Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Complementary Therapies in Medicine 71 (2022) 102900

Contents lists available at ScienceDirect

Complementary Therapies in Medicine

journal homepage: www.elsevier.com/locate/ctim

Auricular acupressure for adverse events following immunization after COVID-19 vaccine injection: A multicentre, blinded, randomized controlled trial

Qinwei Fu [a,1], Hui Xie [a,1], Li Zhou [a,1], Xinrong Li [a], Yang Liu [a], Hongyan Luo [b], Chunyan Zhang [c], Wenyu Peng [a], Zhiqiao Wang [a], Chang Su [d], Zhiyong Xiao [d], Hanwen Lin [a], Xiang Xiao [a], Xuanyu Wu [a], Jiali Huang [d], Xiaocen Wang [a], Sihan Hu [d], Jinfan Tang [d], Huan Xiao [e], Jing Zhou [e], Chengzhi Feng [a], Li Wang [f], Zhimin Ao [g], Xi Chen [a], Qinxiu Zhang [a,h,i,*], Luyun Jiang [a,*]

[a] Hospital of Chengdu University of Traditional Chinese Medicine, Chengdu university of Traditional Chinese Medicine, Chengdu 610075, China
[b] Caotang Community Health Service Center, Chengdu 610071, China
[c] Xi'an Road Community Health Service Center, Chengdu 610000, China
[d] Acupuncture and Tuina School, Chengdu University of Traditional Chinese Medicine, Chengdu 610075, China
[e] Eye School of Chengdu University of Traditional Chinese Medicine, Chengdu 610075, China
[f] The Third Clinical Medical College & School of Rehabilitation Medicine, Zhejiang Chinese Medical University, Hangzhou 311400, China
[g] Department of Integrative Medicine, West China Hospital, Sichuan University, Chengdu 610041, China
[h] School of Medical and Life Sciences, Chengdu University of Traditional Chinese Medicine, Chengdu 611137, China
[i] World Health Organization Collaborating Centre (WHOCC), CHN-56, Chengdu 610041, China

ARTICLE INFO

Keywords:
Auricular acupressure
COVID-19
Vaccine
Adverse events
Randomized controlled trial

ABSTRACT

Background: Some adverse events following immunization (AEFI) were observed in potential corelation with COVID-19 vaccination but without prevention or ongoing trial for it. We aimed to investigate efficacy of auricular acupressure (AuriAc) therapy in preventing AEFI after first dosage of the vaccine.

Methods: We performed a multicentre randomized controlled trial with three arms, including AuriAc, SAuriAc (sham auricular acupressure), and TrAsU (treatment as usual) group, carried out in four medical institutions in Chengdu, China, from March 17th to April 23rd, 2021. We enrolled participants based on eligibility criteria and randomized them into three groups: AuriAc (AEFI-specific auricular points applied, n = 52), SAuriAc (n = 51) or TrAsU (n = 44) group. Primary outcomes were percentages of any AEFI and local pain, and secondary outcomes were percentages who reported other AEFI. They were followed at 1, 3, 5, 7, and 14 days, by phone or online, with severity evaluated.

Results: 147 participants (73.47% females) were included with median age as 31 years (25–45, IQR). One day after the injection, participants in AuriAc group reported significant reduction on percentages of any AEFI [intention-to-treat, difference of percentage (DP) = −20.13, 95%CI: − 0.39, − 0.02, p = 0.01; per-protocol, DP = −22.21, 95%CI: − 0.40, − 0.03, P = 0.02] and local pain (per-protocol, DP = −18.40, 95%CI: −0.36, −0.01, P = 0.04), compared with TrAsU group. The effects were slight at other follow-up days and for other outcomes, and with a low percentage of mild local allergic reactions.

Conclusions: We firstly explored potential of AuriAc for preventing AEFI related to COVID-19 vaccine injection, which is beneficial for the vaccine recipients, but evidence is limited.

Trial registration: chictr.org.cn no. ChiCTR2100043210 (http://www.chictr.org.cn/showproj.aspx?proj=121519)

Abbreviations: AEFI, Adverse events following immunization; AuriAc, Auricular acupressure; SAuriAc, Sham auricular acupressure; TrAsU, Treatment as usual; DP, Difference of percentage; VAS, Visual analog scale; ITT, Intention-to-treat; PP, Per-protocol.

* Corresponding authors at: Hospital of Chengdu university of Traditional Chinese Medicine, Chengdu university of Traditional Chinese Medicine, Chengdu 610075, China.
E-mail addresses: zhqinxiu@163.com (Q. Zhang), jly666@163.com (L. Jiang).
[1] Co-first author

https://doi.org/10.1016/j.ctim.2022.102900
Received 2 March 2022; Received in revised form 2 October 2022; Accepted 9 November 2022
Available online 11 November 2022
0965-2299/© 2022 The Author(s). Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

1. Background

As of May 2nd, 2021, a total of 151,803,822 cases were diagnosed as COVID-19 infection with 3,186,538 deaths in the world [1]. From March 1st, 2021, the increases of confirmed cases rose from 70,000 to more than 680,000, weekly [1]. Building immunity through COVID-19 vaccine injection provides a decreased risk of being infected, and helps to fight the virus if exposed, which can save uncounted lives and give us a pathway out of the global disaster [2]. According to the WHO, until April 23rd, 2021, five types of COVID-19 vaccines were within WHO EUL/PQ evaluation process worldwide, including adenoviral (six manufacturers), inactivated (five), mRNA-based (three), recombinant protein-based (three), and peptide antigen-based (one) [3,4]. Researches showed that the vaccines were of acceptable efficacy, and upgrading on efficacy, especially basic research and clinical trials for emerging variants and new types of vaccines are being designed and conducted [5–11].

Clinical trials revealed some noticeable adverse events following immunization (AEFI) in potential corelation with COVID-19 vaccines injection, although some of them disappeared several or a dozen days later, and without medical intervention required. Mostly observed events were localized reactions (such as soreness, pain, itching, and swelling), and accompanied by fever, chills, fatigue, myalgia, headache, dizziness, nausea, and vomiting [5–11]. Most AEFIs are induced by immune response to vaccine or hypersensitivity of organs, mechanically [12]. Among them, for the inactivated type (Vero cell), produced by Beijing Institute of Biological Products Co. Ltd, Sinopharm Group, which was the only vaccine administered in this study, two trials reported details of AEFIs in people aging from 18 to 59 (Table 1) [7,13].

Until now, in addition to this trial, no research has been conducted or is being conducted on prevention of AEFI after COVID-19 vaccine or other vaccines. In consideration of the huge and growing medical burden and potential anxiety, hesitancy or even resistance of some people toward COVID-19 vaccination, an appropriate and implementable preventive intervention is required, which can promote higher comfort and quality of lives in the short term both physiologically and psychologically [14–18].

Auricular acupressure (AuriAc), a non-pharmaceutical and non-invasive therapy, is characteristics as self-implemented, easily taught and inexpensive, and with few and mild adverse events. By pressing and stimulating auricular acupoints, stimulation can be transferred through the meridians, and influence neurotransmitters release, which transmit signals along neurons, and regulate the function of viscera and endocrine [19–21]. Studies revealed that AuriAc has been applied successfully for hypertension, insomnia, anxiety, depression, and surgery pain, and relieving fatigue, constipation, vomiting, nausea, and lack of appetite due to chemotherapy [19–24]. Weighing up the balance between benefits and harms, indirect evidence suggests potential benefits of AuriAc therapy on preventing AEFI after the vaccination.

As a result, this study aimed to explore whether AuriAc therapy was effective in preventing AEFI of the vaccine compared with sham auricular acupressure (SAuriAc) and treatment as usual (TrAsU) groups.

Table 1
Cases and Percentages of AEFI Concerning the Inactivated Vaccine Applied in this Research.

	Xia et al. 2020[7]]	Liu et al. 2021[13]]
Age, year	18–59	18–59
Country	China	China
Sample size, case	96	406
Injection site (local) reactions, case (n%)		
Local pain	25 (35%)	120 (29.56%)
Local swelling	2 (3%)	28 (6.90%)
Local Redness	1 (1%)	40 (9.85%)
Systemic adverse reactions, case (n%)		
Fatigue	2 (3%)	104 (25.62%)
Dizziness and headache	1 (1%)	56 (13.79%)
Fever	4 (6%)	11 (2.71%)
Diarrhea	NR	25 (6.16%)
Nausea and vomiting	1 (1%)	20 (4.93%)
Abnormal skin and mucosa	1 (1%)	13 (3.20%)

Two trials reported details of THE AEFIs in people aging from 18 to 59. In the two trials, inactivated COVID-19 vaccine (Vero cell), produced by Beijing Institute of Biological Products Co. Ltd, Sinopharm Group, was also the only type applied in this research.

2. Methods

2.1. Study design

A single-blind, multicentre, randomized controlled trial with three arms in a 1:1:1 ratio was performed, including AuriAc, SAuriAc, and TrAsU group. This study was carried out in four medical institutions (two hospitals and two health service centres) in Chengdu, China, from March 17th to April 09th in 2021, with follow-ups from March 18th to April 23rd.

2.2. Ethics approval

Protocol of the trial was approved by local ethics committee (2021KL-015). The trial was registered (chictr.org.cn: ChiCTR2100043210), and the design was pre-published [25]. The study was performed in accordance with the Declaration of Helsinki and the International Conference on Harmonization–Good Clinical Practice, and written informed consent was obtained from all participants included in the study [26,27].

2.3. Setting and participants

The study was advertised by posters and leaflets (flyers) when patients were waiting for a first COVID vaccination and advertisement and recruitment was conducted while patients were waiting in the post vaccination area for observation (at least 30 min). Research investigators assessed those who were interested in participation in the observation areas for initial and final eligibility screening (Fig. S1).

2.4. Inclusion criteria

Potential participants had been strictly screened for matching the criteria of the vaccination shortly before and during registration. We included participants with criteria:

(1) Meeting the criteria of the vaccination with no contraindication according to *Instruction Manual* of the vaccine, and completing the first dose of vaccination no more than 30 min before screening;.

(2) No fatigue, muscle or joint pain, headache, vomiting, diarrhoea, or nausea experienced [no higher than 4 visual analog scale (VAS) scores] within three days before the vaccination, and no diseases (diagnosed) presenting the similar symptoms;.

(3) No swelling, redness, infection or injury on the soft tissue or skin of bilateral auriculas;.

(4) No history of allergy to alcohol, adhesive tape, and Semen Vaccariae contact;.

(5) 18–59 years old, and no restriction on gender;.

(6) Be able to finish the questionnaires during follow-up, online or by phone, independently;.

(7) Volunteer to participate and sign the paper informed consent, and abide by precautions and requirements after the vaccination of the AuriAc therapy.

2.5. Exclusion criteria

participants with any of the following conditions were excluded:

(1) Not suitable for vaccination because of cautionary conditions or contraindications according to *Instruction Manual* of the vaccine;.

(2) Participation in other clinical trials within 4 weeks before enrolment of this trial;.

(3) With fatigue, muscle or joint pain, headache, vomiting, diarrhoea, or nausea experienced (higher than 4 VAS scores) within three days before the vaccination, or with diseases (diagnosed) presenting the similar symptoms;.

(4) Not meeting other requirements on local condition of the ears for the AuriAc therapy;.

(5) Women during pregnancy or lactation;.

(6) With serious psychosis so that cannot sign the consent, abide by the precautions and requirements, or finish the questionnaires online or by phone, independently.

2.6. Randomization and interventions

After eligibility screening, enrolment, and written informed consents collecting, participants were randomized with a software for random allocation, and allocated to the AuriAc group, SAuriAc group, or TrAsU group in a 1:1:1 ratio with stratifying by different centres [25]. Sequentially numbered sequences, which combined letters and numbers, were conducted and listed by researchers for random sequence concealment, outcome evaluators, and statisticians. Sequences generation and concealment were carried out by preassigned assistant researchers. Participants in AuriAc and SAuriAc groups, outcome evaluators, and statisticians were blinded, while the participants in TrAsU group and preassigned acupuncturists were not blinded.

All researchers in this trial received training required by the ethics committee before enrolment, and preassigned acupuncturists who carried out AuriAc and SAuriAc therapy were equipped with at least 4 years of clinical experience. Five acupoints in auricular were selected bilaterally for AuriAc group and SAuriAc group, including Pi (Spleen, CO13), Jiaogan (sympathetic, AH6a), Shenmen (TF4), Pizhixia (Subcortex, AT4), Xin (Heart, CO15) for AuriAc group, and Niaodao (Urethra, HX3), Gangmen (Anus, HX5), Helix 1 (HX9), Helix 2 (HX10), Helix 3 (HX11) for SAuriAc group (Fig. 1).

Auricular acupoints applied for AuriAc and SAuriAc groups were screened, verified and voted based on potential AEFI of the vaccines from previous studies, and according to our experience, expert consultation, and international and national standards of China [5–11,28,29]. Tools employed in AuriAc group and SAuriAc group were *Semen Vaccariae*, which were round, black, very small, hard and without special smell, covered with small tapes (model "Ziyu"; He's Medical Device Co., Ltd, Henshui, China) (Fig. S2) [25,28].

Surface of the auricular acupoints, pictured on stick figures as two protocols for AuriAc and SAuriAc with no specific name (Fig. S3), were wiped by disinfection swabs, and *Semen Vaccariae* tapes for AuriAc therapy were pasted and pressed in the acupoints by preassigned acupuncturists to achieve certain "*Deqi*" sensation of distention or soreness. In this research, getting "*Deqi*" was a requirement. If participant didn't feel "*Deqi*", it was often related to inaccurate acupoint selection, researchers would try again after slight adjustment of position.

The participants in AuriAc group and SAuriAc group were also acknowledged to press the tapes vertically and appropriately by themselves for one minute to achieve the "*Deqi*" sensation, with a duration of four to five times a day and five days in total. The requirement above was listed in *Attention After AuriAc Therapy*, which were distributed to the participants one by one (Fig. S4) [25].

The trial was totally free for participants and they were informed during advertisement and before screening of this trial, together with two times of AuriAc therapy would be given for free upon completement of the study based on their health condition.

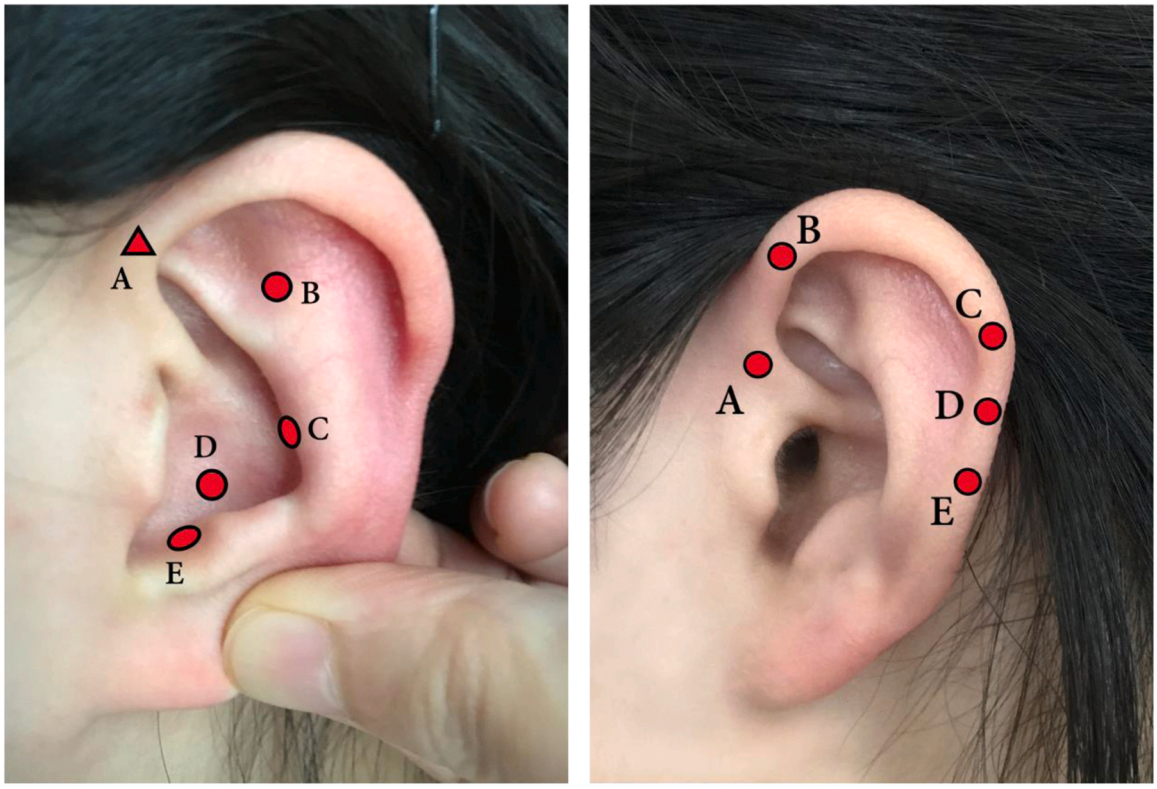

Fig. 1. Auricular acupoints applied for AuriAc and SAuriAc groups, Circular marks indicate the acupoints are located at the outer surface, and triangle mark indicates the acupoint is at inside surface. The left picture is the distribution of auricular acupoints applied for AuriAc group, including A [Jiaogan (sympathetic, AH6a)], B [Shenmen (TF4)], C [Pi (Spleen, CO13)], D [Xin (Heart, CO15)], E [Pizhixia (Subcortex, AT4)]. The picture in the right is the distribution of auricular acupoints applied for SAuriAc group, including A [Niaodao (Urethra, HX3)], B [Gangmen (Anus, HX5)], C [Helix 1 (HX9)], D [Helix 2 (HX10)], E [Helix 3 (HX11)].

2.7. Outcomes

After randomization and before interventions, blinded evaluators collected baseline characteristics by questionaries from the participants on the spot, including gender, age, smoking and alcohol conditions, education level, acknowledgement and anxiety of possible adverse events of COVID-19 vaccine [by visual analog scale (VAS) scores]. In addition, items of potential baseline symptoms, designed based on instruction manual of the vaccine itself and previous research, were also recorded [5–11]. The baseline symptoms included local pain, headache, muscle and (or) joint pain, fatigue, nausea, vomiting, and diarrhoea. Follow-up outcomes of the trial from participants were accessed by blinded evaluators online or by phone in one, three, five, seven, and 14 days after vaccination, which they believed might be due to the vaccination. Primary outcomes included percentages of participants who reported any AEFI (included local pain at injection site, fatigue, muscle pain, joint pain, headache, diarrhoea, vomiting, and nausea, together with other AEFI reported) and percentages of participants who reported local pain at injection site, and with severity evaluated by VAS scores ranging from 0 to 10. Secondary outcomes included percentages of participants who reported fatigue, muscle pain, joint pain, headache, diarrhoea, vomiting, and nausea, together with other AEFI reported by the participants during follow-ups which they believed might be due to the vaccination, and with severity evaluated by VAS scores. AEFI with extra medical intervention required was recorded, and adverse events related to AuriAc therapy in AuriAc group and SAuriAc group were also listed, with numbers, severity, measurement and prognosis.

Time-consuming questionnaire and indicator with high complexity were not carried out due to the large number of vaccinations in the centres, especially in the observation and waiting areas.

2.8. Statistical analysis

Outcomes were collected, analysed and reported in both per-protocol (PP) and intention-to-treat (ITT) participants. Participants belonging to ITT were those who enrolled to this trial and assigned to one of the three groups, and with informed consents signed, while PP were those who had completed all the 14-day observation and with the interventions conducted correctly.

Descriptive analyses were conducted with frequencies and percentages for qualitative variables, and p values (overall) were estimated by $\chi 2$ or fisher $\chi 2$ test as appropriate with the Bonferroni approach. Pairwise comparisons were conducted as differences of percentages (DP), with 95% CIs of the differences calculated by R V4.0.1. Estimations for p values of the pairwise comparisons were conducted by $\chi 2$, continuous or fisher $\chi 2$ test as appropriate in SPSS V23.0. Two-tailed tests with $p < 0.05$ were defined as statistically significant for all analyses.

Originally, sample size estimation was not applicable because this is a preliminary result for the first study of AuriAc for AEFI after injection of the vaccines. Based on the reference of a previous research concerning AuriAc therapy versus SAuriAc therapy for short-term (14 days) effect on pain in 96 patients with lumbar disc herniation, the sample size was estimated by the primary outcome of local pain at injection site in the participants and calculated by using the software EmpowerStats V 4.1.0 [30]. With an estimated difference in means of 0.95 and a population standard deviation of 1.32 at a 5% level of significance with 80% power, 93 participants were minimally required in the three groups with a 1:1:1 ratio. With a considered 10% of the attrition rate, 102 (34 in each group) were to be necessary.

3. Results

3.1. Participants and baseline characteristics

Initially 827 individuals were asked to participate in this research, and 182 people (22%) agreed and were screened. Exclusion and randomization were conducted and 4 remaining individuals withdrew after enrolment and before signing of the consent form. Finally, 147 participants were enrolled and randomized between March 17th and April 9th, 2021, with 52 assigned to AuriAc group, 51 to SAuriAc group, and 44 to TrAsU group. The characteristics were presented with the ITT analysis. In total, they were of the ages [31, median (25, 45), IQR] and (34.08 ± 11.36, mean±SD), with more females recruited (108, 73.47%). Most of the participants had no or little knowledge of (107, 72.79%) the possible AEFI of COVID-19 vaccine, and most participants reported being anxiety-free (126, 85.7%). All participants provided baseline characteristics, including gender, age, smoking and alcohol use patterns, education level, acknowledgement and anxiety of possible adverse events of COVID-19 vaccine, baseline symptoms (local pain, headache, muscle and (or) joint pain, fatigue, nausea, vomiting, and diarrhoea) (Table 2). The characteristics were comparable between groups in addition to the percentage of "any" baseline symptoms observed ($p = 0.03$).

Two participants (3.92%) in SAuriAc group failed to be followed at one day after the injection. Five (3.43%) were unable to complete the intervention due to local allergic reactions related to AuriAc therapy (2 in the AuriAc group and 1 in the SAuriAc group) and lack of tape sticking (2 in the SAuriAc group), but they all adhered to follow-ups (Fig. 2).

In addition, vaccines applied for the participants were all inactivated type (Vero cell), produced by Beijing Institute of Biological Products Co. Ltd, Sinopharm Group, with 0.5 ml injected at upper arm deltoid.

3.2. Results of preventive efficacy of AuriAc therapy for the AEFI

For all the three groups, AEFI were mostly mild, with VAS scores for most of them ranging from 1 to 3 scores (VAS), and none of them were severe except one case of cough (8 scores) in TrAsU group.

Percentages of occurrences of any AEFI differed significantly among the three groups 1 day after the injection. Specifically, percentages of any AEFI occurred were significantly lower in AuriAc group than those in TrAsU group (ITT, DP=−20.13, $p = 0.01$; PP, DP=−22.21, $P = 0.02$), and in SAuriAc group than those in TrAsU group (ITT, DP=−12.57, $p = 0.002$). For local pain at the injection point, results favoured AuriAc group with significantly lower DP compared with TrAsU group 1 day after the injection (PP, DP=−18.40, $P = 0.04$). Results of percentages about headache also showed significant difference among the three groups 1 day after the injection, while a significantly higher percentage was observed in SAuriAc group compared with TrAsU group (ITT, DP=12.24, $p = 0.03$).

Dynamically, percentages of any AEFI and local pain at the injection point were lower in AuriAc group than in SAuriAc or TrAsU group (ITT: Fig. 3; PP: Fig. S5).

Overall, lower percentages of AEFI occurrences were observed in most follow-up points of AuriAc group compared with SAuriAc and TrAsU group, though only several of them were of statistical difference (ITT: Table 3; PP: Table S1).

However, some opposite results were observed concerning percentages of headache, myalgia, fever, and dizziness in AuriAc group compared with SAuriAc or (and) TrAsU group, though none of them was of statistical difference.

Data were in skewed distribution, and none of the outcomes reported the VAS scores≥ 0 in at least 25% of the participants, at any follow-up point in the three groups at the same time. Consequently, quantitative analysis was not performed.

3.3. Safety

Three participants (2 in the AuriAc group and 1 in the SAuriAc group) reported local allergic reactions due to AuriAc therapy during one (1 case), three (1 case) and five (1 case) days after the injection, respectively. The reactions were all mild and disappeared in about 6 h after the AuriAc tapes were removed, with no special medical intervention.

Table 2
Baseline characteristics of 147 participants included.

	AuriAc (n = 52)	SAuriAc (n = 51)	TrAsU (n = 44)	Overall (n = 147)
Male	16 (30.77%)	16 (31.37%)	7 (15.91%)	39 (26.53%)
Female	36 (69.23%)	35 (68.63%)	37 (84.09%)	108 (73.47%)
Age, years				
Median (IQR)	31.5 (26, 46.75)	27 (24, 46)	32 (26, 38)	31 (25, 45)
Mean (SD)	35.52 ± 11.56	32.88 ± 11.94	33.77 ± 10.45	34.08 ± 11.36
Smoking[$]				
Habitual	4 (7.69%)	0 (0%)	1 (2.27%)	5 (3.40%)
Opportunistic	0 (0%)	3 (5.88%)	1 (2.27%)	4 (2.72%)
Never	48 (92.31%)	47 (90.38%)	41 (93.19%)	136(92.52%)
Abstained	0 (0%)	1 (1.96%)	1 (2.27%)	2 (1.36%)
Alcohol[$]				
Habitual	2 (3.85%)	2 (3.92%)	1 (2.27%)	5 (3.40%)
Opportunistic	12 (23.08%)	13 (25.49%)	11 (25.00%)	36 (24.49%)
Never	38 (73.08%)	36 (70.59%)	32 (72.73%)	106 (72.11%)
Abstained	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Education level[%]				
High	41 (78.85%)	38 (74.51%)	34 (77.27%)	113 (76.86%)
Medium	9 (17.31%)	9 (17.65%)	8 (18.18%)	26 (17.69%)
Low	1 (1.92%)	3 (5.88%)	2 (4.55%)	6 (4.08%)
Unknown	1 (1.92%)	1 (1.96%)	0 (0%)	2 (1.37%)
Acknowledgement on possible adverse events of COVID-19 vaccine				
None	25 (48.08%)	26 (50.98%)	28 (63.63%)	79 (53.74%)
Little	9 (17.31%)	9 (17.65%)	10 (22.73%)	28 (19.05%)
Some	13 (25.00%)	11 (21.57%)	6 (13.64%)	30 (20.41%)
Much	4 (7.69%)	4 (7.84%)	0 (0%)	8 (5.44%)
Very much	1 (1.92%)	1 (1.96%)	0 (0%)	2 (1.36%)
Anxiety of possible adverse events of COVID-19 vaccine				
None	34 (65.38%)	36 (70.59%)	28 (63.64%)	98 (66.67%)
Little	10 (19.23%)	7 (13.73%)	11 (25.00%)	28 (19.05%)
Some	7 (13.46%)	5 (9.80%)	5 (11.36%)	17 (11.56%)
Much	1 (1.92%)	3 (5.88%)	0 (0%)	4 (2.72%)
Very much	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Baseline symptoms (occurred in 3 days before the injection), cases*				
Any#	9 (17.31%)	10 (19.61%)	1 (2.27%)	20 (13.61%)
Local pain	1 (1.92%)	3 (5.88%)	0 (0%)	4 (2.72%)
Headache	0 (0%)	3 (5.88%)	0 (0%)	3 (2.04)
Muscle and (or) joint pain	4 (7.69%)	5 (9.80%)	0 (0%)	9 (6.12%)
Fatigue	3 (5.77%)	3 (5.88%)	0 (0%)	6 (4.08%)
Nausea	1 (1.92%)	1 (1.96%)	1 (2.27%)	3 (2.05)
Vomiting	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Diarrhoea	0 (0%)	0 (0%)	0 (0%)	0 (0%)

AuriAc: Auricular acupressure; SAuriAc: Sham auricular acupressure; TrAsU: Treatment as usual; CI: Confidence interval; ITT: Intention-to-treat; Any#: Percentages of the participants who reported any baseline symptoms (occurred in 3 days before the injection); Education level%: "High" refers to university degree or above (including junior college in China); "Medium" refers to junior high school and senior high school education (including technical secondary school in China); "Low" refers to primary school education and below (including simple vocational skills training); Smoking$ & Alcohol$: "Habitual" refers to habitual smoking/drinking, and smoking/drinking almost every day; "Opportunistic" refers to smoking/drinking only at parties, festivals and other special social occasions; and "Abstained" indicates that the participant had quitted smoking/alcohol form "Habitual" smoking/drinking.

4. Discussion

This study firstly showed that AuriAc, a safe therapy, might be related to lower percentages of AEFI in most follow-up points compared with SAuriAc and TrAsU group. Among them, significant reduction on percentages of any AEFI (compared with SAuriAc and TrAsU groups) and local pain at the injection point (compared with TrAsU group) 1 day after the injection were observed. However, the effects were slight at other follow-up days and for other outcomes, and some opposite results without statistical significance were observed concerning percentages of headache, muscle and (or) joint pain, fever, and dizziness in AuriAc group compared with SAuriAc or (and) TrAsU group.

The results are beneficial to vaccine recipients, but they must be interpreted with caution and applied with limited scope of application. Percentages of AEFI in our study were higher than in previous research concerning the same type of vaccine in the first two to three days after the injection, and the reasons were that AEFI were solicited by researchers manually. In addition, different from previous studies [5–11], more screening procedures (including body mass index, axillary temperature and laboratory tests) and limitations (including on alcohol or drug abuse) were not performed due to time (for screening, recruiting, and intervention) and funding limitation. Overall, all causes above might exaggerate the AEFI compared with the previous studies. So, the results of the study should not be applied for evaluating the AEFI of the vaccine, except for comparing the efficacy of AuriAc therapy among the three groups.

Our study also shows some rigor in view of its blinding, computerized randomization, standardized intervention, and pre-published protocol. In addition, the participants in AuriAc group and SAuriAc group, data collectors and statisticians were blinded in all the three groups, aiming at reducing expectancy bias. For the acupuncturists, we tried to reduce expectancy bias by marking the points on stick figures of the two protocols without name of the points identified. However, some results favored SAuriAc group compared with TrAsU group, which was possibly due to potential but limited placebo effects of SAuriAc for the AEFI, and due to physiological effect experienced during pressing the *Semen Vaccariae* tapes [31].

Compared with studies concerning AuriAc therapy for other disorders (including adverse events related to chemotherapy, surgery pain, hypertension, insomnia, anxiety, and depression), smaller effects of the

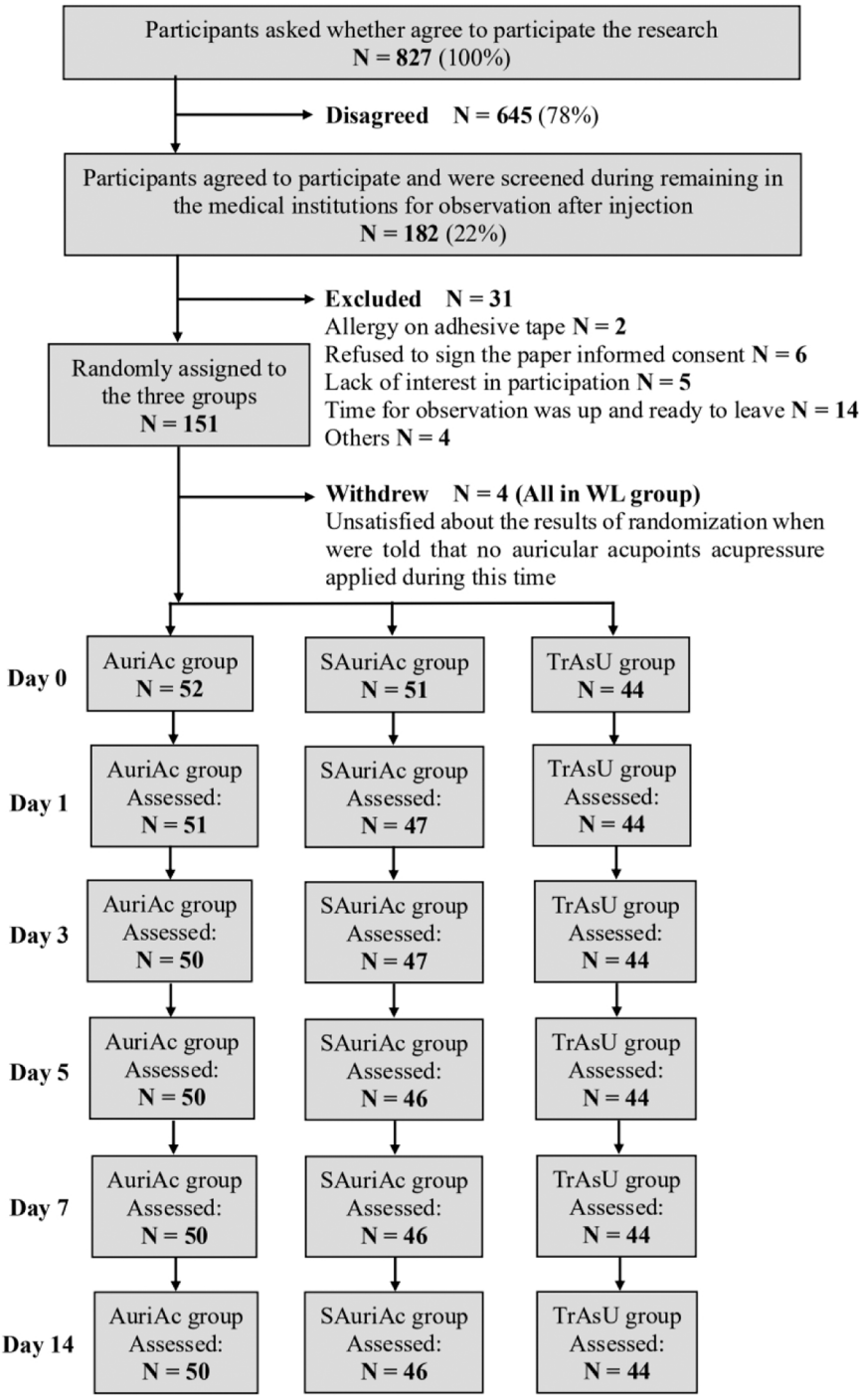

Fig. 2. The Consolidated Standards for Reporting Trials diagram of the study, AuriAc: Auricular acupressure; SAuriAc: Sham auricular acupressure; TrAsU: wait-list. Two participants (3.92%) in SAuriAc group failed to be followed at one day after the injection. Five (3.43%) were unable to complete the intervention due to local allergic reactions related to AuriAc therapy (AuriAc group: 1 case in day 1 and 1 case in day 3; SAuriAc group: 1 case in day 1) and drop of AuriAc tapes (SAuriAc group: 1 case in day 1 and 1 case in day 5), but they all adhered to follow-ups.

therapy were observed in this study, both clinically and statistically [31–34]. In addition to obvious quicker self-relieving and low rate of the AEFI, other possible reasons may be a shorter course of treatment, and more lenient inclusion criteria compared with disease-specific criteria. Some studies revealed the abundant distribution of nerve, blood vessel and lymphatic in auricle, which influences regulation of endocrine hormone and nervous reflex [32–34]. In traditional Chinese medicine, all of the 12 meridians go through our ears, and AuriAc therapy helps to circulate the blood and *Qi*, regulates the functions of the viscera, and the balance of *Yin* and *Yang* and [28,33,34]. Furthermore, AuriAc therapy may also have the potential to be applied for preventing or relieving AEFI of other types of vaccine, but further research is needed.

Our study had some limitations. Firstly, the percentage of any baseline symptoms observed were not comparable among the three groups, which might influence the report of AEFI. Secondly, blinding for the acupuncturists was not applicable due to their expertise. Thirdly, considering limited percentages of AEFI in the participants, the sample size needs more promotion. In the upcoming mass vaccination, we will include more participants and provide better evidence.

Due to adjustments of local and national plans for the vaccination institutions, we couldn't continue to follow the participants included in the study for AEFIs after the second dosage in the same hospitals/healthcare centres. However, we will continue the research for AEFIs after the second dosage by including new recipients, with no crossover between this manuscript in participants, and cooperating with more centres. The second phase of the study will begin after the maximum

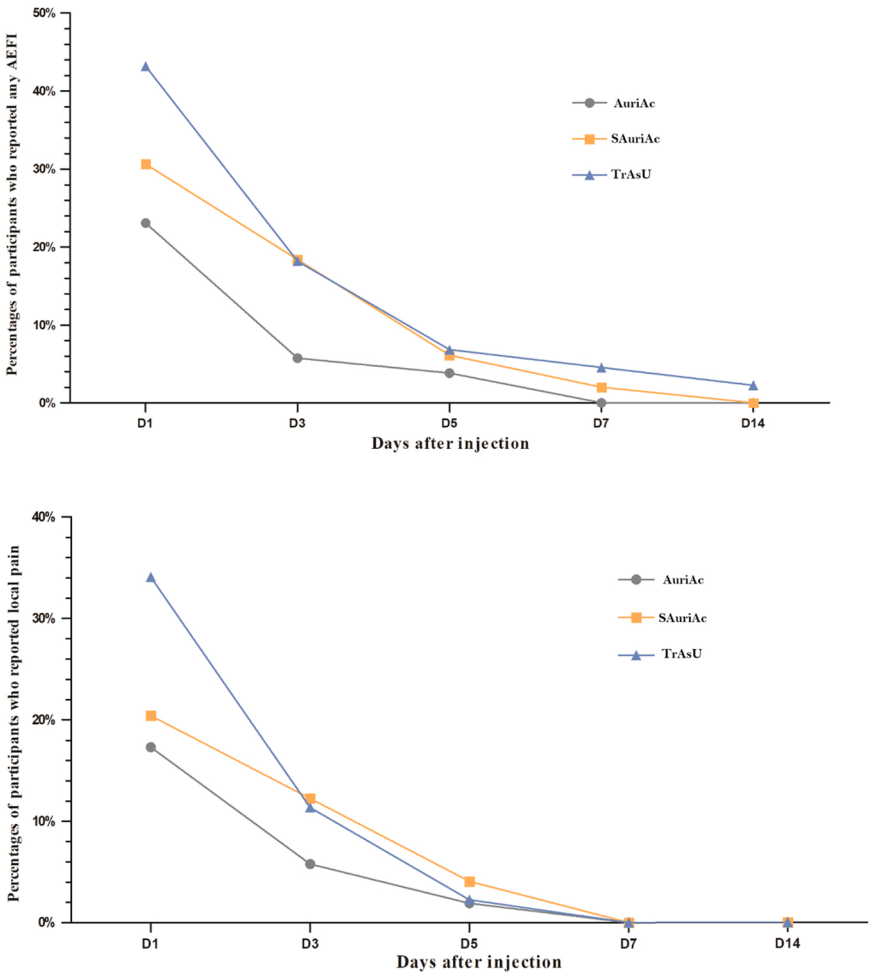

Fig. 3. Percentages of any AEFI and local pain at the injection point throughout the study (ITT test), AEFI: Adverse events following immunization; AuriAc: Auricular acupressure; SAuriAc: Sham auricular acupressure; TrAsU: wait-list; ITT: Intention-to-treat.

interval period (from the first dosage to the second dosage) of the final participant included in this manuscript have been reached, which can avoid unnecessary bias associated with exclusion of duplicative participants.

In addition, possibilities are that AuriAc tape may fail to stick due to its small sticking surface, although it is rare, it exists. Firstly, the function of wiping auricular surface with alcohol swab is not to disinfect, but to remove skin oil as much as possible to increase adherence of the tape. Secondly, users need to be taught to press AuriAc tape vertically, instead of rubbing horizontally, which not only decreases the tape adhering to the ear but also increases the possibility of injuring the skin. Overall, necessary pre-treatment with alcohol before AuriAc tape application and instruction on correct pressing method during application may reduce loss of the tape.

Overall, this is not an interim analysis of a randomized controlled trial, but is a full report of the trial concerning auricular acupressure therapy for AEFIs of the COVID-19 recipients after the first dosage. The participants in this manuscript will not be followed-up more, and the second phase of the study will continue with inclusion of new recipients after enough interval period.

5. Conclusions

In our study, AuriAc firstly manifested efficacy in preventing AEFI related to COVID-19 vaccine injection, including reducing percentages of any AEFI and local pain at the injection point 1 day after the injection significantly. The findings should not be applied for evaluating the AEFI of the vaccine due to bias. AuriAc therapy may also be appropriate for AEFI of other vaccines and fill the gap in this field, but more evidence is needed.

Ethics approval, registration, protocol, and consent to participate

This study is approved by the Ethics Committee of Hospital of Chengdu University of Traditional Chinese Medicine (2021KL-015). Trial registration: chictr.org.cn no. ChiCTR2100043210 (http://www.chictr.org.cn/showproj.aspx?proj=121519). Full trial protocol can be accessed through https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-021-05138-3. All patients signed informed consent.

Funding

This project is jointly supported by 1. Xinglin Scholars Scientific Research Promotion Plan of Chengdu University of Traditional Chinese Medicine-Innovation Team of Traditional Chinese Medicine Otorhinolaryngology Discipline, Natural Science (No. XKTD2021003); 2. Scientific Project of Hospital of Chengdu University of Traditional Chinese Medicine (No. 21LL2×03); 3. Chengdu Medical Research Project (2021002); 4. National College Students' Innovation and Entrepreneurship Project (202110633016); 5. Graduate Scientific Research Innovation Project of Clinical Medical College of Chengdu University of Traditional Chinese Medicine (2020ZS204).

Table 3
Outcome Measurements During the Entire Study (ITT test).

Outcome Measure	AuriAc (n = 52)	SAuriAc (n = 49)	TrAsU (n = 44)	P Value	AuriAc vs. SAuriAc Difference (95 CI)	P Value	AuriAc vs. TrAsU Difference (95 CI)	P Value	SAuriAc vs. TrAsU Difference (95 CI)	P Value
Any AEFI*										
D1	12 (23.08)	15 (30.61)	19 (43.18)	0.009[a]	-7.56(−0.25,0.10)	0.47[c]	-20.13 (−0.39,−0.02)	0.01[c]	-12.57 (−0.32,0.07)	0.002[c]
D3	3(5.77)	9(18.37)	8(18.18)	0.12[a]	-12.60 (−0.25,−0.0004)	0.12[d]	-12.41(−0.25,0.01)	0.10[d]	0.19(−0.16,0.16)	1.00[c]
D5	2(3.85)	3(6.12)	3(6.82)	0.82[b]	-2.27(−0.11,0.06)[g]	0.98[d]	-2.97(−0.12,0.06)[g]	0.83[d]	-0.70 (−0.11,0.09)[g]	1.00[d]
D7	0(0)	1(2.04)	2(4.55)	0.06[b]	-2.04(−0.06,0.02)[g]	0.50[e]	-4.55(−0.11,0.02)[g]	0.20[e]	-2.51 (−0.10,0.05)[g]	0.21[d]
D14	0(0)	0(0)	1(2.27)	0.30[b]	NA	NA	-2.27(−0.07,0.02)[g]	0.45[e]	-2.27 (−0.07,0.02)[g]	0.46[e]
Local pain										
D1	9(17.31)	10 (20.41)	15 (34.09)	0.10[a]	-3.10(−0.18,0.12)	0.76[c]	-16.78(−0.34,0.01)	0.05[c]	-13.68 (−0.32,0.04)	0.10[c]
D3	3(5.77)	6(12.24)	5(11.36)	0.51[a]	-6.47(−0.18,0.05)[g]	0.47[d]	-5.59(−0.17,0.06)[g]	0.51[d]	0.88(−0.12,0.14)	0.98[c]
D5	1(1.92)	2(4.08)	1(2.27)	0.84[b]	-2.16(−0.09,0.05)[g]	0.99[d]	-0.35(−0.06,0.05)[g]	1.00[d]	1.81(−0.05,0.09)[g]	1.00[d]
D7	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
D14	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
Headache										
D1	1(1.92)	6(12.24)	0(0)	0.01[b]	-10.32 (−0.20,−0.004)[g]	0.11[d]	1.92(−0.02,0.06)[g]	1.00[e]	12.24(0.03,0.21)[g]	0.03[e]
D3	0(0)	3(6.12)	0(0)	0.07[b]	-6.12(−0.13,0.01)[g]	0.12[e]	NA	NA	6.12(−0.01,0.13)[g]	0.25[e]
D5	0(0)	1(2.04)	0(0)	0.64[b]	-2.04(−0.06,0.02)[g]	0.50[e]	NA	NA	2.04(−0.02,0.06)[g]	1.00[e]
D7	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
D14	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
Muscle and (or) joint pain										
D1	2(3.85)	1(2.04)	0(0)	0.78[b]	1.81(−0.05,0.08)[g]	1.00[d]	3.85(−0.01,0.09)[g]	0.50[e]	2.04(−0.02,0.06)[g]	1.00[e]
D3	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
D5	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
D7	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
D14	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
Fatigue										
D1	4(7.84)	5(10.20)	2(4.55)	0.63[b]	-2.36(−0.14,0.09)[g]	0.98[d]	3.29(−0.06,0.13)[g]	0.86[d]	5.65(−0.05,0.16)[g]	0.58[d]
D3	1(1.92)	2(4.08)	1(2.27)	0.84[b]	-2.16(−0.09,0.05)[g]	0.99[d]	-0.35(−0.06,0.05)[g]	1.00[d]	1.81(−0.05,0.09)[g]	1.00[d]
D5	1(1.92)	0(0)	1(2.27)	0.75[b]	1.92(−0.02,0.06)[g]	0.11[e]	-0.35(−0.06,0.05)[g]	1.00[d]	-2.27(0.00,0.02)[g]	0.46[e]
D7	0(0)	0(0)	1(2.27)	0.30[b]	NA	NA	-2.27(−0.07,0.02)[g]	0.45[e]	-2.27(0.00,0.02)[g]	0.46[e]
D14	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
Nausea										
D1	0(0)	2(4.08)	1(2.27)	0.40[b]	-4.08(−0.10,0.01)[g]	0.24[e]	-2.27(−0.07,0.02)[g]	0.45[e]	1.81(−0.05,0.09)[g]	1.00[d]
D3	0(0)	1(2.04)	0(0)	0.64[b]	-2.04(−0.06,0.02)[g]	0.50[e]	NA	NA	2.04(−0.02,0.06)[g]	1.00[e]
D5	0(0)	1(2.04)	0(0)	0.64[b]	-2.04(−0.06,0.02)[g]	0.50[e]	NA	NA	2.04(−0.02,0.06)[g]	1.00[e]
D7	0(0)	1(2.04)	0(0)	0.64[b]	-2.04(−0.06,0.02)[g]	0.50[e]	NA	NA	2.04(−0.02,0.06)[g]	1.00[e]
D14	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
Vomiting										
D1	0(0)	1(2.04)	1(2.27)	0.54[b]	-2.04(−0.06,0.02)[g]	0.50[e]	-2.27(−0.07,0.02)[g]	0.45[e]	-0.23 (−0.06,0.06)[g]	1.00[d]
D3	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
D5	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
D7	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
D14	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
Diarrhoea										
D1	1(1.92)	1(2.04)	2(4.55)	0.68[b]	-0.12(−0.06,0.05)[g]	1.00[d]	-2.63(−0.10,0.05)[g]	0.87[d]	-2.51 (−0.10,0.05)[g]	0.21[d]
D3	0(0)	0(0)	1(2.27)	0.30[b]	NA	NA	-2.27(−0.07,0.02)[g]	0.45[e]	-2.27(0.00,0.02)[g]	0.46[e]
D5	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
D7	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
D14	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
Fever*										
D1	1(1.92)	0(0)	1(2.27)	0.75[b]	1.92(−0.02,0.06)[g]	0.11[e]	-0.35(−0.06,0.05)[g]	1.00[d]	-2.27(0.00,0.02)[g]	0.46[e]
D3	0(0)	0(0)	1(2.27)	0.30[b]	NA	NA	-2.27(−0.07,0.02)[g]	0.45[e]	-2.27(0.00,0.02)[g]	0.46[e]
D5	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
D7	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
D14	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
Dizziness										
D1	1(1.92)	0(0)	0(0)	1.00[b]	1.92(−0.02,0.06)[g]	0.11[e]	1.92(−0.02,0.06)[g]	1.00[e]	NA	NA
D3	0(0)	1(2.04)	0(0)	0.64[b]	-2.04(−0.06,0.02)[g]	0.50[e]	NA	NA	2.04(−0.02,0.06)[g]	1.00[e]
D5	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
D7	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
D14	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
Pharyngeal complaints										
D1	1(1.92)	2(4.08)	1(2.27)	0.84[b]	-2.16(−0.09,0.05)[g]	0.99[d]	-0.35(−0.06,0.05)[g]	1.00[d]	1.81(−0.05,0.09)[g]	1.00[d]
D3	0(0)	1(2.04)	1(2.27)	0.54[b]	-2.04(−0.06,0.02)[g]	0.50[e]	-2.27(−0.07,0.02)[g]	0.45[e]	-0.23 (−0.06,0.06)[g]	1.00[d]

(*continued on next page*)

Table 3 (*continued*)

Outcome Measure	AuriAc (n = 52)	SAuriAc (n = 49)	TrAsU (n = 44)	P Value	AuriAc vs. SAuriAc		AuriAc vs. TrAsU		SAuriAc vs. TrAsU	
					Difference (95 CI)	P Value	Difference (95 CI)	P Value	Difference (95 CI)	P Value
D5	0(0)	0(0)	1(2.27)	0.30[b]	NA	NA	-2.27(−0.07,0.02)[g]	0.45[e]	-2.27(0.00,0.02)[g]	0.46[e]
D7	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
D14	0(0)	0(0)	0(0)	NA	NA	NA	NA	NA	NA	NA
Persistent cough										
D1	0(0)	0(0)	2(4.55)	0.85[b]	NA	NA	-4.55(−0.11,0.02)[g]	0.20[e]	-4.55 (−0.11,0.02)[g]	0.21[e]
D3	0(0)	0(0)	2(4.55)	0.85[b]	NA	NA	-4.55(−0.11,0.02)[g]	0.20[e]	-4.55 (−0.11,0.02)[g]	0.21[e]
D5	0(0)	0(0)	2(4.55)	0.85[b]	NA	NA	-4.55(−0.11,0.02)[g]	0.20[e]	-4.55 (−0.11,0.02)[g]	0.21[e]
D7	0(0)	0(0)	1(2.27)	0.30[b]	NA	NA	-2.27(−0.07,0.02)[g]	0.45[e]	-2.27(0.00,0.02)[g]	0.46[e]
D14	0(0)	0(0)	1(2.27)	0.30[b]	NA	NA	-2.27(−0.07,0.02)[g]	0.45[e]	-2.27(0.00,0.02)[g]	0.46[e]

AEFI: Adverse events following immunization; AuriAc: Auricular acupressure; SAuriAc: Sham auricular acupressure; TrAsU: Treatment as usual; D: Day; CI: Confidence interval; NA: Not applicable; ITT: Intention-to-treat; a: Estimated by $\chi 2$ test with the Bonferroni approach; b: Estimated by fisher $\chi 2$ test with the Bonferroni approach; c: Estimated by $\chi 2$ test; d: Estimated by continuous $\chi 2$ test; e: Estimated by fisher $\chi 2$ test; Any AEFI* were percentages of the participants who reported any AEFI.

CRediT authorship contribution statement

Qinwei Fu, Hui Xie and Li Zhou contributed equally to this article. Qinxiu Zhang, Luyun Jiang, Xinrong Li, Qinwei Fu, Hui Xie and Li Zhou conceived and designed the study. Qinxiu Zhang, Luyun Jiang supervised the trial. Qinwei Fu, Xinrong Li, Yang Liu and Qinxiu Zhang planned the statistical analyses and wrote the first draft of the manuscript. Qinxiu Zhang, Hongyan Luo and Chunyan Zhang coordinated the trial. Hongyan Luo and Chunyan Zhang, Zhiyong Xiao, Hanwen Lin, Xiang Xiao, Xuanyu Wu, Jiali Huang, Sihan Hu, Li Wang, Huan Xiao, Jing Zhou and Chengzhi Feng recruited participants and ran the trial. Qinwei Fu, Zhiqiao Wang, Xiaocen Wang, Jinfan Tang, Zhimin Ao and Xi Chen collected and analysed the data. Qinwei Fu, Hui Xie and Li Zhou, Qinxiu Zhang and Luyun Jiang contributed to the analysis, discussions and interpretation of data. All of the authors revised the article critically for important intellectual content and approved the final version submitted for publication.

Consent for publication

Fig. 1 shows distribution of the auricular acupoints selected in our study on the surface of auricle, and it was approved by one of our authors (Zhiqiao Wang, whose auricle is showed in the Fig. 1) with informed consent signed.

Competing interests

The authors declare that they have no competing interests.

Acknowledgements

Not applicable.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ctim.2022.102900.

References

1 World Health Organization. Coronavirus disease 2019 (COVID-19). May 02, 2021. ⟨https://covid19.who.int/⟩.
2 Rubin EJ, Longo DL. SARS-CoV-2 vaccination - an ounce (actually, much less) of prevention. *N Engl J Med*. 2020;383(27):2677–2678. https://doi.org/10.1056/NEJMe2034717.
3 World Health Organization. Coronavirus disease (COVID-19): Vaccines. Status of COVID-19 Vaccines within WHO EUL/PQ evaluation process. April 23, 2021. https://extranet.who.int/pqweb/sites/default/files/documents/Status_COVID_VAX_23April2021.pdf.
4 World Health Organization. Coronavirus disease (COVID-19): Vaccines. https://www.who.int/news-room/q-a-detail/coronavirus-disease-(covid-19)-vaccines?adgroupsurvey=%7badgroupsurvey%7d&gclid=Cj0KCQjw1a6EBhC0ARIsAOiTkrHfb82EsGouq9MNP0JuB3rwtlKUII6RGgvjoxRXwAK70tRBSmmkj10aAnujEALw_wcB
5 Emary KRW, Golubchik T, Aley PK, et al. Efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine against SARS-CoV-2 variant of concern 202012/01 (B.1.1.7): an exploratory analysis of a randomised controlled trial. *Lancet*. 2021;397(10282):1351–1362. https://doi.org/10.1016/S0140-6736(21)00628-0.
6 Zhang Y, Zeng G, Pan H, et al. Safety, tolerability, and immunogenicity of an inactivated SARS-CoV-2 vaccine in healthy adults aged 18-59 years: a randomised, double-blind, placebo-controlled, phase 1/2 clinical trial. *Lancet Infect Dis*. 2021;21(2):181–192. https://doi.org/10.1016/S1473-3099(20)30843-4.
7 Xia S, Zhang Y, Wang Y, et al. Safety and immunogenicity of an inactivated SARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. *Lancet Infect Dis*. 2021;21(1):39–51. https://doi.org/10.1016/S1473-3099(20)30831-8.
8 Baden LR, El Sahly HM, Essink B, et al. Efficacy and safety of the mRNA-1273 SARS-CoV-2 vaccine. *N Engl J Med*. 2021;384(5):403–416. https://doi.org/10.1056/NEJMoa2035389.
9 Vasileiou E, Simpson CR, Shi T, et al. Interim findings from first-dose mass COVID-19 vaccination roll-out and COVID-19 hospital admissions in Scotland: a national prospective cohort study. *Lancet*. 2021;397(10285):1646–1657. https://doi.org/10.1016/S0140-6736(21)00677-2.
10 Collier DA, De Marco A, Ferreira I, et al. Sensitivity of SARS-CoV-2 B.1.1.7 to mRNA vaccine-elicited antibodies. *Nature*. 2021. https://doi.org/10.1038/s41586-021-03412-7.
11 Lai CY, To A, Wong TAS, et al. Recombinant protein subunit SARS-CoV-2 vaccines formulated with CoVaccine HT adjuvant induce broad, Th1 biased, humoral and cellular immune responses in mice. *bioRxiv [Prepr]*. 2021;2021, 433614. https://doi.org/10.1101/2021.03.02.433614.
12 He Q, Mao Q, Zhang J, et al. COVID-19 vaccines: current understanding on immunogenicity, safety, and further considerations. *Front Immunol*. 2021;12, 669339. https://doi.org/10.3389/fimmu.2021.669339.
13 Liu T, Dai J, Yang Z, et al. Inactivated SARS-CoV-2 vaccine does not influence the profile of prothrombotic antibody nor increase the risk of thrombosis in a prospective Chinese cohort. *Sci Bull (Beijing)*. 2021;66(22):2312–2319. https://doi.org/10.1016/j.scib.2021.07.033.
14 Lazarus JV, Ratzan SC, Palayew A, et al. A global survey of potential acceptance of a COVID-19 vaccine. *Nat Med*. 2021;27(2):225–228. https://doi.org/10.1038/s41591-020-1124-9.
15 Kwok KO, Li KK, Wei WI, et al. Editor's choice: influenza vaccine uptake, COVID-19 vaccination intention and vaccine hesitancy among nurses: a survey. *Int J Nurs Stud*. 2021;114, 103854. https://doi.org/10.1016/j.ijnurstu.2020.103854.
16 Detoc M, Bruel S, Frappe P, et al. Intention to participate in a COVID-19 vaccine clinical trial and to get vaccinated against COVID-19 in France during the pandemic. *Vaccine*. 2020;38(45):7002–7006. https://doi.org/10.1016/j.vaccine.2020.09.041.
17 Kadali RAK, Janagama R, Peruru S, et al. Side effects of BNT162b2 mRNA COVID-19 vaccine: a randomized, cross-sectional study with detailed self-reported symptoms from healthcare workers. *Int J Infect Dis*. 2021;106:376–381. https://doi.org/10.1016/j.ijid.2021.04.047.
18 Mathioudakis AG, Ghrew M, Ustianowski A, et al. Self-reported real-world safety and reactogenicity of COVID-19 vaccines: a vaccine recipient survey. *Life (Basel)*. 2021;11(3):249. https://doi.org/10.3390/life11030249.
19 Eghbali M, Yekaninejad MS, Varaei S, et al. The effect of auricular acupressure on nausea and vomiting caused by chemotherapy among breast cancer participants. *Complement Ther Clin Pr*. 2016;24:189–194. https://doi.org/10.1016/j.ctcp.2016.06.006.
20 Shin J, Park H. Effects of auricular acupressure on constipation in participants with breast cancer receiving chemotherapy: a randomized control trial. *West J Nurs Res*. 2018;40(1):67–83. https://doi.org/10.1177/0193945916680362.

21 Lin L, Zhang Y, Qian HY, et al. Auricular acupressure for cancer-related fatigue during lung cancer chemotherapy: a randomised trial. *BMJ Support Palliat Care*. 2021;11(1):32–39. https://doi.org/10.1136/bmjspcare-2019-001937.

22 Yeh ML, Tsou MY, Lee BY, et al. Effects of auricular acupressure on pain reduction in participant-controlled analgesia after lumbar spine surgery. *Acta Anaesthesiol Taiwan*. 2010;48(2):80–86. https://doi.org/10.1016/S1875-4597(10)60018-5.

23 Zhao ZH, Zhou Y, Li WH, et al. Auricular acupressure in participants with hypertension and insomnia: a systematic review and meta-analysis. *Evid Based Complement Altern Med*. 2020;2020:7279486. https://doi.org/10.1155/2020/7279486.

24 Chueh KH, Chang CC, Yeh ML. Effects of auricular acupressure on sleep quality, anxiety, and depressed mood in RN-BSN students with sleep disturbance. *J Nurs Res*. 2018;26(1):10–17. https://doi.org/10.1097/JNR.0000000000000209.

25 Fu Q, Xie H, Zhou L, et al. Traditional Chinese medicine auricular point acupressure for the relief of pain, fatigue, and gastrointestinal adverse reactions after the injection of novel coronavirus-19 vaccines: a structured summary of a study protocol for a multicentre, three-arm, single-blind, prospective randomized controlled trial. *Trials*. 2021;22(1):162. https://doi.org/10.1186/s13063-021-05138-3.

26 Shrestha B, Dunn L. The declaration of Helsinki on medical research involving human subjects: a review of seventh revision. *J Nepal Health Res Counc*. 2020;17(4):548–552. https://doi.org/10.33314/jnhrc.v17i4.1042.

27 Dixon Jr JR. The international conference on harmonization good clinical practice guideline. *Qual Assur*. 1998;6(2):65–74. https://doi.org/10.1080/105294199277860.

28 Huang LC. *Auricular Medicine: A Complete Manual of Auricular Diagnosis and Treatment*. first ed. Orlando, FL: Auricular International Research & Training; 2005.

29 Zhou L., Zhao B., National Technical Committee on Acupuncture and Moxibustion of Standardization Administration of China. Nomenclature and location of auricular points, GB/T 13734–2008. National Administration of Traditional Chinese Medicine of China, 2008–04-23. (http://c.gb688.cn/bzgk/gb/showGb?type=online&hcno=D6A125ED4011A9A625F8A3ACE425EE09).

30 Jinhai Xu, Jianlin Cha, Guodong Wang, et al. Clinical study of auricular acupoint pressure on short-term effect of pain in patients with lumbar disc herniation. *Shanghai J Tradit Chin Med*. 2019;53(11):61–66, 10.163 05/j.1007-1334.2019.11.013.

31 Kuo SY, Tsai SH, Chen SL, et al. Auricular acupressure relieves anxiety and fatigue, and reduces cortisol levels in post-caesarean section women: a single-blind, randomised controlled study. *Int J Nurs Stud*. 2016;53:17–26. https://doi.org/10.1016/j.ijnurstu.2015.10.006.

32 Zhang Y, Huang Y, Li H, et al. Transcutaneous auricular vagus nerve stimulation (taVNS) for migraine: an fMRI study. *Reg Anesth Pain Med*. 2021;46(2):145–150. https://doi.org/10.1136/rapm-2020-102088.

33 Zhao L, Chen J, Li Y, et al. The long-term effect of acupuncture for migraine prophylaxis: a randomized clinical trial. *JAMA Intern Med*. 2017;177(4):508–515. https://doi.org/10.1001/jamainternmed.2016.9378.

34 Zhao L, Li D, Zheng H, et al. Acupuncture as adjunctive therapy for chronic stable angina: a randomized clinical trial. *JAMA Intern Med*. 2019;179(10):1388–1397. https://doi.org/10.1001/jamainternmed.2019.2407.