PEER REVIEW HISTORY

ARTICLE DETAILS

Title (Provisional)

Effect of Acupuncture on Quality of Life in Atrial Fibrillation: study protocol for a randomized controlled trial

Authors

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VERSION 1 - REVIEW

Reviewer	**1**
Name	**Palamà, , Zefferino**
Affiliation	**Casa di Cura Villa Verde Srl, Cardiology**
Date	**15-May-2024**
COI	**none**

The paper is interesting, a distinction must be made on patients with paroxysmal AF.

How many of these had an organized trigger? How were they screened (clinic, electrophysiological study?)

If this has not been done it should be included in the limitations

You can read Russo V, Caturano A, Migliore F, Guerra F, Francia P, Nesti M, Conte G, Perini AP, Mascia G, Albani S, Marchese P, Santobuono VE, Dendramis G, Rossi A, Attena E, Ghidini AO, Sciarra L, Palamà Z, Baldi E, Romeo E, D'Onofrio A, Nigro G; IBRYD Study Group. Long-term clinical outcomes of patients with drug-induced type 1 Brugada electrocardiographic pattern: A nationwide cohort registry study. Heart Rhythm. 2024 May;21(5):555-561. doi: 10.1016/j.hrthm.2024.01.015. Epub 2024 Jan 18. PMID: 38242222.

Reviewer	**2**
Name	**Liao, Dengbin**

Affiliation **West China Hospital of Sichuan University**

Date **23-May-2024**

COI **No interest competition**

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1. The abstract method section, outcome indicators and the description of outcome indicators in the manuscript method section are incomplete. (Lines 30-39)

2. In the introduction, due to the lack of literature review on acupuncture and moxibustion improving the quality of life of AF patients, it suddenly leads to the abrupt research purpose. Please add.

3. Will the different ablation methods and parameters chosen during surgery have an impact on the postoperative quality of life of AF patients? (Line 130-136)

4. Is there a difference in quality of life between patients who experience recurrent AF after ablation and those who receive oral medication or electrical cardioversion, compared to those who do not experience recurrence? How to control this gap? How to determine the impact of recurrence on quality of life? (Line 177-186)

5. Why is the outcome indicator only the AFEQT score of 6 months, and the score of 3 months and 12 months is not included? What are the reasons? (Line 190-192)

6. Are these AF patients undergoing outpatient follow-up? How to ensure that it can improve the 12-lead electrocardiogram examination in time when it recurs? Especially in patients with paroxysmal atrial fibrillation, the measurement of recurrence rate as an evaluation indicator needs to be considered (Line 219-226).

5. How does SF-6D to identify the patient's stated medical costs? Are there uniform evaluation criteria? If so, please describe it in detail (Line 236-239).

6. Trustworthiness and expectations How is the trustworthiness/Expectations questionnaire assessed? What is the impact on quality of life? Why you need to evaluate it (242-243)

7. Data analysis Please write down the statistical methods used to compare the baseline, 3-month, 6-month and 12-month data. Missing data control within a few percent can be filled, if the missing rate is more than 50% can be filled? (Line 304-314)

8. There are too many outcome indicators, it is recommended to leave the indicators related to quality of life, do not deviate from the purpose of the study.

9. The language could be improved.

VERSION 1 - AUTHOR RESPONSE

Response Letter

Dear editor,

We are grateful for your valuable feedback and insightful comments on our manuscript titled “Effect of Acupuncture on Quality of Life in Atrial Fibrillation: study protocol for a randomized controlled trial” (ID: bmjopen-2024-087460). We have carefully considered each of suggestions and have made the necessary revisions to enhance the clarity and quality of our work. Below, we provide a detailed response to the editors and reviewers' comments and outline the changes made to the manuscript.

We thank the editors again for your constructive feedback and the opportunity to improve our manuscript. We look forward to your favorable consideration of our revised submission.

Sincerely,

Li-Qiong Wang

Response to the comments of Reviewer #1

Comments to the Author:

The paper is interesting, a distinction must be made on patients with paroxysmal AF.

How many of these had an organized trigger? How were they screened (clinic, electrophysiological study?)

If this has not been done it should be included in the limitations

Response: Thank you for your suggestions. We plan to conduct a subgroup analysis to distinguish paroxysmal or persistent AF and has been added to the revised manuscript. (Line 334-337, Page 17)

“In addition, we will conduct subgroup analysis on the impact of AF types (paroxysmal or persistent), different ablation methods and parameters on patient QoL, as well as the impact of recurrence on patient QoL, based on clinical and demographic characteristics.”

Unfortunately, our study design did not include screening for organized trigger. Based on your suggestion, we have added this as one of the limitations in the discussion section. (Line 386-388, Page 19)

“Fifthly, no organised trigger-related screening was conducted for patients, making it difficult to elucidate the potential triggers of their condition.”

You can read Russo V, Caturano A, Migliore F, Guerra F, Francia P, Nesti M, Conte G, Perini AP, Mascia G, Albani S, Marchese P, Santobuono VE, Dendramis G, Rossi A, Attena E, Ghidini AO, Sciarra L, Palamà Z, Baldi E, Romeo E, D'Onofrio A, Nigro G; IBRYD Study Group. Long-term clinical outcomes of patients with drug-induced type 1 Brugada electrocardiographic

pattern: A nationwide cohort registry study. Heart Rhythm. 2024 May;21(5):555-561. doi: 10.1016/j.hrthm.2024.01.015. Epub 2024 Jan 18. PMID: 38242222.

Response: Thank you for your recommendation, and we carefully read this clinical study. We have cited this article in the revised manuscript.

Response to the comments of Reviewer #2

1. The abstract method section, outcome indicators and the description of outcome indicators in the manuscript method section are incomplete. (Lines 30-39)

Response: Thanks for your valuable feedback and constructive suggestions. We have added a description of all outcome measures to the Methods and Design section of the abstract. (Lines 30-40, Page 2)

“This multicentre randomised clinical trial will be conducted in China. A total of 146 eligible patients will be randomly assigned in a 1:1 ratio to either the acupuncture group or the sham acupuncture group. All patients will receive standard post-ablation care and undergo 18 sessions of acupuncture/sham acupuncture within 12 weeks following CA, followed by a 9-month follow-up period. The primary outcome is the change in the Atrial Fibrillation Effect on Quality-of-Life (AFEQT) summary score from baseline to months 6 after CA. Secondary outcomes include the changes in the AFEQT subscale scores at months 6, the AFEQT summary and subscale score at months 3 and 12, AF burden, AF recurrence, heart rate variability, number of cardioversions, repeat CA procedures, European Heart Rhythm Association (EHRA) score, number of arrhythmia-related hospitalisations, average heart rate, use of SF-6D to assess health status, costs incurred by disease treatment, Credibility/Expectancy Questionnaire, and blinded assessments.”

2. In the introduction, due to the lack of literature review on acupuncture and moxibustion improving the quality of life of AF patients, it suddenly leads to the abrupt research purpose. Please add.

Response: Thanks for your suggestion, we conducted a renewed search of the literature on the impact of acupuncture and moxibustion on the quality of life (QoL) of atrial fibrillation (AF) patients. However, few previous studies have focused on the improvement of QOL in AF patients with acupuncture. Therefore, we summarized other cardiovascular disease studies that involved QoL assessments and incorporated these into the introduction section. (Lines 82-85, Page 5)

“It has been reported that acupuncture can improve exercise tolerance in patients with congestive heart failure, 18 improved cardiac function in patients with chronic heart failure, 19 reduce the frequency of pain episodes in patients with stable angina, 20 and potentially benefit QoL in patients with cardiovascular diseases.18-20”

3. Will the different ablation methods and parameters chosen during surgery have an impact on the postoperative quality of life of AF patients? (Line 130-136)

Response: Many thanks for your comment. Different ablation methods and surgical parameters maybe affect the QoL of patients with AF after surgery. However, the surgical plan needs to consider individual differences of patients to determine the most appropriate ablation methods and parameters. Therefore, we did not control for the ablation methods and parameters, which enhances the generalizability of the study results. We have added this as one of the limitations in the discussion section. (Line 334-337, Page 17)

“In addition, we will conduct subgroup analysis on the impact of AF types (paroxysmal or persistent), different ablation methods and parameters on patient QoL, as well as the impact of recurrence on patient QoL, based on clinical and demographic characteristics.”

4. Is there a difference in quality of life between patients who experience recurrent AF after ablation and those who receive oral medication or electrical cardioversion, compared to those who do not experience recurrence? How to control this gap? How to determine the impact of recurrence on quality of life? (Line 177-186)

Response: Thanks for your insightful comments. There may be a difference in QoL among these patients, but we have not yet retrieved relevant evidence. To ensure the generalizability of the results, we did not exclude patients with repeat ablations. However, our study used central randomization to ensure that the patients in the two groups were as comparable as possible, and we will performe subgroup analyses to further explore the effect of recurrence on QoL. (Line 334-337, Page 17)

“In addition, we will conduct subgroup analysised on the impact of AF types (paroxysmal or persistent), different ablation methods and parameters on patient QoL, as well as the impact of recurrence on patient QoL, based on clinical and demographic characteristics.”

5. Why is the outcome indicator only the AFEQT score of 6 months, and the score of 3 months and 12 months is not included? What are the reasons? (Line 190-192)

Response: Thanks for your feedback. Lines 190-192 describe our study's primary outcome measure evaluation time point, which is the change in the AFEQT scale score from baseline to the 6-month mark. In our description of secondary outcome measures, we have detailed the change in the AFEQT scale score from baseline to the 3-month and 12-month scores. (Line 214-221, Page 11)

6. Are these AF patients undergoing outpatient follow-up? How to ensure that it can improve the 12-lead electrocardiogram examination in time when it recurs? Especially in patients

with paroxysmal atrial fibrillation, the measurement of recurrence rate as an evaluation indicator needs to be considered (Line 219-226).

Response: Thank you very much. After enrolment, patients with AF followed the treatment recommendations of cardiology specialists, attending outpatient follow-up visits at 1 month and 3 months post-procedure. Independent recruitment evaluators recorded patient visits at each acupuncture treatment session and conducted outpatient follow-ups at 3 months, 6 months, and 12 months post-enrolment. In addition to the necessary ECG examinations recommended by cardiologists, our study provides non-invasive portable long-term ECG patch monitoring for patients at 3, 6, and 12 months post-enrolment, with each monitoring period lasting 7 days, to observe the current state of cardiac recovery. Furthermore, outside of these evaluation time points and non-scheduled cardiology examinations, if patients experience symptoms related to AF (such as palpitations, dizziness, or chest tightness), we encourage them to independently visit the hospital for a 12-lead ECG examination to ensure that any recurrence of AF is promptly detected.

5. How does SF-6D to identify the patient's stated medical costs? Are there uniform evaluation criteria? If so, please describe it in detail (Line 236-239).

Response: Thanks for your invaluable comments. I'm sorry for my unclear expression. The SF-6D is used solely to assess patients' QoL, while we have separately recorded patients' medical costs, including direct and indirect costs. The costs of ablation, acupuncture treatments, and AF-related treatments are recorded during follow-up visits and linked to the patients' payment records. This information has been added to the revised manuscript. (Line 254-259, Page 13)

“Additionally, the Six-Dimensional Health State Short Form (SF-6D) will be used to assess the health status of the patients. All direct costs (including hospitalisation fees, surgical fees, medication costs, consultation fees, echocardiography fees, acupuncture treatment costs, and registration fees, etc.) and indirect costs (including travel expenses for patients and accompanying family members, as well as loss of earnings due to illness, etc.) incurred by the participants for the treatment of the disease will be recorded.”

6. Trustworthiness and expectations How is the trustworthiness/Expectations questionnaire assessed? What is the impact on quality of life? Why you need to evaluate it (242-243)

Response: Thanks for your rigorous and meticulous comments. The Credibility/Expectancy Questionnaire will be used by evaluators to assess the credibility and expectancy of participants following their first acupuncture treatment.

Research has shown that the credibility/expectations of treatment can significantly affect the outcome of treatment. For example, high expectations are associated with better treatment effect. Patients' expectations/credibility of treatment may change treatment effect by

influencing their psychological state and treatment compliance, thereby improving their QoL. Therefore, the impact maybe identified by comparing the comparability of expectations/credibility between groups after patients received treatment.

[1] Haanstra TM, Tilbury C, Kamper SJ, Tordoir RL, Vliet Vlieland TP, Nelissen RG, Cuijpers P, de Vet HC, Dekker J, Knol DL, Ostelo RW. Can Optimism, Pessimism, Hope, Treatment Credibility and Treatment Expectancy Be Distinguished in Patients Undergoing Total Hip and Total Knee Arthroplasty? PLoS One. 2015 Jul 27;10(7):e0133730.

[2] Fei YT, Cao HJ, Xia RY, Chai QY, Liang CH, Feng YT, Du YR, Yu MK, Guyatt G, Thabane L, Lao LX, Liu JP, Zhang YQ. Methodological challenges in design and conduct of randomised controlled trials in acupuncture. BMJ. 2022 Feb 25;376:e064345.

7. Data analysis Please write down the statistical methods used to compare the baseline, 3-month, 6-month and 12-month data. Missing data control within a few percent can be filled, if the missing rate is more than 50% can be filled? (Line 304-314)

Response: Thank you for your suggestions, which we have described in detail in the revised manuscript. (Lines 325-339, Page 16-17)

“Baseline characteristics will be summarised by treatment group. Continuous variables will be presented as mean ± standard deviation (normally distributed) or median and interquartile range (non-normally distributed), and categorical variables will be expressed as frequencies (percentages).

For the primary outcome, the change in AFEQT summary score from baseline to 6 months will be analysised using the t-test or the Wilcoxon rank-sum test by the intention-to-treat (ITT) approach. For secondary outcomes, continuous variables, such as AFEQT subscale scores at months 6, AFEQT summary and subscale score at months 3 and 12, AF burden, etc., will be compared using the t-test or Wilcoxon rank-sum test. Categorical variables will be compared using the $\chi 2$ test or Fisher's exact test. Time-to-event data will be analysed using Kaplan-Meier survival curves, with group comparisons made using the log-rank test. In addition, we will conduct subgroup analysised on the impact of AF types (paroxysmal or persistent), different ablation methods and parameters on patient QoL, as well as the impact of recurrence on patient QoL, based on clinical and demographic characteristics.

All statistical analyses will be conducted by an independent statistician using SAS version 9.3. The significance level will be set at 0.05 (two-sided).”

The handling of missing data, as you mentioned, is indeed a critical issue. According to the literature, it is generally recommended that if the missing data rate is within 20%, methods such as Multiple Imputation (MI) can be used to fill in the gaps.[1] If the missing rate exceeds 20%, caution is advised, as the greater the amount of missing data, the greater the

uncertainty in the imputation results. Generally, if the missing rate exceeds 50%, the reliability of the imputed data decreases significantly, and most studies do not recommend imputing data with more than 50% missing rates. [2,3]

To ensure the scientific rigor and robustness of our study, we will strive to keep missing data below 20% and will only impute missing data for the primary outcome measures. If the missing rate exceeds 50%, we will carefully consider whether to impute these data and may choose to report the specific reasons and distribution of the missing data rather than impute, to maintain the accuracy and reliability of the study results. We have also included the handling of missing data in the revised manuscript (Lines 339-341, Page 17).

“To ensure the scientific rigour and reliability of the study, we will aim to keep missing data below 20% and impute missing data for the primary outcome measure.”

[1] Schafer JL, Graham JW. Missing data: our view of the state of the art. Psychological Methods. 2002;7(2):147-177.

[2] Little RJA, Rubin DB. Statistical Analysis with Missing Data. 2nd ed. Wiley-Interscience; 2002.

[3] Jakobsen JC, Gluud C, Wetterslev J, Winkel P. When and how should multiple imputation be used for handling missing data in randomised clinical trials – a practical guide with flowcharts. BMC Medical Research Methodology. 2017;17(1):162.

8. There are too many outcome indicators, it is recommended to leave the indicators related to quality of life, do not deviate from the purpose of the study.

Response: Thanks for your constructive comments. Recurrence of AF can also affect the QoL of patients, so we evaluated other outcome measures such as recurrence, AF burden, European Heart Rhythm Association score associated with QoL of patients.

9. The language could be improved.

Response: Thanks for your invaluable suggestions and kind reminders. We have undertaken comprehensive revisions and refinements to the manuscript to ensure the language is more concise and professional, thereby enhancing the overall quality of the paper.