International Journal of General Medicine Dovepress

Open Access Full Text Article ORIGINAL RESEARCH

Effect of Electronic Moxibustion in Patients with IDH: A Randomized Crossover Pilot Study

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Objective: Intradialytic hypotension (IDH), a common complication of hemodialysis (HD), is associated with increased cardiovascular risk, morbidity, and mortality. Fatigue is one of the most frequent symptoms of IDH, and deteriorates the quality of life of patients. This study aimed to evaluate the efficacy and safety of electronic moxibustion for improving IDH and its associated symptoms.

Methods: We prospectively recruited 32 end-stage renal disease patients with IDH who underwent regular HD at our hospital's dialysis center between April 2019 and April 2020. A randomized, controlled, two-arm crossover trial was performed to evaluate the efficacy of adding one-hour electronic moxibustion during HD. The outcome measurements included patients' subjective assessment of the degree of fatigue, recovery time of fatigue from HD, cold intolerance before and after each intervention, frequency of IDH episodes and nursing interventions needed during HD, and blood pressure changes during HD.

Results: Thirty (94%) patients completed the study. Intervention with electronic moxibustion improved the degree of fatigue (95% CI, −2.95 to −0.18, p = 0.027), specifically in patients prescribed with midodrine (95% CI, −4.20 to −0.53, p = 0.013). The short-term use of electronic moxibustion during HD did not significantly alter the frequency of IDH or reduce the degree of decrease in blood pressure. Serious adverse effects were not observed. One patient complained of heat, whereas two patients had local transient erythema and pruritus.

Conclusion: Electronic moxibustion appears to be safe and efficacious for improving IDH-related fatigue, thus acting as an adjuvant therapy in HD units to enhance patient comfort and treatment adherence. Further studies with larger sample sizes are required to confirm the benefits of this novel technique.

Plain Language Summary: Intradialytic hypotension (IDH) during hemodialysis is linked to increased mortality, often results in fatigue, and reduces the patients' quality of life. This study assessed the effectiveness of electronic moxibustion, an infrared device that mimics traditional moxibustion, in alleviating fatigue in IDH patients. In a 4-week randomized controlled crossover trial, patients underwent 12 sessions of electronic moxibustion at acupoint CV4 during hemodialysis. While the treatment notably improved fatigue, especially in patients on regular midodrine, it did not significantly affect IDH frequency or blood pressure drop. No major adverse events were reported. This pioneering study evaluated this device for IDH-related fatigue and offered insights for future research on its potential to stabilize blood pressure.

Keywords: cross-over studies, moxibustion, fatigue, renal dialysis

Received: 12 August 2024
Accepted: 19 November 2024
Published: 4 December 2024

Introduction

Intradialytic hypotension (IDH) occurs in approximately 10–12% of patients receiving hemodialysis (HD).[1] The features of IDH include a considerable symptom burden, end-organ ischemia, underdialysis, vascular access thrombosis, and mortality.[2–5] The pathogenesis of IDH is multifactorial and is associated with intravascular hypovolemia, impaired vascular resistance, and reduced cardiovascular reserve.[1,6] The risk factors include older age, female sex, longer dialysis vintage, and several medical diseases.[7,8] Moreover, it can lead to dialysis inadequacy, as patients often shorten treatments owing to associated symptoms such as muscle cramps, pruritus, nausea, and fatigue, which can be debilitating.[7,9,10] The prevalence of intradialytic fatigue ranges from 60% to 97%,[11–14] and in HD patients, it has been associated with lower quality of life[15–17] and survival rates.[18] A self-reported questionnaire interviewing weekly HD patients revealed that the most common symptoms were fatigue (62%) and low blood pressure (BP) (42%).[10]

Frequent assessment of dry weight, modification of dialysate composition and temperature, and increased dialysis time and frequency can reduce the incidence of IDH. Antihypertensive medications may be discontinued before dialysis. Moreover, the administration of a predialysis dose of the alpha agonist midodrine 30 minutes prior to dialysis initiation can be used off-label for the prevention of IDH.[19] However, complete prevention of IDH is unlikely, given the intermittent nature of dialysis therapy. In addition, current interventions are reactive, relying on rapid nursing assessment and management, thus posing a burden to nursing care. Immediate management of IDH includes repositioning patients to optimize hemoperfusion of vital organs (supine or Trendelenburg position), cessation of ultrafiltration, fluid resuscitation, albumin supplementation, and cessation of dialysis.[7,20–22] Although these interventions are necessary and beneficial, they may not prevent the adverse consequences of IDH events. Therefore, it remains necessary to seek novel, effective, and safe interventions.

According to the theory of traditional Chinese medicine (TCM), moxibustion, an external treatment, can dredge meridians and regulate qi-blood. Traditional moxibustion involves burning herbal preparations containing *Artemisia argyi* (mugwort) on or above the skin at the acupuncture points. The leaves of mugwort, in Chinese called *ai ye*, are the main material used for moxibustion. Mugwort is considered to be warm, acidic and bitter. It has the ability to warm the body's meridians, thereby promoting better circulation. TCM considers chronic fatigue to be the result of an unbalanced state among internal organs, or a deficient vital energy (called Qi) condition with characteristic blood symptoms. Previous research on moxibustion and acupressure has found beneficial results in chronic fatigue syndrome, cancer-related fatigue, and fatigue in patients with end-stage renal disease patients.[23–28] Another study suggested that moxibustion might modulate the autonomic nervous system, thus improving fatigue.[24] Indirect moxibustion on CV4 and CV8 has been shown to improve chronic fatigue and its effect may be due to the antioxidant properties of moxibustion.[23] CV4 belongs to the Conception Vessel and has connections with three Yin meridians as well as internal organs. A previous study utilizing herbal acupoint, a type of modified moxibustion therapy, had beneficial effects on improving the frequency of IDH and fatigue recovery.[29]

However, traditional moxibustion is not entirely risk-free, with potential adverse events such as allergies, burns and infection.[30] Moxibustion with moxa burner seems safe with less adverse effects but may be more skill-dependent.[31] Some studies have found that the smoke of moxa contains a variety of complex components, and previous research reported some anti-inflammatory effects through nitric oxide production,[32] but smoke may also be harmful to the human body, such as causing allergic reactions.[33] Research has been carried out to evaluate the efficacy of conventional moxibustion and smokeless moxibustion.[34] To date, no study has evaluated the effectiveness of traditional moxibustion therapy during HD. Herbal acupoint therapy may be effective in improving the frequency of IDH and fatigue recovery; however, it may also cause local erythema and pruritus.[29] Moreover, the thermal and radiation effects of traditional moxibustion are difficult to quantify. A modern, precise, microchip-controlled device can help solve this issue. The objective of this study was to determine whether infrared (IR) electronic moxibustion with a controlled temperature of 56 ± 8 °C, mimicking traditional moxibustion, offers any benefits for the prevention of IDH-related symptoms or complications. A randomized controlled trial was designed for this study.

Material and Methods

This two-period, randomized, controlled, two-arm crossover pilot study was conducted at the dialysis center of Keelung Chang Gung Memorial Hospital, Taiwan, from April 2019 to April 2020. The crossover design is used to reduce the influence of confounding covariates, since patients on ESRD often have multiple comorbidities and parallel controls may be hard to balance in randomized trials. The study protocol was approved by the Institutional Review Board of Chang Gung Memorial Hospital (IRB no. 201801853A3), registered at ClinicalTrials.gov (NCT03856151) and conducted following the Declaration of Helsinki. All patients provided written informed consent before participation.

Study Participants

Patients were recruited from outpatient HD units and their IDH diagnoses were confirmed by certified nephrologists. IDH was defined as (1) KDOQI criteria: a decrease in systolic blood pressure (SBP) ≥ 20 mmHg or a decrease in mean arterial pressure (MAP) ≥ 10 mmHg with accompanying symptoms (dizziness, cramps, or fatigue), according to the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation for IDH; (2) NADIR criteria: intradialytic nadir SBP less than 90 mmHg; or (3) regular prescription of midodrine.[7,21]

Participants who were (1) aged 20–80 years, (2) on thrice-weekly HD with a dialysis time of at least 180 minutes, and (3) had IDH in at least 15% of their dialysis sessions during the past 8 weeks or regular administration of midodrine were included. Participants were excluded if they had (1) severe comorbidities, including cirrhosis, heart failure, and autoimmune diseases; (2) active malignancy; (3) insensitivity to heat or inability to effectively express themselves in heated situations; (4) pregnancy or lactation; (5) undergoing other types of alternative treatments, including Chinese medicine and regional remedies; or (6) were unable to fill out questionnaires.

Sample Size Calculation

This study used a preliminary, open-label design. Because this trial was a pilot study, statistical power and sample size were not calculated.

Randomization and Allocation Concealment

Patients were randomly and equally assigned to Group 1 or Group 2 using permuted block randomization at http://www.jerrydallal.com/random/randomize.htm. Masking the treatment allocation for doctors, nurses, and patients was not feasible.

Study Design

The study design is illustrated in Figure 1. Treatment 1 was regular HD according to the nephrologists' suggestions for 4 weeks for a total of 12 sessions. Questionnaire assessments were conducted at the beginning and end of the study period. Treatment 2 was regular HD with an electronic IR heating device (HEALTHYBOX® Powered heating pad) with wavelength ranging from 5–14 μm and fixed temperatures at 56 ± 8°C on acupoint CV4 (Figure 2) during the second hour of HD. The intervention also lasted for 4 weeks, with a total of 12 sessions. To prevent heat injury, a piece of cork wood pad provided by the manufacturer was placed between the skin and the heating device (Figure 3). Moreover, for patients' safety, the whole process was monitored by

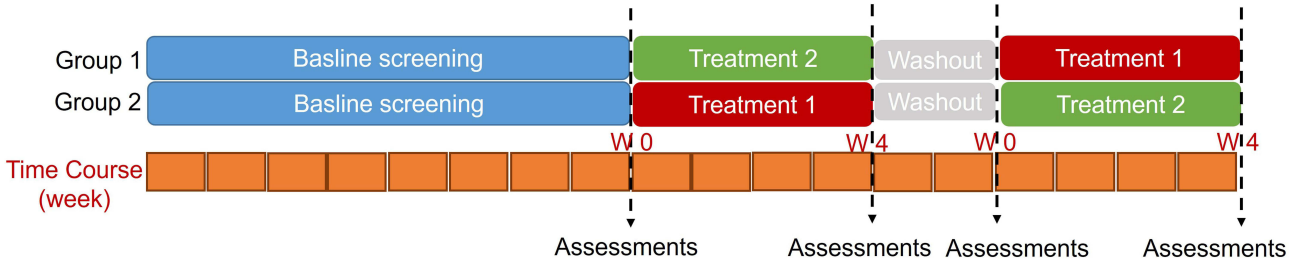

Figure 1 Study design.

Figure 2 Location of CV4.

Figure 3 Electronic moxibustion device with its insulating material.

certified nurses to prevent burn injury caused by the device. Similarly, questionnaire assessments were made at the beginning and end of this study period.

Study Outcomes

Subjective Questionnaire Assessment: Degree of Fatigue, Recovery Time of Fatigue from HD and Degree of Cold Intolerance

Questionnaires assessed the patients' subjective assessment of the degree of fatigue after dialysis using a visual analog scale (VAS) (scale from 0 to 10; 0, not at all, 10, extremely. Specific questions like if the patient is bothered by fatigue, gets tired quickly, do not do much in the day, feeling exhausted or energetic is asked)., the recovery time of fatigue from HD using a scale modified from Gil et al and rated as within minutes (0), when arriving home (0), at bedtime (2), the next morning (5), and by the next HD (10),[30] and the degree of cold intolerance using a VAS (scale from 0 to 100, 25 per range; 0 not at all, 100, extremely. Specific questions like shivering, extremities numbness, still feeling cold after adding clothes, the feeling of coldness bothers me is asked).

Frequency of IDH Episodes and Number of Nursing Interventions During HD

The number of HD sessions affected by IDH episodes and nursing interventions (Trendelenburg position, reduction in ultrafiltration rate, infusion of isotonic saline or hypertonic fluid, and lowering of dialysate temperature) was counted. Data was collected by reviewing the patient's nursing records which included the above interventions.

BP Change During HD

BP was measured using an electronic digital sphygmomanometer before dialysis, every 60 min during HD, and after dialysis in each HD session. In the event of IDH, BP was measured every 10 minutes. Pre-, nadir-, and post-dialysis SBP, diastolic blood pressure (DBP) and MAP values were recorded during each HD session. Differences in SBP, DBP, and MAP between pre-and nadir HD and between pre- and post-HD were calculated. In addition, data on dialysis adequacy, hemoglobin levels, and blood chemistry results were collected.

Statistical Analyses

Statistical analyses were performed using the per-protocol population, defined as participants who followed the study protocol and completed therapy.

Differences in IDH frequency and nursing interventions were analyzed using Poisson regression. Differences in BP, degree of fatigue after dialysis, recovery time of fatigue from HD, and cold intolerance between Treatments 1 and 2 were analyzed using a generalized linear mixed model. Data comparing dialysis adequacy and laboratory parameters were analyzed using a generalized linear mixed model. The generalized linear mixed model is chosen as it can incorporate both random and fixed effects of the study. Poisson regression is a type of generalized linear model used for counts of events, in this case, IDH frequency and nursing interventions occurring during HD. Differences were considered statistically significant when the $P\text{-}value < 0\,0.05$. Data were collected and analyzed using IBM SPSS version 22.0, and Microsoft Excel 2016.

Results

This study was conducted between April 2019 and April 2020. A total of 52 patients undergoing chronic HD in our hospital were eligible for this study. Twenty patients declined to participate, and the remaining 32 patients were enrolled (Figure 4). Two patients were excluded because they received alternative treatments during enrollment. Thirty participants were randomly divided into groups 1 and 2, and both groups received IR electronic moxibustion.

Table 1 shows the baseline characteristics of the 30 Taiwanese participants. For the IDH criteria, a total of 19 patients had regular midodrine prescriptions, with 9 in Group 1 and 10 in Group 2; 20 patients met the KDOQI criteria, 9 in Group 1 and 10 in Group 2; and 23 patients met the NADIR criteria, 14 in Group 1 and 9 in Group 2 (Table 1).

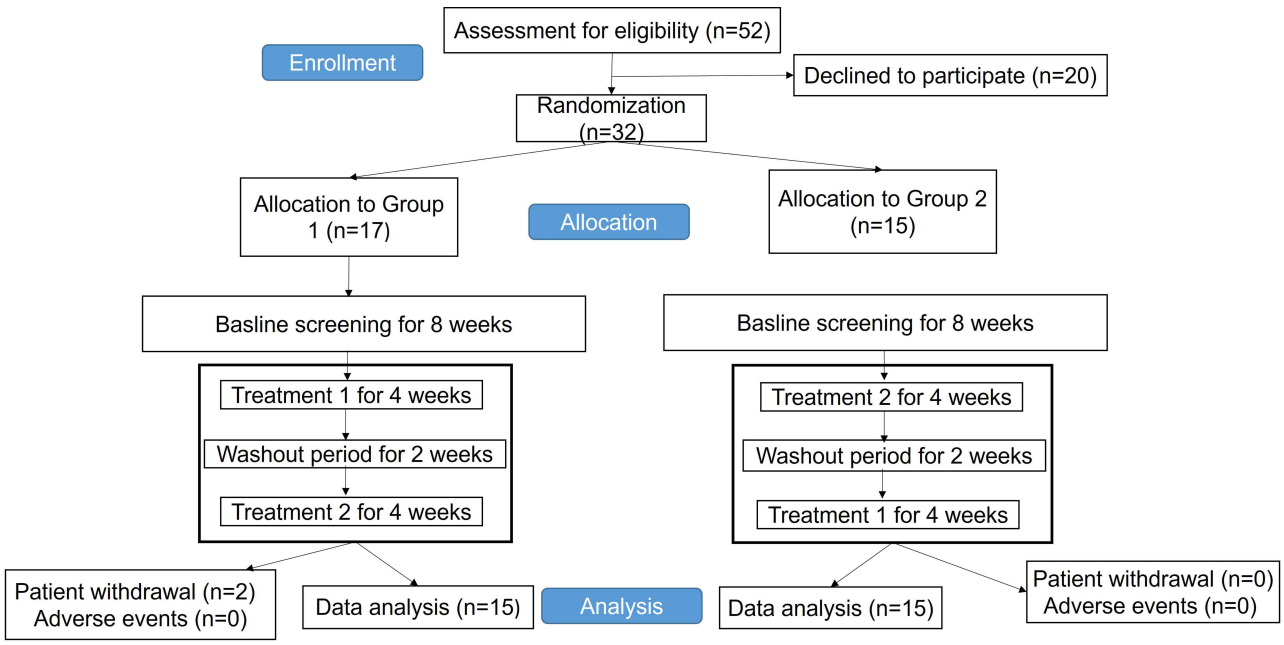

Figure 4 Flow chart of patient recruitment.

Table 1 Baseline Characteristics of Study Population

	Total	Group 1	Group 2
Age (yr)	58.80 ± 12.75	57.73 ± 14.44	59.87 ± 11.22
Dialysis time per session (hr)	3.98 ± 0.16	3.93±0.18	4.03 ± 0.13
Time on dialysis (month)	118.00 ± 105.19	100.87±102.19	135.13 ± 108.85
Female gender (%)	19 (63.33)	9 (60.00)	10 (66.67)
BMI	23.68 ± 3.88	23.58 ± 2.65	23.79 ± 4.91
Dry weight (kg)	59.55 ± 10.71	60.21 ± 8.19	58.89 ± 12.72
UF %	98.68 ± 0.08	99.36 ± 0.08	97.99 ± 0.08
Comorbidities			
HTN under medication (%)	2 (6.67)	2 (13.33)	0 (0)
DM (%)	11 (36.67)	6 (40.00)	5 (33.33)
Previous stroke (%)	3 (10.00)	1 (6.67)	2 (13.33)
CAD or AMI (%)	6 (20.00)	3 (20.00)	3 (20.00)
AV block (%)	1 (3.33)	0 (0.00)	1 (6.67)
IDH criteria			
Midodrine prescription (%)	19 (63.33)	9 (60.00)	10 (66.67)
KDOQI (%)	20 (66.67)	9 (60.00)	11 (73.33)
NADIR (%)	23 (76.67)	14 (93.33)	9 (60.00)

Notes: The values are expressed as the mean and standard deviation or number and percentage where appropriate.
Abbreviations: UF, ultrafiltration; % target UF, percentage of actual UF/target UF; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; AMI, acute myocardial infarction; AV block, atrioventricular block.

Efficacy Assessment

Tables 2–5 show the results of this study.

Effect of Electronic Moxibustion on Severity of Fatigue and Cold Intolerance

The subjective assessments of the degree of fatigue, recovery time of fatigue from HD, and cold intolerance in both groups are shown in Table 2. Figure 5 presents the degree of fatigue after dialysis in week 0 and 4 during Treatment 1 and 2 for all IDH criteria. The overall baseline VAS score for the degree of fatigue was 4.60 ± 2.95. In Treatment 1, the VAS scores for the degree of fatigue were 4.60 at week 0 and 4.87 at week 4; in Treatment 2, the VAS scores for the degree of fatigue were 5.30 at week 0 and 4.00 at week 4 (Figure 5a) indicated a notable improvement ($p = 0.027$) in the degree of fatigue between the two treatments (Δ Fatigue Week 0–4). In contrast, there was no significant reduction in the recovery time of fatigue from HD (Δ Recovery Week 0–4), and cold intolerance (Δ Cold intolerance Week 0–4) between Treatments 1 and 2. Upon further assessment of the degree of fatigue, a notable improvement was found in the subgroup prescribed with midodrine ($p = 0.013$). In the KDOQI and NADIR subgroups, there was also an improvement in the degree of fatigue; however, this difference was not statistically significant ($p = 0.053$ and 0.051, respectively) (Table 3 and Figure 6).

Table 2 Patients' Subjective Questionnaire Assessments

	Treatment 1			Treatment 2			Regression Coefficient (95% CI)
	Week 0	Week 4	Δ Week 0–4	Week 0	Week 4	Δ Week 0–4	Treatment 2 versus Treatment 1
Fatigue	4.60 ± 2.98	4.87 ± 3.12	−0.27 ± 2.59	5.30 ± 3.13	4.00 ± 2.53	1.30 ± 2.51	−1.57 (−2.95, −0.18)*
Recovery	2.87 ± 2.32	3.27 ± 2.39	−0.40 ± 1.73	2.77 ± 2.64	3.00 ± 2.42	−0.23 ± 1.81	−0.17 (−0.98, 0.65)
Cold intolerance	40.00 ± 36.32	39.17 ± 31.95	0.83 ± 29.71	48.33 ± 34.07	35.83 ± 29.86	12.50 ± 33.32	−11.67 (−26.83, 3.49)

Notes: *P- value = 0.027.

Table 3 Subgroup Analysis of Degree of Fatigue According to Different IDH Criteria

	No. of Patients	Treatment 1			Treatment 2			Regression Coefficient (95% CI)	
		Week 0	Week 4	Δ Week 0–4	Week 0	Week 4	Δ Week 0–4	Treatment 2 versus Treatment 1	P-value
Total	30	4.60 ± 2.98	4.87 ± 3.12	−0.27 ± 2.59	5.30 ± 3.13	4.00 ± 2.53	1.30 ± 2.51	−1.57 (−2.95, −0.18)	0.027*
Midodrine prescription	19	4.05 ± 3.15	4.74 ± 3.16	−0.68 ± 2.85	5.21 ± 3.22	3.53 ± 2.57	1.68 ±2.75	−2.37 (−4.20, −0.53)	0.013*
KDOQI	20	4.95 ± 2.84	5.60 ± 2.74	−0.65 ± 2.72	5.70 ± 2.81	4.60 ± 2.64	1.10 ± 1.71	−1.75 (−3.52, 0.02)	0.053
NADIR	23	4.30 ± 2.84	4.61 ± 2.93	−0.30 ± 2.75	5.26 ± 3.00	3.96 ± 2.58	1.30 ± 2.51	−1.61 (−3.23, 0.01)	0.051

Notes: *P-value < 0.05.

Table 4 Comparison of Number of IDH Frequency, Nursing Intervention Needed and BP Changes During HD in 2 Months Before Study, After Treatment 1 and Treatment 2

	Mean±SD			Rate Ratio* or Regression Coefficient (95% CI)		
	Baseline	Treatment 1	Treatment 2	Treatment 1 versus Baseline	Treatment 2 versus Baseline	Treatment 2 versus Treatment 1
KDOQI*	5.57±3.45	5.70±3.83	6.00±3.59	0.02 (0.84, 1.25)	0.64 (0.94, 1.21)	0.40 (0.88, 1.23)
NADIR*	5.60±3.47	4.87±3.19	5.20±3.71	−0.14 (0.72, 1.05)	−0.74 (0.81, 1.06)	0.66 (0.88, 1.30)
Intervention*	8.20±2.83	7.57±3.61	8.43±2.24	−0.80 (0.82, 1.04)	0.03 (0.94, 1.12)	0.11 (0.97, 1.28)
Pre SBP (mmHg)**	117.96±23.23	119.70±21.32	119.24±21.16	1.74 (−17.37, 20.85)	1.28 (−2.65, 5.21)	−0.46 (−5.86, 4.93)
Pre DBP (mmHg)**	62.69±14.79	63.97±14.70	63.14±13.89	1.28 (<-1000, >1000)	0.45 (−3.72, 4.61)	−0.84 (−3.92, 2.25)
Pre MAP (mmHg)**	81.29±16.88	82.55±16.17	81.84±15.71	1.26 (<-1000, >1000)	0.54 (−3.45, 4.54)	−0.71 (−4.56, 3.14)
Nadir SBP (mmHg)	93.71±12.50	94.46±13.64	92.84±12.16	0.75 (−2.84, 4.35)	−0.86 (−3.76, 2.03)	−1.62 (−4.24, 1.00)
Nadir DBP (mmHg)	52.56±9.95	53.00±13.25	52.63±9.31	0.44 (−3.87, 4.76)	0.77 (−1.87, 2.03)	−0.37 (−9.12, 8.39)
Nadir MAP (mmHg)	66.18±10.11	66.82±13.00	66.02±9.63	0.64 (−2.81, 4.09)	−0.16 (−2.26, 1.94)	−0.80 (−5.06, 3.16)
Post SBP (mmHg)	107.62±12.52	105.24±15.57	107.02±13.03	−2.38 (−7.33, 2.51)	−0.60 (−4.13, 2.93)	1.78 (−1.88, 5.43)
Post DBP (mmHg)	58.86±11.17	59.69±13.42	59.30±11.06	0.83 (−6.19, 7.84)	0.44 (−1.81, 2.69)	−0.39 (−4.99, 4.22)
Post MAP (mmHg)	75.08±10.82	74.87±13.45	75.20±11.22	−0.21 (−6.31, 5.90)	0.12 (−2.27, 2.52)	0.33 (−3.33, 3.99)
Δpre-post SBP (mmHg)	10.34±16.80	14.46±17.55	12.22±15.44	−4.12 (−9.79, 1.55)	−1.88 (−5.74, 1.98)	2.24 (−1.55, 6.03)
Δpre-post DBP (mmHg)	3.83±9.98	4.29±10.10	3.83±9.70	−0.46 (−9.19, 8.27)	−0.01 (−2.91, 2.90)	0.45 (−1.67, 2.57)
Δpre-post MAP (mmHg)	6.21±12.03	7.68±12.10	6.63±11.21	−1.46 (−7.47, 4.54)	−0.42 (−3.40, 2.56)	1.04 (−1.44, 3.53)
Δpre-nadir SBP (mmHg)	24.25±17.64	25.24±18.12	26.39±19.24	−0.99 (−5.15, 3.17)	−2.14 (−5.57, 1.29)	−1.15 (−4.03, 1.73)
Δpre-nadir DBP (mmHg)	10.13±11.05	10.97±10.29	10.50±10.55	−0.84 (−4.66, 2.98)	−0.37 (−2.72, 1.98)	0.47 (−1.59, 2.53)
Δpre-nadir MAP (mmHg)	15.11±12.95	15.73±12.58	15.81±13.14	0.62 (−4.15, 2.92)	−0.70 (−3.26, 1.85)	−0.08 (−2.12, 0.195)
Δpre-nadir SBP/pre SBP (%)	19.05±0.10	19.76±0.11	20.64±0.12	0.72 (−1.94, 3.37)	1.59 (−1.02, 4.20)	0.88 (−1.49, 3.24)
Δpre-nadir DBP/pre DBP (%)	20.26±0.26	22.51±0.23	20.53±0.21	2.25 (−2.78, 7.28)	0.27 (−12.26, 12.80)	−1.98 (−7.46, 3.49)
Δpre-nadir MAP/pre MAP (%)	17.08±0.11	18.01±0.11	17.82±0.12	0.93 (−1.72, 3.59)	0.75 (−1.68, 3.17)	−0.19 (−2.31, 1.94)

Notes: *Statistics analysis using Poisson regression, coefficients interpreted in rate ratio. **SBP range: 80.38–170.79 (mmHg). **DBP range: 44.92–106.75 (mmHg). **MAP range: 56.22–128.10 (mmHg).

Table 5 Comparison of Laboratory Parameters and Dialysis Adequacy in 2 Months Before Study, After Treatment 1 and Treatment 2

	Mean±SD			Regression Coefficient (95% CI)		
	Baseline	Treatment 1	Treatment 2	Treatment 1 versus Baseline	Treatment 2 versus Baseline	Treatment 2 versus Treatment 1
Hb (g/dL)	10.79±1.16	10.61±1.21	11.02±1.19	−0.10 (−0.42, 0.22)	0.18 (−0.14, 0.50)	0.28 (−0.04, 0.60)
Hct (%)	32.48±3.43	32.00±3.49	33.22±3.53	−0.22 (−1.14, 0.71)	0.63 (−0.32, 1.58)	0.85 (−0.12, 1.81)
Albumin (g/dL)	4.09±0.29	4.09±0.24	4.02±0.62	0.01 (−0.06, 0.07)	−0.07 (−0.35, 0.20)	−0.08 (−0.36, 0.19)
BUN (mg/dL)	74.83±22.30	69.64±20.48	68.77±19.57	−2.31 (−6.32, 1.71)	−3.55 (−8.08, 0.98)	−1.25 (−6.51, 4.02)
Ca (mg/dL)	9.45±1.07	9.65±1.17	9.59±0.83	0.17 (−0.02, 0.34)	0.17 (−0.09, 0.42)	<-0.01 (−0.62, 0.62)
P (mg/dL)	5.48±1.64	5.59±1.37	5.30±1.28	0.21 (−0.42, 0.83)	−0.05 (−0.30, 0.21)	−0.25 (−0.63, 0.12)
K (mEq/L)	4.94±0.69	4.89±0.78	4.87±0.76	0.04 (−0.18, 0.26)	−0.04 (−0.21, 0.14)	−0.08 (−0.30, 0.14)
*Dry weight (kg)	59.55±10.88	59.93±10.95	59.95±10.86	0.38 (<-1000, >1000)	0.40 (0.06, 0.74)	0.01 (<-1000, >1000)
*Predialysis BW (kg)	62.30±11.31	62.75±11.42	62.76±11.28	0.45 (<-1000, >1000)	0.46 (<-1000, >1000)	0.01 (<-1000, >1000)
*Postdialysis BW (kg)	59.66±10.88	60.11±11.01	60.11±10.87	0.46 (<-1000, >1000)	0.45 (−4.54, 5.44)	−0.01 (<-1000, >1000)
Actual UF (L)	2.64±0.76	2.63±0.75	2.65±0.74	−0.01 (−0.12, 0.01)	0.01 (−0.10, 0.12)	0.18 (−0.11, 0.14)
Target UF (L)	2.75±0.87	2.81±0.92	2.81±0.91	0.07 (−0.08, 0.21)	0.06 (−0.08, 0.20)	−0.07 (−0.21, 0.08)
% Target UF	98.68±0.08	96.75±0.10	97.60±0.11	−1.92 (−4.46, 0.62)	−1.08 (−4.50, 2.35)	0.85 (−1.70, 3.39)

Notes: *dry weight: range 38–90.5 (kg); *predialysis BW range: 39.9–95.05 (kg); *postdialysis BW range: 37.9–90.15 (kg).
Abbreviations: BW, body weight; UF, ultrafiltration; % target UF, percentage of actual UF/target UF.

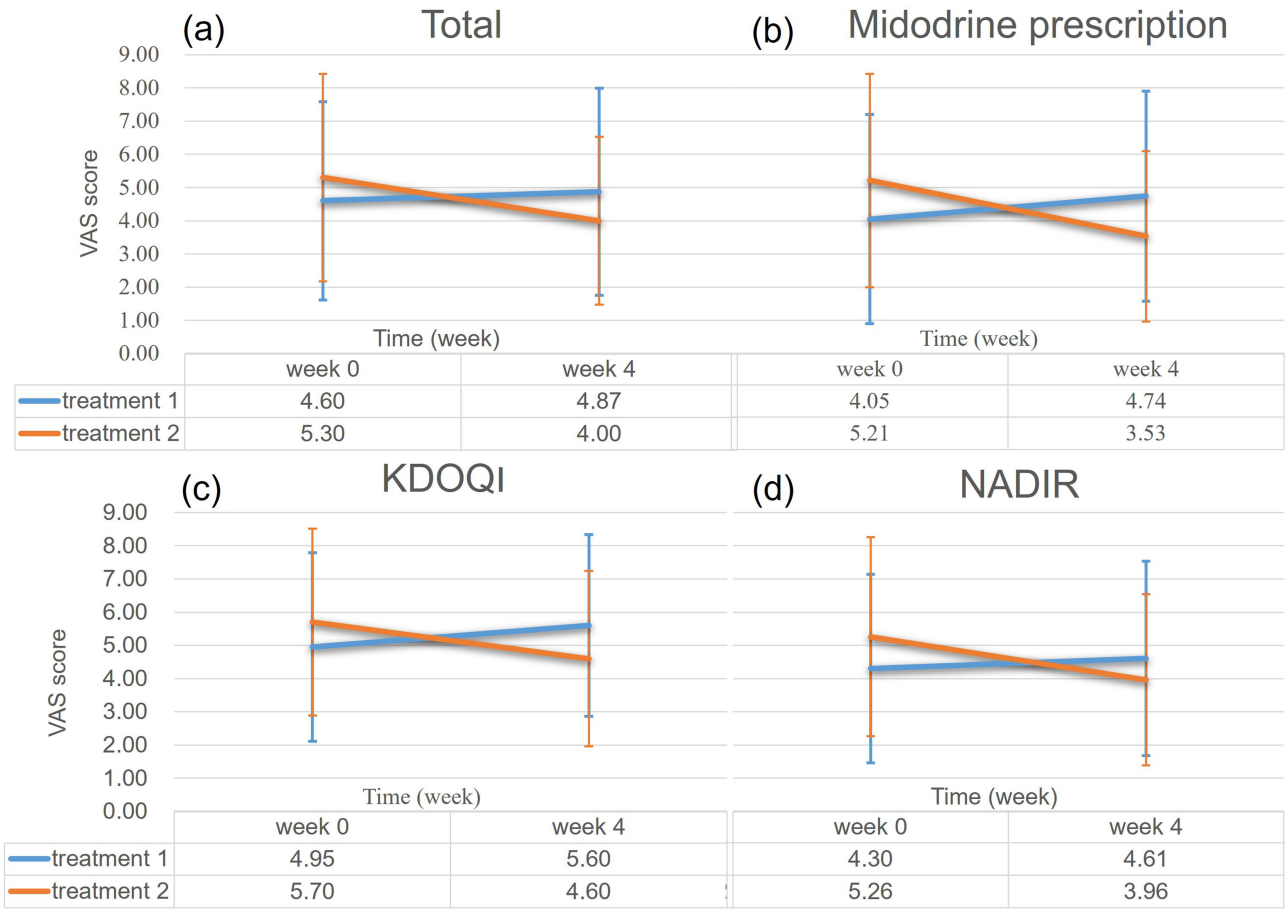

Figure 5 Degree of fatigue after dialysis in weeks 0 and 4 during Treatment 1 and Treatment 2. VAS score of degree of fatigue in (**a**) all IDH patients, (**b**) patients with midodrine prescription, (**c**) patients meeting KDOQI criteria, and (**d**) patients meeting NADIR criteria. A decreasing trend of degree of fatigue was found in all groups during Treatment 2.

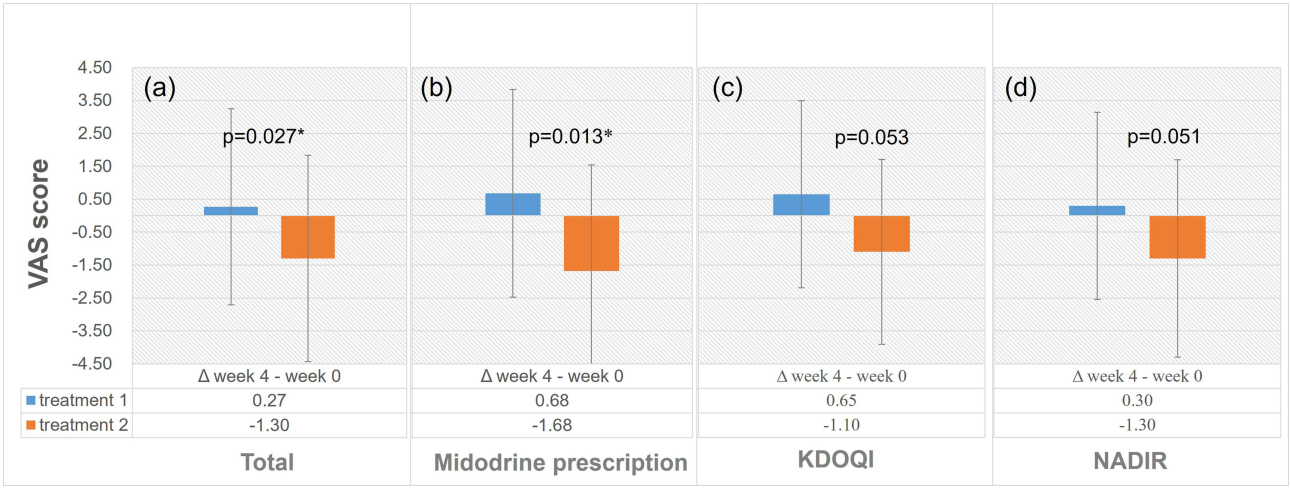

Figure 6 Comparison of the degree of fatigue in Treatment 1 and Treatment 2. Change in VAS score (ΔWeeks 0–4) between Treatment 2 vs Treatment 1 (**a**) −1.30 vs 0.27, P = 0.027 in all IDH patients, (**b**) −1.68 vs 0.68, P = 0.013 in patients with midodrine prescription, (**c**) −1.10 vs 0.65, P = 0.053 in KDOQI criteria, and (**d**) −1.30 vs 0.30, P = 0.051 in NADIR criteria.
Notes: *P-value < 0.05.

Effect of Electronic Moxibustion on IDH Frequency and Nursing Intervention

Among the three study periods, there was no significant reduction in the number of IDH frequencies according to the KDOQI and NADIR criteria or the number of sessions that required nursing intervention. (Table 4).

Effect of Electronic Moxibustion on BP

Among the three study periods, there was no significant difference in BP changes due to IR electronic moxibustion (Table 4).

Effect on HD Parameters

Among the three study periods, there were no significant differences in the mean pre- and post-dialysis body weight, dry weight, target ultrafiltration, amount of actual ultrafiltration, dialysis adequacy measured by % target ultrafiltration achieved, and hematologic or biochemical parameters. (Table 5)

Assessment of Adverse Events

Serious adverse events were not observed. One of the patients complained of heat tolerance. Two other 2 patients had local transient erythema and pruritus that subsided within a few hours after moxibustion treatment. None of the patients experienced skin burns during the moxibustion course.

Discussion

This randomized, two-arm crossover trial included 30 patients with IDH. While moxibustion improved the degree of fatigue, it did not affect IDH frequency, BP changes, fatigue recovery time and cold intolerance. The overall baseline VAS score for the degree of fatigue was 4.60 ± 2.95. The average VAS score of the degree of fatigue before Treatment 1 and Treatment 2 was 4.60 and 5.30, respectively. A slight increase in the degree of fatigue was noted after four weeks of Treatment 1. In contrast, a decreasing trend was noted in Treatment 2 during the 4 weeks. This study found that one-hour electronic moxibustion treatment during HD for 4 weeks improved the degree of fatigue in IDH patients (Δ Fatigue Week 0–4 in Treatment 2 = 1.30 ± 2.51 vs Treatment 1 = −0.27±2.59, $p = 0.027$), especially in the subgroup with midodrine prescription (Δ Fatigue Week 0–4 in Treatment 2 = 1.68 ± 2.75 vs Treatment 1 = −0.68 ± 2.85, $p = 0.013$).

Midodrine is the prodrug of the specific alpha 1 adrenergic receptor agonist, desglymidodrine. This metabolite induces constriction of both arterial and venous capacitance vessels, and prevents venous pooling of the blood whilst increasing BP.[35,36] It is now often prescribed to patients and administered before dialysis to lessen the chance of an adverse hypotension event during HD.[37–39] Patients who meet the IDH criteria of the KDOQI and NADIR have a BP drop or nadir BP within a certain range; however, their IDH-associated symptoms may still be tolerable. Clinically, midodrine is often prescribed as the last option for attempting additional volume removal during HD[37] in patients with severe associated symptoms interfering with ultrafiltration. Our study observed that patients on midodrine experienced greater fatigue improvement with moxibustion compared to those not on midodrine. While the improvement in fatigue was statistically significant, there was no corresponding significant change in IDH frequency or BP. The potential reasons for this interaction may be due to sympathetic nervous system modulation, difference in fatigue mechanisms and increased resilience. Midodrine works by increasing peripheral vascular resistance to counteract the drop in BP during dialysis, which is closely tied to autonomic nervous system regulation.[35,40–42] Moxibustion, particularly via its thermal effects[33,43] and potential modulation of the autonomic nervous system,[24] may complement midodrine by reducing the physical and psychological strain associated with dialysis. This synergistic effect might help explain the improved fatigue outcomes in patients on midodrine. While midodrine focuses on BP regulation, it may not directly address the broader range of symptoms contributing to fatigue, such as inflammation, sleep disturbances, or discomfort during dialysis. Moxibustion, known for its potential to promote relaxation and improve energy flow (Qi) according to Traditional Chinese Medicine (TCM), could be addressing these broader fatigue-related mechanisms,[23,26,44] particularly in patients on midodrine, whose overall treatment regimen is more complex. The combination of midodrine and moxibustion may increase patients' resilience to the physical stresses of dialysis. Midodrine helps prevent severe BP drops, while moxibustion might mitigate the subjective feelings of fatigue, leading to an overall sense of well-being, despite the

lack of significant changes in BP or IDH frequency. Clinically, this suggests that while moxibustion alone may not have a strong impact on BP or IDH frequency, its use as an adjunct therapy, particularly in patients on midodrine, could enhance fatigue recovery and improve patient outcomes during dialysis.

While trends in BP changes were observed, they did not reach statistical significance and were consistent with baseline data upon review, suggesting that moxibustion did not impact BP directly in our study. This observation aligns with previous studies[29] on intradialytic hypotension (IDH) adjunct therapies, which also reported limited effects on BP parameters despite improvements in subjective symptoms like fatigue.

In addition, we recognize that our study adds a new perspective on combining moxibustion with midodrine. While prior research, such as Tsai et al[29] demonstrated that herbal acupoint therapy reduced IDH frequency and improved fatigue, it did not specifically address midodrine interactions and utilized narrower IDH criteria (limited to KDOQI). While herbal acupoint therapy may show more effectiveness in reducing IDH frequency, potential drug interactions are a clinical concern, especially considering the common use of multiple medications among HD patients. Our findings suggest that moxibustion, when combined with midodrine, may primarily benefit patients by alleviating fatigue rather than altering BP or IDH frequency.

Shengmai Injection[45] or oral intake of Ginseng[46] may help BP in HD but increases the medication burden and therefore may not be widely accepted by patients and physicians.

A case report by Jung et al[45] found that intradialytic acupuncture decreased IDH frequency in one patient and another study done by Kim et al[47] found acupuncture may be beneficial in HD patients in terms of symptom management. These studies, like moxibustion, may not independently affect BP or IDH frequency but can contribute to patient well-being when used alongside other treatments.

The patients' subjective assessment results showed a significant improvement in the degree of fatigue, but not in the recovery time of fatigue from HD and cold intolerance. TCM categorizes patients with the same disease into different patterns or constitutions, and the major constitution of chronic HD patients is Yang deficiency (up to 43.7%).[48] Nevertheless, the feeling of weakness and chronic fatigue is also highly associated with Qi-deficiency, while preference for warm things is associated with Yang-deficiency.[49] Another study has suggested that Yin-deficiency may also play a role in chronic fatigue.[50] Given the heterogeneity of different TCM constitutions in patients with IDH, the improvement in cold intolerance was not significant in these patients, and further investigations should be conducted.

This study applied electronic moxibustion in the second hour of HD; however, a previous study that explored the behavior of SBP during HD noted a relatively steeper decline in the first quarter of HD, followed by a gentler decrease.[51] This phenomenon seems less likely to be explained by the excessive volume removal during the early period.[21] Therefore, we speculated that electronic moxibustion could be applied before HD to stabilize BP in patients with IDH. To further optimize electronic moxibustion, a decrease in BP during different quarters of HD should be observed to better understand its effect on BP.

To our knowledge, this is the first crossover study to apply electronic moxibustion to patients with IDH. The results showed that electronic moxibustion can improve the severity of IDH-related fatigue, thus contributing to better quality of life and HD treatment adherence. Moreover, electronic moxibustion is generally safe and causes no skin burn injuries, allergic reactions, or hazardous smoke exposure. Compared to frequent nursing interventions which puts a burden on healthcare or additional TCM consultation fee and charges (about 360–400 USD per month treatment), the price is about 45–75 USD per device and easy to instruct patients to use by themself. The feeling of heat intolerance can be alleviated by slightly moving the device up and down the Conception Vessel, although most patient feel comfortable using this warm device.

However, our study had some limitations. First, only 30 patients were recruited for this preliminary study, which may affect the study's power and further large-scale clinical trials are warranted. Second, due to the crossover design, patient blinding was not feasible and may have potential bias when assessing questionnaires. Third, the inclusion criteria for IDH were broad, and this heterogeneity made it more difficult for trials to achieve significant stabilization of BP and decrease in IDH frequency during HD. Fourth, most patients with IDH have multiple comorbidities, and our study patients were no exception. Three patients were hospitalized during the trial due to gastrointestinal bleeding, bacteremia suspected of

arteriovenous graft infection, and ventricular tachycardia. The other two patients had emergency visits due to vascular access malfunction. All of these factors reflect the clinical instability and heterogeneity of patients with IDH.

Conclusions

We conclude that our thermostatic electronic moxibustion is safe and beneficial in improving fatigue in patients with IDH. Electronic moxibustion is more effective than harmful; hence, this cost effective and easy-to-use device is worth promoting in HD units. Our results may also provide novel concepts for designing further studies that aim to optimize the intervention timing and narrow specific IDH patient groups such as those with midodrine prescription to evaluate the efficacy of electronic moxibustion in stabilizing BP.

Abbreviations

IDH, intradialytic hypotension; HD, hemodialysis; BP, blood pressure; TCM, traditional Chinese medicine; IR, infrared; SBP, systolic blood pressure; MAP, mean arterial pressure; KDOQI, Kidney Disease Outcomes Quality Initiative; VAS, Visual Analogue Scale; DBP, diastolic blood pressure.

Data Sharing Statement

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

Ethics Approval and Informed Consent

This study was conducted according to the principles of Declaration of Helsinki and good clinical practice guidelines. Prior to the commencement of the study, ethical approval was obtained from the Institutional Review Board of the Chang Gung Medical Foundation (IRB no. 201801853A3). All methods were performed in accordance with the relevant guidelines and regulations. All the participants provided written informed consent.

Acknowledgments

The authors would like to thank the dialysis staff at the hemodialysis center in Keelung Chang Gung Memorial Hospital for their excellent technical assistance and all participants who completed the study protocol.

Funding

This study did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure

The authors declare that they have no competing interests.

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