Received: 25 October 2023 | Revised: 20 December 2023 | Accepted: 27 December 2023

DOI: 10.1111/1744-9987.14107

ORIGINAL ARTICLE

Therapeutic Apheresis and Dialysis

WILEY

The efficacy and safety of ivabradine hydrochloride in hemodialysis patients with chronic heart failure

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Abstract

Introduction: There is little evidence for ivabradine hydrochloride in patients undergoing hemodialysis.

Methods: In this open-label prospective interventional trial of hemodialysis patients with chronic heart failure, during 12 weeks of treatment, changes in Heart rate (HR), frequency of dialysis-related hypotension were examined, and we investigated health-related quality of life (HR-QOL) and adverse effects.

Results: 18 patients from 6 facilities were enrolled in the study. HR significantly decreased over time, from 87 ± 12.61/min at baseline to 75.85 ± 8.91/min ($p = 0.0003$), and systolic blood pressure also increased significantly ($p < 0.0001$). The frequency of dialysis-related hypotension was markedly reduced ($p = 0.0001$). The HR-QOL survey showed significant improvements in Social Functioning among others ($p = 0.0178$). No specific adverse events occurred.

Conclusion: Ivabradine hydrochloride improved dialysis-related hypotension. Furthermore, the HR-QOL improvement effect were suggested. These results demonstrated the safety and effectiveness of ivabradine hydrochloride.

KEYWORDS

dialysis-related hypotension, heart failure, heart rate, hemodialysis, ivabradine hydrochloride

1 | INTRODUCTION

In patients undergoing hemodialysis, heart failure is an important prognostic factor; in Japan, it is the leading cause of death among such patients. According to a 2021 survey by the Japanese Society for Dialysis Therapy, 22.4% of deaths in patients undergoing chronic hemodialysis were attributed to heart failure [1]. A previous report has shown a negative correlation between the prognosis of chronic heart failure and resting heart rate (HR) [2]; resting HR and cardiovascular events are correlated [3, 4]. Therefore, controlling HR is an important issue in treating chronic heart failure in patients undergoing hemodialysis. However, patients undergoing hemodialysis complicated by chronic heart failure often suffer from dialysis-related hypotension [5], thereby performing adequate treatment with β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II-receptor antagonists becomes impossible, which poses a problem. Additionally, dialysis-related hypotension makes it difficult to

maintain an appropriate dry weight (DW) by water removal, leading to worsened heart failure control [6].

Ivabradine hydrochloride is a hyperpolarization-activated cyclic nucleotide-gated channel (HCN) blocker with the effect of blocking HCN channels [7]. It is known to inhibit HCN4 channels, which are responsible for generating hyperpolarization-activated cation and pacemaker currents in the sinus node, delaying rise time in the diastolic depolarization phase of action potentials and lowering HR. In February 2012, chronic heart failure was approved as an indication of ivabradine hydrochloride in Europe based on the Systolic Heart failure treatment with the *If* inhibitor ivabradine Trial (SHIFT) study results [8], and in Japan, it was approved based on the Japanese-SHIFT (J-SHIFT) study in September 2019 [9].

However, there is still no study verifying the safety and effectiveness of ivabradine hydrochloride in patients undergoing hemodialysis. The dose of β-blockers cannot be adequately increased in patients undergoing hemodialysis due to dialysis-related hypotension. However, despite the complications of chronic heart failure, ivabradine hydrochloride, which reduces only HR without negative inotropic effects, may be an effective drug for treating heart failure. Therefore, we designed this study to prove that ivabradine hydrochloride reduces resting HR and suppresses the onset of dialysis-related hypotension in patients undergoing hemodialysis complicated with chronic heart failure.

2 | METHODS

2.1 | Study design and population

This is an open-label prospective intervention trial conducted across multiple centers, and a single-group exploratory study using before-and-after comparison. The study patients were those in sinus rhythm with a resting HR of 75 beats/min or higher despite standard heart failure treatment including β-blockers, among patients undergoing hemodialysis complicated with chronic heart failure. Patients aged 20 years or older undergoing hemodialysis for 12 months or more at the time of consent acquisition were recruited as subjects. In addition, the exclusion criteria were as follows.

1. Patients with a history of hypersensitivity to ivabradine hydrochloride.
2. Patients with unstable or acute heart failure.
3. Patients with cardiogenic shock.
4. Patients with severe hypotension (systolic blood pressure below 90 mmHg, diastolic blood pressure below 50 mmHg).
5. Patients with atrial fibrillation.
6. Patients with sick sinus syndrome, sinoatrial block, or third-degree atrioventricular block.
7. Patients with severe hepatic dysfunction (Child-Pugh C).
8. Patients under treatment with the following drugs: ritonavir-containing medications, josamycin, itraconazole, clarithromycin, cobicistat-containing medications, indinavir, voriconazole, nelfinavir, saquinavir, and telaprevir.
9. Patients who are pregnant/breastfeeding, may be pregnant, or are planning to become pregnant.
10. Patients who are under oral verapamil and diltiazem treatments.
11. Patients scheduled for surgery during the study period.
12. Patients requiring a legal representative.
13. Other patients deemed unsuitable by the principal investigator.

2.2 | Endpoints

1. Primary endpoint:

Change in resting HR from baseline to 12 weeks after treatment.

2. Secondary endpoint:
    1. Comparison of frequency of dialysis-related hypotension.
    2. Comparison of DW achievement rates.
    3. Change in left ventricular ejection fraction (LVEF) from baseline to 12 weeks.
    4. Change in cerebral (B-type) natriuretic peptide (BNP) and human atrial natriuretic peptide (HANP) from baseline to 12 weeks.
    5. Change in health-related quality of life (HR-QOL) Scale from baseline to 12 weeks using short form-36 (SF36) v2.
    6. Change in cardiac troponin T (TnT) from baseline to 12 weeks.
3. Safety endpoints:
4. Frequency of hypertension during hemodialysis.
5. Frequency of adverse events and diseases.

2.3 | Protocol

Figure 1 shows a schematic of the study protocol. Ivabradine hydrochloride of 2.5 mg was administered orally twice a day after meals. For each administration, the oral dosage was adjusted in stages of 2.5, 5, and 7.5 mg with

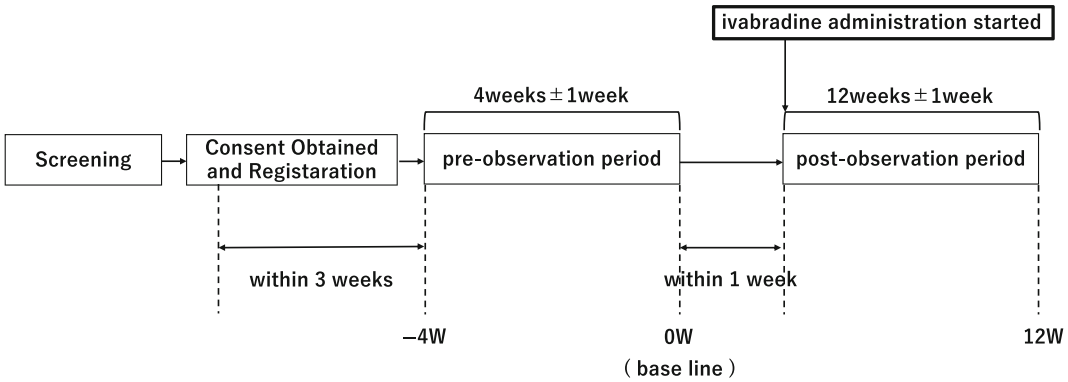

FIGURE 1 Schematic of this study protocol.

an interval of at least 2 weeks to achieve a resting HR of 50–60 beats/min.

Standard therapeutic drugs for chronic heart failure were taken as concomitant medications. The dosage of β-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II-receptor antagonists taken orally at week −4 remained unchanged until the end of the observation period.

Echocardiography, electrocardiogram, chest X-ray imaging, and blood test were performed within 3 weeks after consent acquisition as the −4 week examination (−4 W). Then, the oral administration of ivabradine hydrochloride was started after a 4-week pre-observation period (0 W). After the start of the oral administration of ivabradine hydrochloride, observation was performed every 4 weeks, and examination for the post-observation period was performed after 12 weeks (12 W).

Blood laboratory findings were evaluated for N-terminal prohormone of brain natriuretic peptide (Nt-proBNP), BNP, HANP, and TnT, in addition to biochemical tests and blood counts (Table 2).

In accordance with the Kidney Disease Outcome Quality Initiative/a United States kidney disease guideline [10], dialysis-related hypotension was defined as a decrease of 20 mmHg or higher in systolic blood pressure during dialysis, or 10 mmHg or higher in mean blood pressure accompanied by symptoms that include: abdominal discomfort; yawning; sighing; nausea; vomiting; muscle cramps; restlessness; dizziness or fainting; and anxiety. Dialysis-related hypotension was diagnosed when the decrease in blood pressure fulfilling the above definition occurred at least once in one dialysis session.

In addition, the study evaluated the effect of ivabradine hydrochloride on HR-QOL using SF-36 v2. The patients were requested to complete a self-administered questionnaire regarding Table 3. The scoring was performed using the Japanese SF-36 v2 scoring program recommended by the Institute for Health Outcomes and Process Evaluation Research (iHope International).

2.4 | Statistical analyses

All the laboratory values and scores have been presented as mean ± standard deviation values. The values of $p < 0.05$ were considered statistically significant. The continuous variables were compared using the one-way analysis of variance (ANOVA) and the paired t-test. Fisher's exact test was used for various inter-group comparisons. All the statistical analyses were performed using Prism® software version 10 (GraphPad Software、La Jolla, CA, USA).

3 | RESULTS

3.1 | General information

Eighteen patients from six facilities (Nippon Medical School Hospital, Kidney Clinic of Nippon Medical School, Akihabara Kidney Clinic, Ayase-ekimae Kidney Clinic, Kisen Hospital, and Iidabashi West-Gate Clinic) were enrolled in the study. They consisted of 16 males and two females, with a mean age of 62.78 years. In terms of therapeutic drugs for heart failure taken orally at the time of enrolment, 14 (77.8%) patients were taking β-blockers, 8 (44.4%) were taking angiotensin-converting enzyme inhibitors or angiotensin II-receptor antagonists, and four (22.2%) were taking vasodilators. With regard to underlying diseases, hypertension was confirmed in 13 (72.2%) patients, while type 2 diabetes mellitus was confirmed in 10 patients (55.6%). The detailed results are shown in Table 1.

3.2 | The results of laboratory parameters

Table 2 shows blood test data from the pre-observation period to the end of the post-observation period. Changes in complete blood count, biochemistry, and special blood collection were evaluated. Items with five observation points were tested using the ANOVA test, while items with two points were tested using the paired t-test. However, no significant change was observed in any of the items.

3.3 | The results of chest X-ray examination, electrocardiogram, and transthoracic echocardiography

Then, Table 2 shows the results of chest X-ray examination, electrocardiogram, and transthoracic echocardiography. HR significantly decreased over time, from 87 ± 12.61/min at baseline to 75.85 ± 8.91/min at the end of the observation period ($p = 0.0003$). The actual measurement of HR at the start of dialysis also decreased significantly at all the time points of 4, 8, and 12 weeks after the start of oral ivabradine administration (Figure 2).

The cardiothoracic ratio showed no significant change from baseline ($p = 0.8024$). On the other hand, echocardiography revealed improvement in LVEF, from $50.89 \pm 17.53\%$ before the start of ivabradine to $52.65 \pm 5.89\%$ at the end of the 12-week observation period but no significant difference was found ($p = 0.6104$). Additionally, in the examination of patients with heart failure with reduced ejection fraction (HFrEF) ($n = 4$), a more improved trend was observed ($p = 0.1214$).

3.4 | Changes in blood pressure

Figure 4 shows the changes in systolic blood pressure at the start of dialysis. Systolic blood pressure increased at all the time points of 4, 8, and 12 weeks after the start of oral ivabradine administration ($p < 0.0001$) (Figure 3). However, no significant change was observed in diastolic blood pressure.

Figure 4 shows the comparison of the occurrence frequencies of dialysis-related hypotension. The onset frequencies of dialysis-related hypotension in the 4 weeks of the pre-observation period and 12 weeks of the post-observation period were compared, and it was found that the onset frequency improved significantly ($p = 0.0001$).

3.5 | The results of DW achievement rate

DW achievement rate in pre- and post-observation periods tended to improve, but no significant change was observed ($p = 0.3676$). Additionally, the trend of changes over the entire period was investigated, but similarly, no significant change was found ($p = 0.5447$).

3.6 | The results of HR-QOL survey

Table 3 shows the changes in each item of HR-QOL using SF-36. Improvement was seen in social functioning (SF) in 0–100 points at the end of the observation period ($p = 0.0178$) (Figure 5A). In addition, SF also improved significantly in norm-based scoring, scoring based on national standard values of the subscale of SF-36 ($p = 0.0180$) (Figure 5B). No significant difference was observed in all three component summary scores before and after the oral administration, and $p = 0.1986$ for SF-RCS.

3.7 | Adverse effects

Two patients died during the observation period. One patient was complicated with severe aortic stenosis

TABLE 1 Patient baseline characteristics.

Total, *n*	**18**
Female, *n* (%)	2 (11.1)
Age (years)	62.78 ± 12.33
BMI (kg/m^2)	24.41 ± 4.59
HD Duration (months)	91.33 ± 40.83
Dialysis time (hour/session)	3.75 ± 0.46
HDF, *n* (%)	12 (66.7)
Smoking, *n* (%)	9 (50.0)
β-blocker, *n* (%)	14 (77.8)
RASi, *n* (%)	8 (44.4)
Vasodilator, *n* (%)	4 (22.2)
Primary disease	
DM, *n* (%)	10 (55.6)
Hypertension, *n* (%)	13 (72.2)
CGN, *n* (%)	3 (16.7)
PKD, *n* (%)	2 (11.1)
SLE, *n* (%)	1 (5.6)

Abbreviations: BMI, body mass index; CGN, chronic glomerular nephritis; DM, diabetes mellitus; HD, hemodialysis; HDF, hemodiafiltration; PKD, polycystic kidney disease; RAS, renin-angiotensin system; SLE, systemic lupus erythematosus.

TABLE 2 The results of laboratory parameters, chest X-ray examination, electrocardiogram, and transthoracic echocardiography of patients.

	−4 W	0 W	4 W	8 W	12 W	*p* value
Blood chemistry test						
WBC	7150 ± 3468	7147 ± 4041	7025 ± 4352	7583 ± 4977	8143 ± 5326	0.2941
RBC	365.60 ± 66.70	368.83 ± 61.82	343.58 ± 112.99	386.81 ± 74.87	390.12 ± 88.89	0.2661
Hb	10.91 ± 1.55	10.99 ± 1.72	12.63 ± 7.16	11.41 ± 1.66	11.51 ± 1.97	0.3907
Ht	34.95 ± 5.28	35.15 ± 5.28	34.08 ± 7.19	35.29 ± 8.75	36.76 ± 7.05	0.6441
Plt	28.95 ± 35.15	20.07 ± 8.99	31.74 ± 51.31	19.97 ± 10.90	20.00 ± 8.21	0.4716
TP	6.58 ± 0.51	6.88 ± 0.78	6.74 ± 0.65	6.75 ± 0.47	6.73 ± 0.60	0.2637
Alb	3.55 ± 0.43	3.70 ± 0.37	3.69 ± 0.29	3.70 ± 0.32	3.68 ± 0.35	0.0884
AST	12.83 ± 5.13	14.13 ± 7.40	14.06 ± 9.09	12.13 ± 4.88	12.13 ± 4.81	0.3362
ALT	11.17 ± 6.77	9.94 ± 3.57	10.87 ± 5.08	10.73 ± 5.80	11.25 ± 4.81	0.5761
LDH	205.08 ± 40.89	236.2 ± 56.69	215.12 ± 45.59	224.21 ± 57.20	216.5 ± 43.46	0.1223
γGT	40.00 ± 41.14	25.64 ± 26.74	26.01 ± 32.75	35.00 ± 47.30	34.62 ± 42.52	0.0756
ALP	82.30 ± 32.40	84.33 ± 34.92	86.38 ± 42.20	93.20 ± 43.17	98.75 ± 46.28	0.4385
T-Cho	148.27 ± 39.30	153.90 ± 38.95	158.60 ± 34.15	153.93 ± 34.19	154.87 ± 37.22	0.2701
TG	198.45 ± 170.86	164.64 ± 104.20	179.12 ± 121.61	177.87 ± 134.30	151.47 ± 81.92	0.1453
LDL	71.00 ± 28.40	91.64 ± 31.56	87.25 ± 29.52	81.00 ± 28.97	86.31 ± 37.11	0.4184
HDL	44.55 ± 16.27	48.30 ± 17.17	48.53 ± 19.13	49.86 ± 23.92	47.33 ± 15.53	0.2598
UA	6.30 ± 1.91	6.29 ± 2.34	6.44 ± 2.27	6.36 ± 1.95	6.59 ± 2.11	0.5262
BUN	60.78 ± 17.77	59.64 ± 22.93	60.94 ± 24.03	60.46 ± 19.49	66.41 ± 23.98	0.2175
Cr	11.21 ± 3.63	10.75 ± 3.54	10.75 ± 3.65	10.81 ± 3.08	10.76 ± 3.34	0.2324
Na	137.44 ± 2.01	137.89 ± 2.25	139.35 ± 1.96	138.13 ± 2.89	138.88 ± 1.63	0.0569
K	4.77 ± 0.69	4.80 ± 0.98	4.93 ± 0.82	4.97 ± 0.70	4.99 ± 0.98	0.6042
Cl	100.00 ± 2.77	99.89 ± 3.16	102.00 ± 3.45	101.43 ± 3.98	100.87 ± 3.81	0.0341
BS	114.75 ± 21.41	112.80 ± 53.54	143.76 ± 45.57	123.40 ± 42.02	118.7 ± 44.05	0.1073
Special blood collection						
NT-proBNP	119955 ± 62 644				63 010 ± 55 452	0.3606
BNP	573.77 ± 717.03				269.05 ± 280.05	0.2407
HANP	166.62 ± 194.76				329.97 ± 516.25	0.6019
TnT	0.0748 ± 0.0429				0.0825 ± 0.0393	0.589
X-ray and physiological examinations						
HR	89.56 ± 7.01	87.00 ± 12.61	78.38 ± 13.27	76.27 ± 9.90	75.86 ± 8.91	0.0003
CTR	50.86 ± 5.35	51.56 ± 5.55	50.82 ± 4.65	50.82 ± 4.72	51.09 ± 5.89	0.8024
TTE						
LVEF	50.89 ± 17.53				52.65 ± 16.79	0.6104
LVDd	51.46 ± 6.95				49.68 ± 7.79	0.2635
LVDs	37.92 ± 9.98				36.07 ± 10.04	0.2745
E/A Ratio	1.1886 ± 1.1425				1.00 ± 0.8452	0.9982
E/e	11.455 ± 7.558				13.824 ± 7.051	0.057

Abbreviations: γGT, γ glutamic pyruvic transaminase; ALB, albumin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BNP, brain natriuretic peptide; BS, blood sugar; BUN, blood urea nitrogen; Cl, chloride; Cr, creatinine; CTR, cardiothoracic ratio; E/A, early diastolic inflow velocity waveform/Atrial systolic inflow velocity waveform; E/e(ave), Early diastolic wave/atrial systolic wave; HANP, human atrial natriuretic peptide; Hb, hemoglobin; HDL, high-density lipoprotein cholesterol; HR, heart rate; Ht, hematocrit; K, potassium; LDH, lactate dehydrogenase; LDL, low-density lipoprotein cholesterol; LVDd, left ventricular end-diastolic diameter; LVDs, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; Na, sodium; Nt-proBNP, N-terminal prohormone of brain natriuretic peptide; Plt, platelet count; RBC, red blood cell count; T-Cho, total cholesterol; TG, triglyceride; TnT, Troponin T; TP, total protein; TTE, transthoracic echocardiography; UA, uric acid; WBC, white blood cell count.

TABLE 3 Scoring results of SF-36.

	−4 W	12 W	*p* value
PF	55.58 ± 32.59	57.94 ± 28.50	0.6175
RP	71.71 ± 27.33	71.71 ± 27.68	>0.9999
BP	63.058 ± 20.83	63.64 ± 28.72	0.9144
GH	39.94 ± 14.45	41.64 ± 11.72	0.5853
VT	51.48 ± 17.74	50.39 ± 11.72	0.8227
SF	67.64 ± 27.62	77.94 ± 27.07	0.0178
RE	76.96 ± 28.80	75.98 ± 27.07	0.8344
MH	63.23 ± 19.60	68.52 ± 21.41	0.2004
PF_N	32.88 ± 17.79	34.16 ± 15.54	0.6182
RP_N	43.61 ± 12.64	43.62 ± 12.80	0.9981
BP_N	44.31 ± 9.45	44.59 ± 13.04	0.9113
GH_N	40.47 ± 7.46	41.38 ± 6.04	0.5749
VT_N	47.51 ± 8.64	46.96 ± 10.00	0.8179
SF_N	43.14 ± 12.41	47.76 ± 12.16	0.018
RE_N	46.52 ± 12.83	46.08 ± 11.95	0.8308
MH_N	48.60 ± 9.90	51.25 ± 10.81	0.2022
3PCS	33.17 ± 13.46	35.10 ± 11.53	0.2305
3MCS	49.78 ± 8.69	50.55 ± 8.98	0.6879
3RCS	51.81 ± 13.88	49.04 ± 11.89	0.1986

Abbreviations: BP, bodily pain; GH, general health; MCS, mental component summary; MH, mental health; _N, Norm-based Scoring; PCS, physical component summary; PF, physical functioning; RCS, and role-social component score; RE, role emotional; RP, role limitations due to physical health; SF, social functioning; VT, vitality.

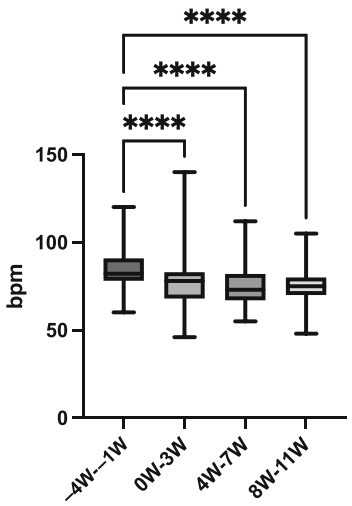

FIGURE 2 Change in HR at the start of dialysis session. bpm, beats per minute; HR, heart rate.

(AS) and lung disease and died suddenly due to AS during the observation period. The other patient suffered from sudden unexplained death.

Not a single adverse event attributable to oral administration of ibabradine hydrochloride, such as

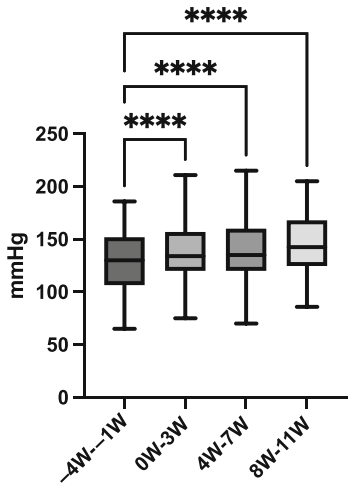

FIGURE 3 Changes in systolic blood pressure at the start of dialysis.

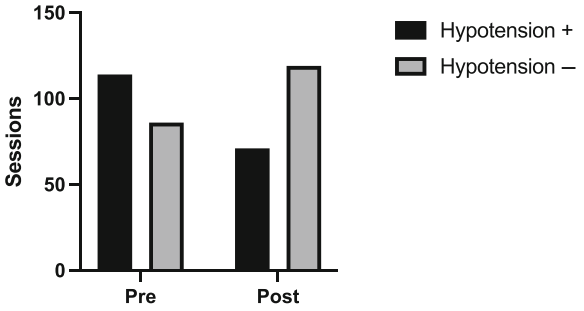

FIGURE 4 Comparison of the occurrence frequencies of dialysis-related hypotension.

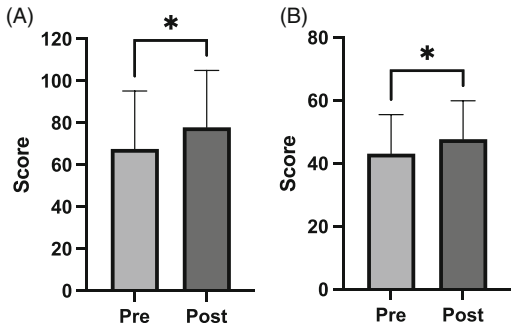

FIGURE 5 Changes in SF and SF_N score in 0–100 points (A: SF, B: SF_N). _N, Norm-based scoring; SF, social functioning.

hypertension, bradycardia, atrial fibrillation, or blurred vision, was observed during the observation period.

4 | DISCUSSION

To date, no clinical study has examined the experience of using ivabradine hydrochloride on patients undergoing hemodialysis, and this study is the first of its kind.

This study prospectively examined at other facilities whether combining ivabradine hydrochloride with existing standard treatment in patients undergoing hemodialysis complicated with chronic heart failure lowers HR and its potential to improve the associated dialysis-related hypotension. In addition, it was also investigated whether there were findings suggesting improvement in the QOL of patients undergoing dialysis with chronic heart failure. The results of this study could be useful evidence when deciding treatment policies for patients undergoing hemodialysis complicated with chronic heart failure.

4.1 | HR-lowering effect of ivabradine

Firstly, as in studies targeting patients not undergoing dialysis, this study showed that orally administering ivabradine hydrochloride to patients undergoing hemodialysis had the effect of lowering HR. During the observation period in this study, no patient developed atrial fibrillation or severe bradycardia, suggesting that the effectiveness and safety of ivabradine hydrochloride are also maintained in patients undergoing hemodialysis. In previous studies to date, lowering HR with β-blockers is known to contribute to a decrease in mortality rate in patients with chronic heart failure [2, 4], and similarly controlling resting HR with β-blockers has been shown to also reduce mortality rate in patients undergoing hemodialysis complicated by chronic heart failure [11, 12]. In dialysis patients with chronic heart failure, HR reduction is also an important goal in controlling chronic heart failure. A large-scale study on ivabradine hydrochloride has shown that administering ivabradine to patients with HFrEF reduces cardiovascular death and hospitalization due to heart failure [8, 9]. Ivabradine hydrochloride has shown efficacy as an additional treatment for patients whose HR is difficult to control with existing heart failure medications. Ivabradine hydrochloride is mostly metabolized by CYP3A4, with a urinary excretion rate of less than 20% [13]. A sub-analysis of large studies of ivabradine hydrochloride with and without renal dysfunction showed that the effect of ivabradine on HR reduction was similar in patients with renal dysfunction (eGFR<60), as was the incidence of adverse drug reactions [14]. With a dialysis rate of approximately 10%, it is considered possible to administer the same dose to dialysis patients as to patients with normal renal function. Several case reports on the introduction of ivabradine in hemodialysis patients have shown that it can be safely administered at normal doses [15, 16]. The results of this study suggest that ivabradine can be used safely in hemodialysis patients as well as in patients with chronic kidney disease prior to starting dialysis, showing a reduction in HR.

4.2 | Effects of ivabradine on blood pressure

In this study, blood pressure at the start of dialysis increased after administering ivabradine hydrochloride. The J-SHIFT study, which combined the use of β-blockers and ivabradine hydrochloride on patients with heart failure, showed that systolic blood pressure tended to increase in the ivabradine treatment group, and it has been shown that the mean amount of change increased significantly in the ivabradine group compared to the placebo group [9]. In addition, according to a previous study that evaluated hemodynamic changes caused by ivabradine hydrochloride, the drug increases stroke volume with a decrease in HR [17]. It is thought that the increase in blood pressure following ivabradine introduction in this study is also due to the prolongation of ventricular diastolic filling time by the decrease in HR, thereby increasing stroke volume. HR control is an extremely important factor in treating chronic heart failure, but the characteristic of ivabradine, which lowers only HR without lowering cardiac output, was considered particularly beneficial for patients with dialysis-related hypotension associated with chronic heart failure.

4.3 | Heart function improvement effect of ivabradine

According to a previous study, ivabradine reduces LV end-systolic volume index (LVESVI) and contributes to LVEF improvement, suggesting the possibility of reverse remodeling [18, 19]. In the present study, echocardiography revealed no improvement with a significant difference, but LVEF tended to improve before and after the observation period.

4.4 | Improvement of dialysis-related hypotension

The results of this study showed significant improvement in the occurrence frequency of dialysis-related hypotension. Dialysis-related hypotension is known to be caused by various factors, and the conditions that are more likely to cause dialysis-related hypotension include old age, female, diabetes mellitus, hispanic, long history of dialysis, obesity, high ultrafiltration rate, and large water

removal amount [20]. Compared to patients without dialysis-related hypotension, it is known that patients with frequent onsets of dialysis-related hypotension have a higher mortality rate, a higher frequency of hospitalization, and a longer length of hospital stay. Therefore, preventing dialysis-related hypotension is important in improving the prognosis of patients undergoing dialysis [21, 22]. Midodrine and sertraline have been suggested to be effective as promising drugs for preventing dialysis-related hypotension, but their effects are limited, and they were often found to be ineffective in patients [5, 23, 24]. In addition, these treatments have been reported to be independent risk factors for death in patients undergoing hemodialysis [25].

In patients with heart failure exhibiting tachycardia, in addition to originally reduced cardiac output due to tachycardia, the decrease in preload associated with water removal tends to cause dialysis-related hypotension, and the results of this study showed that ivabradine hydrochloride improved this element by lowering HR and increasing cardiac output.

4.5 | Improvement of QOL

To date, some reports have demonstrated the relationship between heart function and HR-QOL [26, 27]. In this study, improvement was seen in SF using SF-36, which evaluates changes in HR-QOL after the start of oral ivabradine administration. No significant change was observed in physical functioning (PF) and vitality (VT). The correlation between changes in echocardiography and HR-QOL items was investigated, but no item was significantly correlated with LVEF, and only average ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity and BP showed a correlation (data not shown). In addition, it has also been reported that the parameters of echocardiography and the HR-QOL of patients with heart failure are not correlated [28]. The Effect of Carvedilol, Ivabradine or their combination on exercise capacity in patients with Heart Failure (CARVIVA HR) trial has shown that combining ivabradine hydrochloride with β-blockers in patients with HFrEF improves exercise tolerance, compared to the administration of β-blockers alone [29]. This could be because β-blockers have limitations in improving exercise tolerance as they have a dominant negative effect where the sympathetic nerve inhibitory effect is strongly manifested during exercise, while ivabradine has no such limitation. Even though this was a small-scale study, it has been shown that ivabradine may improve exercise tolerance in patients with heart failure with preserved ejection fraction [30]. The improvement of social functioning shown in the present study is thought to be consistent with the results shown in this previous study.

4.6 | Limitations

The largest limitation of this study is the small number of cases. The small sample size may have affected the results obtained and their statistical significance, and should be interpreted with caution.

The number of patients undergoing dialysis with chronic heart failure, for which ivabradine is indicated, was limited. The reasons for the limited indications could be the following:

1. Ivabradine is only indicated for chronic heart failure and cannot be used for mere sinus tachycardia caused by other reasons.
2. It cannot be used for tachycardia of atrial fibrillation.
3. It is only indicated for sinus rhythm and HR of 75 or higher.
4. HR can be controlled to 75 or less in many patients with β-blockers alone.
5. It cannot be used alone as the patient must be receiving standard treatment for chronic heart failure, including β-blockers.

In the future, it is important to accumulate experience in selected cases in which effects can be expected and appropriately used on patients undergoing dialysis. In addition, whether observing the treatment for a longer period contributes to suppressing coronary artery disease, changing LV mass, and improving mortality rate should be evaluated.

5 | CONCLUSION

In conclusion, this study showed that administering ivabradine, in addition to existing standard treatment for heart failure, to patients undergoing hemodialysis complicated by chronic heart failure improved dialysis-related hypotension. Furthermore, findings suggesting the QOL improvement effect were obtained. The results of this study demonstrated the safety and effectiveness of ivabradine hydrochloride and could be useful evidence when deciding treatment policies for patients undergoing hemodialysis complicated by chronic heart failure.

ACKNOWLEDGMENTS

The authors thank all the participants and the staff involved in blood purification therapy at all facilities that participated in this study.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

All data generated and analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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How to cite this article: Kawasaki S, Sakai Y, Harasawa S, Inatsu A, Kubota Y, Hirama A, et al. The efficacy and safety of ivabradine hydrochloride in hemodialysis patients with chronic heart failure. Ther Apher Dial. 2024;28(3):354–63. https://doi.org/10.1111/1744-9987.14107