. A small sample size can potentially affect the statistical reliability as well as

the robustness of the conclusions, but these findings provide a valuable basis for further, more extensive studies. Therefore, it is recommended that future studies use larger sample sizes and long-term follow-up to validate these findings.

CONCLUSION

The combination of Tuina and TRP holds promise as an effective therapeutic approach for alleviating insomnia in elderly CHF patients. This TCM technique exhibited sustained efficacy, and it potentially reduced the onset of drug resistance. A broader application of this TCM regimen in the CHF patient population may substantially enhance sleep quality, mental health, immune function, and overall quality of life, thereby boosting the confidence of patients in overcoming the disease.

Conflict of interest: None declared.

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Table 1. Comparison of baseline characteristics of the four groups of patients*

Group	**n**	**Male (n)**	**Age (years)**	**Han nationality (n)**	**BMI (kg/m^2)**	**Hyperlipidemia (n)**
Combination therapy	80	49	68.1 ± 6.1	73	21.5 ± 1.8	33
Tuina	80	41	67.3 ± 6.0	76	21.2 ± 1.9	30
TRP	80	43	68.1 ± 5.7	70	21.1 ± 1.9	37
Control	80	48	68.4 ± 5.5	76	20.9 ± 1.8	29
F/χ^2		1.625	0.554	2.818	1.640	1.651
p		0.202	0.646	0.093	0.180	0.199
Group	n	MI (n)	Arrhythmias (n)	Type 2 DM (n)	Hypertension (n)	Stroke (n)
Combination therapy	80	41	12	27	33	9
Tuina	80	43	16	30	37	12
TRP	80	37	10	21	33	7
Control	80	46	17	29	41	17
F/χ^2		2.028	2.183	2.331	1.609	4.902
p		0.154	0.140	0.127	0.205	0.027

TRP – *Tetradium ruticarpum* (A. Juss.) patch; DM – diabetes mellitus; BMI – body mass index;

*normally-distributed continuous variables are expressed as mean ± standard deviation, and differences amongst the groups were determined with ANOVA; categorical variables are expressed as frequencies, and differences between the groups were determined using χ^2 test (i.e., comparison of the group with the highest frequency and the group with the lowest frequency)

Table 2. Comparison of baseline cardiac function among patients in four groups

Group	n	NYHA I–II stage (n)	6MWD (m)	LVEF (%)	MET
Combination therapy	80	62	321.7 ± 30.6	43.5 ± 3.1	2.6 ± 0.4
Tuina	80	66	318.0 ± 29.5	44.5 ± 3.2	2.5 ± 0.3
TRP	80	60	326.8 ± 29.1	43.9 ± 3	2.7 ± 0.4
Control	80	71	323.3 ± 27.5	43.8 ± 3	2.7 ± 0.3
F/χ^2		0.181	1.266	1.485	2.226
p		0.671	0.286	0.219	0.085

TRP – *Tetradium ruticarpum* (A. Juss.) patch; NYHA – New York Heart Association; 6MWD – six-minute walk distance test; LVEF – left ventricular ejection fraction; MET – metabolic equivalents

Table 3. Comparison of Pittsburgh Sleep Quality Index Scale subscales for patients in four groups*

Group	Sleep time	Drugs	Sleep quality	Sleep efficiency	Sleep disorders	Sleep duration	Daytime dysfunction	Total score
Baseline								
Combination therapy	1.9 ± 0.8	2.0 ± 0.7	2.1 ± 0.1	2.2 ± 0.3	1.7 ± 0.1	2.1 ± 0.9	2.1 ± 0.8	14.1± 2
Tuina	2 ± 0.7	1.9 ± 0.5	2 ± 0.7	2.1 ± 0.7	2 ± 0.6	2 ± 0.8	2.2 ± 0.7	14.1± 2
TRP	2.1 ± 0.1	2.2 ± 0.2	2.2 ± 0.8	2 ± 0.6	1.8 ± 0.3	2.1 ± 0.1	2 ± 0.6	14.3± 1.7
Control	1.9 ± 0.6	2 ± 0.7	2 ± 0.6	2.2 ± 0.6	1.8 ± 0.7	2.0 ± 0.3	2 ± 0.8	13.9± 1.8
F	1.130	1.885	2.192	1.913	2.278	0.837	1.658	0.564
p	0.337	0.132	0.089	0.127	0.080	0.474	0.176	0.639
Day 7 of treatment								
Combination therapy	0.6 ± 0.5	0.7 ± 0.5	0.6 ± 0.5	0.7 ± 0.6	0.6 ± 0.5	0.7 ± 0.5	0.7 ± 0.5	4.5 ± 1.4
Tuina	0.9 ± 0.7	1 ± 0.7	1 ± 0.4	0.9 ± 0.7	0.9 ± 0.8	1 ± 0.8	0.9 ± 0.7	6.7 ± 1.9
TRP	1.2 ± 0.7	1.1 ± 0.7	1 ± 0.2	1.1 ± 0.3	1 ± 0.7	0.9 ± 0.7	1 ± 0.8	7.2 ± 2.2
Control	0.8 ± 0.6	1.1 ± 0.6	0.9 ± 0.7	0.9 ± 0.9	1 ± 0.8	1.1 ± 0.7	1 ± 0.7	6.9 ± 1.6
F	10.060	6.112	5.148	5.687	6.240	5.109	5.030	36.636
p	< 0.001	< 0.001	0.002	0.001	< 0.001	0.002	0.002	< 0.001
Day 14 of treatment								
Combination therapy	0.7 ± 0.5	0.6 ± 0.5	0.7 ± 0.6	0.7 ± 0.5	0.6 ± 0.6	0.6 ± 0.5	0.6 ± 0.5	4.5 ± 1.4
Tuina	1 ± 0.7	1 ± 0.5	0.9 ± 0.8	1 ± 0.5	1 ± 0.3	1 ± 0.6	1 ± 0.7	6.9 ± 1.8
TRP	1 ± 0.6	1.1 ± 0.8	1 ± 0.7	1.1 ± 0.7	1.1 ± 0.6	1 ± 0.7	1 ± 0.6	7.2 ± 1.6
Control	2 ± 0.4	2.1 ± 0.3	1.9 ± 0.8	2.1 ± 0.4	2.0 ± 0.5	1.9 ± 0.8	1.9 ± 0.7	13.9 ± 1.8
F	64.971	68.309	52.285	75.236	69.383	52.182	59.998	474.276
p	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001	< 0.001

TRP – *Tetradium ruticarpum* (A. Juss.) patch;

*normally-distributed continuous variables are expressed as mean ± standard deviation, and differences amongst groups were compared with ANOVA

Table 4. Comparison of Pittsburgh Sleep Quality Index Scale total scores for patients at the three time points*

Group	PSQI total scores				
	Baseline	**Day 7 of treatment**	**Day 14 of treatment**	**F**	**p**
Combination therapy	14.1 ± 2	4.5 ± 1.4 †	4.5 ± 1.4 †	935.070	< 0.001
Tuina	14.1 ± 2	6.7 ± 1.9 †	6.9 ± 1.8 †	399.757	< 0.001
TRP	14.3 ± 1.7	7.2 ± 2.2 †	7.2 ± 1.6 †	389.285	< 0.001
Control	13.9 ± 1.8	6.9 ± 1.6 †	13.9 ± 1.8	423.606	< 0.001

PSQI – Pittsburgh Sleep Quality Index Scale; TRP – *Tetradium ruticarpum* (A. Juss.) patch;

*normally-distributed continuous variables are expressed as mean ± standard deviation, and differences amongst groups were determined using ANOVA;

†$p < 0.05$ *vs*. baseline

Table 5. Multifactorial logistic analysis of the comparison of Pittsburgh Sleep Quality Index Scale total scores after treatment among patients in the four groups*

Group	B	SE	Wald $\chi 2$	p	OR	95% CI
Day 7 of treatment						
Combination therapy	-1.523	0.364	17.509	<0.001	0.218	0.107 - 0.445
Tuina	0.542	0.756	0.515	0.473	1.720	0.391 - 7.567
TRP	0.212	0.652	0.106	0.745	1.237	0.344 - 4.442
Control	—	—	—	—	—	—
Day 14 of treatment						
Combination therapy	-2.236	0.457	23.909	<0.001	0.107	0.044 - 0.262
Tuina	-4.233	0.791	28.656	<0.001	0.015	0.003 - 0.068
TRP	-5.306	1.121	22.411	<0.001	0.005	0.001 - 0.045
Control	—	—	—	—	—	—

TRP – *Tetradium ruticarpum* (A. Juss.) patch;

*multifactorial logistic regression was adjusted for sex, age, ethnicity, body mass index, past medical history, and cardiac function indicators

