A clinical randomized controlled trial: moxibustion at Laogong interval with *Panax notoginseng* promoted the maturation of arteriovenous fistulae

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**Abstract**

**Background:** We aim to study the clinical effect of moxibustion at Laogong interval with *Panax notoginseng* on the short-term maturation and long-term patency of arteriovenous fistula.

**Methods:** Seventy-four pre-dialysis uremic patients who received distal forearm radial-cephalic fistula creations were enrolled in this study and randomly assigned to the control group and experimental group. After arteriovenous fistula creations, the control group underwent handgrip exercise, and the experimental group received moxibustion at Laogong acupoint interval with *Panax notoginseng*. Both groups received a 12-week treatment and were followed up for 24 weeks in all at the following time points: before creations and 2, 4, 8, 12, 24 weeks after creations. The diameter of anastomosis, the diameter and outflow of draining-veins 5 cm above anastomosis, the diameter and outflow of brachial arteries evaluated the maturation and patency of arteriovenous fistula. Enzyme linked immunosorbent assay determined serum levels of endothelin and nitric oxide.

**Results:** The maturity rate in the experimental group was significantly higher than that in the control group at 4 weeks after arteriovenous fistula creations (P = 0.048). The diameter of anastomosis, the diameter of draining veins, and the blood flow of draining veins increased in both groups during the whole 24 weeks. The diameter and blood flow of brachial arteries ascended in both groups during the previous 12 weeks. Compared with the control group, moxibustion at Laogong interval with *Panax notoginseng* significantly improved the value of the diameter of draining-veins (P = 0.016), the blood flow of draining-veins (P = 0.015), the diameter of brachial arteries (P < 0.001), and the blood flow of brachial arteries (P = 0.012) at 2 weeks, and enhanced the blood flow of draining-veins (P = 0.029) and brachial arteries (P < 0.001) at 12 weeks. Serum levels of endothelin were significantly lower (P = 0.047), and serum levels of nitric oxide were markedly higher (P < 0.001) in the experimental group than that in the control group at 2 weeks after creations.

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Background
Arteriovenous fistula (AVF) is a commonly used vascular pathways [1, 2] when venous segments need to be expanded and thickened to mature for usage. After AVF creation, the hemodynamic changes such as the sudden increasing blood flow of draining veins (BFV), the velocity variation of distributed and turned blood flow at anastomotic stoma, and the non-laminar and disordered blood flow in vessels may induce adaptive alteration of AVF, particularly when combined with other risk factors, for example, uremic toxin accumulation, systemic inflammatory responses, oxidative stress, and vascular lesions. Currently, the short-term maturation and the long-term patency rate are still unsatisfied in clinical practice. The failure rate of maturation in 5 months after AVF creation is as high as 60% [3]. Although there have been many strategies to promote the maturation and long-term patency of AVF in clinics, most of them are not effective [4]. Vessel stenosis due to neointimal hyperplasia and blood flow insufficient for dialysis are two critical causes for the immature and dysfunction of AVF [5]. The immature and dysfunction of AVF is associated with weakening pulse, shudder and murmur at venous segments and swelling hands sometimes combined with pain and finger paralysis, which is like "Hand arthralgia," a traditional Chinese medicine (TCM) disease. "Hand arthralgia" presents with painful hands or arms associated with “Qi” stagnation and blood stasis due to vessel injury. The TCM therapeutic principle “HuoXue Huayu” promotes blood circulation and eliminates blood stasis, is widely applied in China to cure "Hand arthralgia." Panax notoginseng is a kind of "HuoXue Huayu" medicine. Pharmacological studies have showed that Panax notoginseng prevents thrombosis formation by inhibiting the production of thromboxane A2 and releasing calcium 5-hydroxytryptamine [6]. Moxibustion is one of the most effective "HuoXue Huayu" therapies in China. Modern studies have suggested that thermal stimulation of moxibustion improves microcirculation [7] and increases the blood flow of local capillaries, acrovascular [8], and visceral vessels [9]. Moxibustion may benefit vasodilation due to the release of norepinephrine [10] and vasoactive intestinal peptide [11] after nerve-muscle sympathetic excitation. Laogong acupoint is one of the primary acupoints for treating "Hand arthralgia," according to TCM experience. Based on mentioned above, we hypothesize that moxibustion at Laogong interval with Panax notoginseng (MLPN) would benefit AVF. In this study, we observe the effect of MLPN on the short-term maturation and long-term patency of AVF.

Methods
Study design and participants
The study was a prospective, single-center, randomized controlled trial with a 24-week follow-up (Fig. 1). This study was carried out between June 2019 and November 2020 in the Department of nephrology, Shuguang Hospital Affiliated to Shanghai University of TCM, China. Seventy-four predialysis uremic patients, aged 18 to 80 years old with signed informed consents, underwent radial-cephalic AVF (RC-AVF) creations were enrolled. The exclusion criteria included the following factors:

(a) without chronic renal failure (CRF);
(b) with severe cerebrovascular, liver diseases;
(c) after kidney transplantation;
(d) with acute renal failure;
(e) pregnant or lactating women;
(f) hypersensitive to pseudo-ginseng or moxibustion;
(g) with mental disease;
(h) participation in other clinical trials in the meantime;
(i) using other antithrombotic medicine within 3 months;
(j) unwilling to participate in this trial.

A random counting Excel table was in use. Before the intervention, patients were randomly allocated to the experimental group or the control group (1: 1 ratio).

Drug preparation
Panax notoginseng powder was provided by Instant Herb of Shuguang Hospital Affiliated to Shanghai University of Traditional Chinese Medicine, mixed with millet wine (2:1 ratio) and made as circle cakes with 2–3 cm diameters. 5–10 holes were burrowed into each herbal cake by 0.45 mm needle [12, 13]. Moxa was bought from Hanyi Moxa of Henan Nanyang Limited Company and kneaded
to be cones with 1.2 cm in diameter in the bottom and 1.5 cm in height.

**Interventions**
Both groups underwent RC-AVF creations in the distal forearm by two experienced surgeons who had been engaged in vascular-access surgery for over 10 years. After AVF creations, participants in the experimental group received moxibustion interval with *Panax notoginseng* cakes (PNC) at Laogong (Fig. 2). Laogong is located between the second and third metacarpals in the palm, which could be touched by the middle finger when making a fist. Moxa cones were put on PNC and kindled from the tips. A total of three moxa cones burned up for 30-45 min per session. Moxibustion was performed daily at the first week after creations and three times per week from the second week. Participants in the control group were instructed to squeeze rubber balls for 15 min twice a day and advised to perform the exercise per day [14]. Both interventions lasted for 12 weeks.

Both groups received integrated therapy on CRF. When such severe uremic symptoms as high potassium, severe metabolic acidosis, and acute heart failure appeared, the participants began to dialysis according to the objective laboratory parameters and the subjective judgment of doctors.

**Outcome measures**
The primary outcomes of this study were the diameter and outflow of draining-veins 5 cm above anastomosis, the maturity rate of AVF at 4 weeks and the patency rate at 24 weeks after creations. AVF maturity was assessed by two experienced nephrologists skilled in AVF examination. Clinical AVF maturation was defined as an easily palpable vein by physical examination, including the arm-raising and augmentation tests, with a straight-superficial segment, length of more than 10 cm, sufficient diameter, and good palpable thrill. Ultrasound criteria for AVF maturation were defined as diameter of draining vein (DV) ≥ 5 mm, distance of skin-vein ≤ 6 mm, and BFV ≥ 500 ml/min [1].

The secondary outcomes were the diameter of anastomosis (DA), the diameter of brachial artery (DBA), the blood flow of brachial artery (BFBA), and the incidence of adverse events such as thrombosis, hemorrhage, aneurysm and heart failure for 24 weeks. DBA and BFBA were measured at 2 cm above antecubital fossa in the inner
arm. A color Doppler ultrasound scanner (MyLab30CV, 104730010) equipped with a linear probe was applied to measure vessels’ blood flow and diameter by two trained nephrologists, strictly following the measurement guidelines [15]. Ultrasonographic datum were collected at six time points: before AVF creations (baseline T0) and 2 (T1), 4 (T2), 8 (T3), 12 (T4), 24 (T5) weeks after the creation. Serum samples were collected at T0, T4, T5 and stored at −80°C for further enzyme linked immunosorbent assay tests (endothelin (ET) kits: Jianglai Biology Company, JL10968, 96T, nitric oxide (NO) kits: Shanghai Hailing Biotechnology Co. Ltd, HLE11572, 96T).

Statistical methods
The sample size calculation was performed as described by our previous study, in which the maturity rate of MLPN at 4 weeks after AVF creations was 76%. With a power of 0.8 and a type I error rate of 5%, the estimated sample size was 37 patients in each group calculated by the formula $n = \frac{2\text{Pr}(\text{Pr} + \text{Pr})}{(\text{p}1 - \text{p}2)^2}$. All datum were analyzed by SPSS software (version 22.0). The statistical variables in this study were in normal distribution and described as $\bar{x} \pm SD$. An independent t-test was used for comparing continuous variables between the MLPN group and the control group. The categorical variables were tested by the chi-square test or Fisher’s exact test. The variations in diameter and blood flow in each group at six-time points were analyzed by one-way ANOVA test. P-value < 0.05 was considered statistically significant.

Results

Participants
Table 1 showed the baseline characteristics of the participants in this trial. There was no significant difference in baseline parameters between the MLPN group and the control group.

Primary outcome
Table 2 displayed the short-term maturity rate and long-term patency rate of AVF. At 4 weeks after creations, there were 34 cases in the MLPN group, and 26 cases in the control group met the mature criteria. The maturity rate of the MLPN group was 91.89%, and it was higher

Table 2 4-week maturity rate and 24-week patency rate of AVF secondary outcomes

|                        | MLPN group (n = 37) | Control group (n = 37) | P       |
|------------------------|---------------------|------------------------|---------|
| Maturity rate, % (n)   | 91.89 (34)          | 70.27 (26)             | 0.048   |
| Patency rate, % (n)    | 75.68 (28)          | 75.68 (28)             | 1.000   |

AVF: arteriovenous fistula; MLPN: moxibustion at Laogong interval with panax notoginseng

Table 1 Baseline characteristics of the participants in MLPN group and control group

|                        | MLPN group (n = 37) | Control group (n = 37) | t      | P      |
|------------------------|---------------------|------------------------|--------|--------|
| Age, years, $\bar{x} \pm SD$ | 61.57 ± 10.02       | 56.59 ± 12.76          | 1.864  | 0.066  |
| Gender, male/female, n | 26/11               | 26/11                  | 0      | 1      |
| Primary disease, n (%) |                     |                        | 3.5    | 0.316  |
| Chronic glomerulonephritis | 8 (21.6)           | 12 (32.4)              |        |        |
| Hypertensive nephropathy  | 9 (24.3)            | 8 (21.6)               |        |        |
| Diabetic nephropathy     | 9 (24.3)            | 12 (32.4)              |        |        |
| Others                  | 11 (29.7)           | 5 (13.5)               |        |        |

MLPN: moxibustion at Laogong interval with panax notoginseng
than that in control one (70.3%, \(p=0.048\)). At 24 weeks after AVF creations, there were both 28 effective fistulas, and the patency rates were 75.68%.

**Secondary outcomes**

Table 3 displayed the dynamic changes in DA, DV, and BFV over time. Both DA and DV in the MLPN group ascended in the whole 24-week follow-up (Fig. 3). During the 12-week intervention, BFV in MLPN group continued increasing, while reversed to decrease after the intervention. One statistical difference between two groups appeared at T1. Compared to those in the control group, DV (\(p=0.016\)) and BFV (\(p=0.015\)) in the MLPN group was significantly increased. Another at T4, BFV in the MLPN was higher than in the control group (\(p=0.029\)). Taken together, MLPN improved DV and BFV compared with single handgrip exercise.

Table 4 presented the changes in DBA and BFBA. The same as DV and BFV, DBA increased in the whole follow-up and BFBA from the previous 12 weeks after AVF creations. DBA and BFBA in the MLPN group significantly improved since T1 (both \(p<0.001\)). There was no statistical difference in both DBA and BFBA between the two groups at T0, while the value of DBA (Fig. 4) and BFBA (Fig. 5) were significantly higher in the MLPN group than those in the control group at T1 (\(p<0.001\), \(p=0.012\)). BFBA further increased in the MLPN group at T4 (\(p<0.001\)). Together, MLPN improved DBA and BFBA in contrary to the single handgrip exercise in the short term.

**Discussion**

Our study compared the effect of MLPN with that of handgrip exercise on the short-term maturation and long-term patency of AVF. Compared with that in the handgrip group, a significantly increased value in DV, DBA, BFV, and BFBA were observed in the MLPN group at 2 weeks after AVF creations, implying that MLPN arterialized and expanded the draining veins and brachial arteries to accommodate the larger volume of blood flow in the short term. However, although the vascular diameter and the blood flow in the MLPN group were remarkably higher than in the handgrip group at 2 weeks, the

### Table 3  DA, DV, and BFV of AVF in six-time points (\(\bar{x}\pm SD\))

|       | MLPN group (n = 37) | Control group (n = 37) | t     | P     |
|-------|--------------------|------------------------|-------|-------|
| T0    | DA, mm             | 2.59±0.99              | 2.51±0.76 | 0.425 | 0.672 |
|       | DV, mm             | 2.69±0.79              | 2.76±0.86 | 0.387 | 0.700 |
| T1    | DA, mm             | 3.60±0.96**            | 3.41±0.76** | 0.912 | 0.375 |
|       | DV, mm             | 4.12±0.98**            | 3.59±0.89** | 2.463 | 0.016 |
|       | BFV, ml/min        | 771.9±374.42           | 571.51±305.38 | 2.503 | 0.015 |
| T2    | DA, mm             | 3.97±0.96**            | 3.91±0.88** | 0.266 | 0.791 |
|       | DV, mm             | 4.44±0.82**            | 3.99±1.22** | 1.831 | 0.071 |
|       | BFV, ml/min        | 935.49±444.01          | 752.97±395.38\(d\) | 1.867 | 0.066 |
| T3    | DA, mm             | 4.26±1.03**            | 4.08±0.94** | 0.776 | 0.440 |
|       | DV, mm             | 4.86±1.00**            | 4.37±1.28** | 1.849 | 0.069 |
|       | BFV, ml/min        | 996.30±456.86\(d\)     | 811.72±424.29\(d\) | 1.801 | 0.076 |
| T4    | DA, mm             | 4.65±1.03**            | 4.23±1.00** | 1.780 | 0.079 |
|       | DV, mm             | 5.03±1.07**            | 4.70±1.47** | 1.138 | 0.259 |
|       | BFV, ml/min        | 1183.87±739.26\(d\)    | 864.67±467.01\(d\) | 2.232 | 0.029 |
| T5    | DA, mm             | 4.72±1.26**            | 5.07±1.14** | 0.370 | 0.712 |
|       | DV, mm             | 5.13±1.08**            | 4.90±1.51** | 0.706 | 0.483 |
|       | BFV, ml/min        | 1078.10±590.04\(d\)    | 957.75±648.43\(d\) | 0.780 | 0.438 |

\(***\) Significant different compared to T0 (\(p<0.001\))

\(d\) Significant different compared to T1 (\(p<0.05\)), **Significant different compared to T1 (\(p<0.01\))

AVF: arteriovenous fistula; MLPN: moxibustion at Laogong interval with Panax notoginseng; DA: diameter of anastomosis; DV: diameter of draining veins; BFV: blood flow of draining veins
numbers of mature fistulae of these two groups were similar. Therefore, the maturity rate of the MLPN group was not higher than that of the handgrip group. At 4 weeks after AVF creations, the number of mature fistulae in the MLPN group was larger than that in the handgrip group. As a result, our current study showed that MLPN promoted the maturation at 4 weeks after creations.

We were interested in the reasons why MLPN could promote AVF maturation. First of all, it was confirmed that moxibustion and *Panax notoginseng* speeded up blood circulation and eliminated blood stasis [16, 17]. Plus, we found it might be associated with ET and NO in terms of physiology and pathology. NO and ET is a pair of vasodilator and vasoconstrictor factors, playing an essential role in maintaining vascular tension. NO is a membrane penetrated molecule produced by endothelial cells, which produces endothelial NO synthase that prevents platelet aggregation, leukocyte adhesion, and proliferation of vascular smooth muscle cells [18]. ET is an active substance secreted by endothelial cells, which can promote the proliferation of vascular endothelial cells, vascular smooth muscle cells, and fibroblasts [19]. Combined with the enlarged DV, DBA, BFV and BFBA at 2 weeks after creations, the higher serum levels of ET and the lower serum levels of ET in the MLPN groups...
indicated that vasodilation of MLPN might closely related to NO increase and ET decrease.

From the perspective of anatomy, two reasons could account for the improvement. On one side, the therapeutic acupoint—Laogong belongs to the pericardial meridian of hand Jueyin, a channel that coincides with the anatomical location of AVF to a certain extend (Fig. 6). On the other side, the vascular network below Laogong is connected with radial arteries and cephalic veins, the significant parts of AVF (Fig. 7). Based on the meridian theory, "Qi" runs and circulates in the whole meridian [20]. Therefore, even treating Laogong alone would influence the whole hand Jueyin pericardial meridian and the AVF nearby. Laogong as the moxibustion position enhanced the therapeutic effect.

Besides the short-term maturation of AVF, we also compared the effect of MLPN on the long-term patency of AVF with handgrip exercise. Unfortunately, the effect of MLPN on the patency rate of AVF at 24 weeks after operation was not significant. However, the values of

|        | MLPN group (n = 15) | Control group (n = 15) | t     | P         |
|--------|---------------------|------------------------|-------|-----------|
| T0     | DBA, mm 5.57±0.75   | 5.61±0.32              | 0.160 | 0.874     |
|        | BFBA, ml/min 439.13±56.57 | 413.93±51.32 | 1.278 | 0.212     |
| T1     | DBA, mm 6.30±0.29*** | 5.77±0.36***           | 4.391 | 0.000     |
|        | BFBA, ml/min 678.67±45.31*** | 629.20±54.99*** | 2.689 | 0.012     |
| T2     | DBA, mm 6.83±0.57*** | 764.20±47.45***        | 1.781 | 0.086     |
|        | BFBA, ml/min 805.13±75.33*** | 748.07±65.52*** | 1.650 | 0.110     |
| T3     | DBA, mm 6.97±0.27*** | 870.27±65.42***        | 1.600 | 0.012     |
|        | BFBA, ml/min 904.87±48.15*** | 871.89±63.73*** | 0.033 | 0.974     |
| T4     | DBA, mm 7.36±0.31*** | 7.15±0.40***           | 1.600 | 0.121     |
|        | BFBA, ml/min 1048.70±61.62*** | 942.24±63.79*** | 4.651 | 0.000     |
| T5     | DBA, mm 7.93±0.34*** | 7.76±0.45***           | 1.162 | 0.255     |
|        | BFBA, ml/min 972.84±91.38*** | 971.89±63.73*** | 0.033 | 0.974     |

*** Significant changes compared to T0 (P < 0.001)

MLPN: moxibustion at Laogong interval with Panax notoginseng; DBA: diameter of arteria brachialis; BFBA: blood flow of arteria brachialis

Fig. 4 DBA of two groups at six-time points. ***Significant changes compared to T0 (P < 0.001), △△△Significant differences between two groups (P < 0.001). DBA: diameter of brachial arteries
BFV and BFBA in the MLPN group were higher than that in the handgrip group during the previous 12-week intervention, implying that continuous MLPN treatment might improve the AVF patency in the long term. The hypothesis needed to be confirmed by extended period of MLPN treatment.

There were several limitations to our study. Firstly, the study was a single-center trial, and most participants came from east of China. Secondly, the scope of samples needed to expand to guarantee the universality of the result. Lastly, measuring conditions should be controlled, such as room temperature, measuring time, and fixed place.

**Conclusions**
MLPN improved the maturation of AVF in the short term. Our study suggested that CRF patients who needed to start hemodialysis as soon as possible might benefit from this new non-invasive, practical therapeutic application.

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**Table 5** Serum levels of ET and NO at six-time points (±SD) (μml/l)

|                | MLPN group (n = 37) | Control group (n = 37) | P      |
|----------------|---------------------|------------------------|--------|
|                | ET                                | NO                                |        |
| T0             | 5.51 ± 0.25***         | 29.21 ± 2.67             |        |
| T1             | 5.16 ± 0.44***         | 37.78 ± 2.75***          | 0.428  |
| T2             | 5.10 ± 0.60***         | 39.13 ± 3.24***          | 0.047  |
| T3             | 4.92 ± 0.30***         | 39.71 ± 3.05***          | 0.047  |
| T4             | 4.87 ± 0.27***         | 41.03 ± 3.71***          | 0.047  |
| T5             | 4.80 ± 0.34***         | 40.92 ± 3.28***          | 0.047  |

**Significant changes compared to T0 (P < 0.01), **Significant changes compared to T0 (P < 0.001)
MLPN: moxibustion at Laogong interval with panax notoginseng; ET: endothelin; NO: nitric oxide

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**Fig. 5** BFBA of two groups at six-time points. **Significant changes compared to T0 (P < 0.001), △Significant differences between two groups (P < 0.05), △△△Significant differences between two groups (P < 0.001). BFBA: blood flow of brachial arteries
Abbreviations
AVF: Arteriovenous fistula; BFV: Blood flow of draining veins; TCM: Traditional Chinese medicine; MLPN: Moxibustion at Laogong interval with Panax notoginseng; RC-AVF: Radial-cephalic AVF; CRF: Chronic renal failure; PNC: Panax notoginseng Cakes; DV: Diameter of draining vein; DA: Diameter of anastomosis; DBA: Diameter of brachial artery; BFBA: Blood flow of brachial artery; ET: Endothelin; NO: Nitric oxide.

Acknowledgements
Thanks for the cooperation of our participants during the whole follow-up. It was grateful that the two nephrologists took ultrasound examination carefully and patiently. Thanks to the nurses in Nephropathy Department and Hemodialysis Room for giving treatment to our participants.

Author contributions
YCY and XL designed the study. CYR served as the writer of this manuscript and was responsible for data collection and analysis. CDP and WF conducted the AVF creations. WLB and ZJ were in charge of the ultrasonic examination. HD, LTY, and QXH contributed to the study. All authors read and approved the final manuscript.

Funding
This research was supported by the following foundation: 1) The Three Year Action Plan Project of Shanghai Accelerating Development of Traditional Chinese Medicine (ZY(2018-2020)-CCXX-2003-08, ZY(2018-2020)-FWTX-7005); 2) Key Disciplines Group Construction Project of Pudong New District Health Bureau of Shanghai (PWZxq2017-07); 3) Budget project of Shanghai University of Traditional Chinese Medicine (2020JKH043).

Availability of data and materials
The datum that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations
Ethics approval and consent to participate
This research was reviewed and approved by the Ethics Committee of Shuguang Hospital Affiliated to Shanghai University of TCM (No. 2019-666-21-01). Informed consent was obtained from all participants.

Consent for publication
Individual person’s datum contained in the article were consent for publication from those people.

Competing interests
The authors declared that they had no competing interests.

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Received: 19 September 2021 Accepted: 5 April 2022
Published online: 20 April 2022

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