Nicardipine Versus Nitroglycerin for The Treatment of Hypertensive Acute Heart Failure Syndrome: A Single-Center Observational Study

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Abstract

Background: Nitroglycerin is considered a first-line agent for hypertensive acute heart failure syndromes (AHFS). In this study, we compared the effectiveness of nicardipine and nitroglycerin in patients with hypertensive AHFS.

Methods: We conducted a single-center, retrospective, observational study at the intensive care unit of a Japanese hospital. Patients diagnosed with AHFS and systolic blood pressure exceeding 140 mmHg on arrival between April 2013 and August 2019 were included. The outcomes were the time to optimal blood pressure control, duration of the continuous infusion of anti-hypertensive agents, duration of positive pressure ventilation, need for additional anti-hypertensive agents, length of hospital stay, and body weight changes. Outcomes were compared between the nicardipine and nitroglycerin groups. We also compared these outcomes between the groups after excluding patients who received renal replacement therapy.

Results: Forty-five patients were enrolled (25 and 20 were treated with nitroglycerin and nicardipine, respectively). The nicardipine group had a shorter time to optimal blood pressure control (1.0 [interquartile range, 1.0–3.0] h vs. 0.5 [0.5–1.0] h), shorter duration of the continuous infusion of anti-hypertensive agents (65.5 [32.5–127.5] h vs. 31.0 [18.5–61.0] h), less frequent need for additional anti-hypertensive agents (0 patients vs. 10 patients [40.0%]), and shorter length of hospital stay (19.0 [10.0–33.0] days vs. 8.0 [5.0–12.3] days) than the nitroglycerin group. The duration of positive pressure ventilation and body weight changes were similar between the groups. These outcomes were similar after excluding patients who received renal replacement therapy.

Conclusions: Nicardipine may be more effective than nitroglycerin for treating hypertensive AHFS.

Background

Heart failure is a syndrome caused by structural and/or functional compromise of the circulatory system[1]. Even with advanced medical treatments in the modern era, the morbidity and mortality of heart failure remain high[2–4], making this condition a significant burden among the global elderly population[4, 5].

Acute heart failure syndromes (AHFS) are life-threatening conditions associated with rapidly deteriorating dyspnea. The pathophysiology of AHFS involves intravascular fluid accumulation and/or excessive fluid influx into the central vasculature that is sometimes associated with sympathoadrenal system activation[6] termed “central volume shift,” followed by rapid elevation in left ventricular filling pressure, leading to increased hydrostatic pressure in pulmonary capillaries and severe pulmonary edema[7]. Once pulmonary edema occurs, the respiratory function of patients is severely decreased, thereby necessitating urgent or emergency medical interventions[8, 9]. AHFS have been categorized according to several aspects, including the duration (acute vs. chronic), preservation of ejection function (yes vs. no), and affected side of the heart (left vs. right). In addition, Mebazaa et al. suggested a classification of AHFS consisting of five clinical scenarios covering systolic blood pressure (SBP), right heart failure, and acute
coronary syndromes[10]. Because of its simplicity, this categorization of AHFS is useful for clinicians who treat patients in an emergency setting. This report recommended nitrates, including nitroglycerin, as the main agents for treating patients with hypertensive AHFS.

Nitrates induce vascular smooth muscle cells to generate nitric oxide, which stimulates guanylate cyclase, resulting in the relaxation of smooth muscles. Low-dose nitrates mainly act on venous vessels, and more specifically, they dilate venous beds and reduce preload. Through this effect, nitrates are expected to relieve the central volume shift and subsequently alleviate pulmonary edema[11]. In particular, nitroglycerin acts on coronary arteries at high doses, making it the preferred treatment for AHFS associated with myocardial ischemia[12]. Therefore, nitroglycerin is recommended as a first-line agent for AHFS in patients with coexisting hypertension in several guidelines[1, 13]. However, in a systemic review of nitrates in the treatment of AHFS, Wakai et al. concluded that nitrates were not more effective than other therapies in terms of symptom relief and hemodynamic variables, although high-quality studies were not included in this review[14]. Therefore, therapies for patients with AHFS vary by region because the effectiveness of nitrates has not been sufficiently established[15–18].

Nicardipine belongs to the dihydropyridine class of calcium channel blockers. Because nicardipine acts quickly and safely, it is often used to treat hypertensive emergencies and postoperative hypertension[19–22]. Nicardipine mainly induces arterial relaxation, resulting in decreased blood pressure[23, 24]. Thus, nicardipine has been used to treat AHFS[19, 25] and relieve symptoms by reducing afterload in patients with hypertensive AHFS.

However, there is limited information regarding the effectiveness of nicardipine in patients with hypertensive AHFS. Furthermore, nicardipine and nitroglycerin have not been compared regarding efficacy. Thus, we conducted a retrospective observational study to compare the effectiveness of nicardipine and nitroglycerin for patients with hypertensive AHFS.

**Methods**

This was a single-center, retrospective, observational study conducted at the intensive care unit of an academic hospital in Japan. Patients diagnosed with AHFS and SBP > 140 mmHg on arrival at the emergency room of the University of Miyazaki Hospital from April 2013 to August 2019 were included. AHFS were diagnosed according to the Framingham criteria[26]. We excluded patients with acute coronary syndrome, those who did not continuously receive anti-hypertensive agents (nitroglycerin or nicardipine), those admitted to other departments, and those who refused to participate.

We collected baseline information regarding age, sex, SBP, and heart rate on arrival, hemodialysis among patients with end-stage renal failure, medical history, medication usage, laboratory variables (serum hemoglobin, serum creatinine, serum sodium, cardiac troponin T), and cardiac ultrasonography (left ventricular ejection fraction). We investigated treatments after admission, the maximum dose of anti-hypertensive agents, concomitant treatments (diuretics, human atrial natriuretic peptide [hANP], nitroglycerin sublingual spray, intravenous nicardipine), positive pressure ventilation, and the use of renal
replacement therapy. Outcome measures were defined as follows: i) length of hospital stay, ii) time to optimal SBP control (SBP decrease by 20% from the initial SBP [1]) without increasing the nitroglycerin or nicardipine dose (blood pressure control time), iii) duration of the continuous infusion of antihypertensive agents, iv) additional administration of the opposite anti-hypertensive agent (use of nicardipine in the nitroglycerin group or vice versa), v) duration of positive pressure ventilation (including non-invasive positive pressure ventilation), and vi) body weight changes. We compared these outcomes between the nicardipine and nitroglycerin groups. We also compared these outcomes between the groups after excluding patients who received renal replacement therapy.

Statistical analysis was performed using SPSS software, version 23 (IBM Corporation, Armonk, NY, USA). Data are presented as the mean and standard deviation (SD) for normally distributed variables and as the median and interquartile range (IQR) for other variables. Student's t-test was used for comparisons of normally distributed data; otherwise, the Mann–Whitney U test was used. We used the $\chi^2$ test and Fisher's exact test for comparisons of all categorical variables. Statistical significance was defined as an alpha value of less than 5% for all analyses.

Targeted patients were notified of the purpose of the study, and only patients who did not request to be excluded were included in the analyses. This study protocol was approved by the University of Miyazaki Hospital's ethics committee (O-0646).

**Results**

This study included 47 patients who visited the hospital during the study period. We excluded two patients (one with acute coronary syndrome and one who was hospitalized in another department), and the remaining 45 patients (25 patients in the nitroglycerin group and 20 patients in the nicardipine group) were included. Overall, the mean age was 75.8 ± 13.1 years, and 25 (55.6%) patients were men. In total, six (13.3%) patients received hemodialysis for end-stage renal failure, and the mean SBP on arrival was 202.0 ± 32.3 mmHg. No patients died in the hospital.

The SBP (208.6 ± 34.5 mmHg vs. 193.0 ± 27.9 mmHg, $p = 0.12$) and heart rate on arrival (115.4 ± 25.4 beats/min vs. 105.7 ± 17.0 beats/min, $p = 0.15$) were higher in the nitroglycerin group than in the nicardipine group, albeit without statistical significance. Regarding laboratory variables (serum hemoglobin, serum creatinine, serum sodium serum) on arrival, serum hemoglobin levels were higher in the nitroglycerin group than in the nicardipine group (12.7 ± 2.2 g/dL vs. 10.5 ± 2.0 g/dL, $p < 0.01$), whereas serum creatinine, serum sodium, and cardiac troponin T levels were similar between the two groups (Table 1). Additionally, no differences were noted in baseline characteristics between the two groups regarding age, sex, the use of renal replacement therapy, medication usage, and medical history (Table 1). Table 2 presents the treatments after admission. The maximum dose was 0.68 ± 0.37 µg/kg/min for nitroglycerin and 3.25 ± 1.25 µg/kg/min for nicardipine. There were no differences between the groups in the proportion of patients who received positive pressure ventilation, renal replacement therapy, and concomitant treatments (diuretics, hANP). Nitroglycerin spray was used only in
the nitroglycerin group (20%). Intravenous nicardipine was more frequently used in the nicardipine group than in the nitroglycerin group (14 [56.0%] vs. 17 [85.0%), p < 0.05, Table 2).
Table 1
Baseline characteristics of the patients

| Characteristics on admission | All patients (N = 45) | Excluding patients on renal replacement therapy (N = 39) | p value | All patients (N = 45) | Excluding patients on renal replacement therapy (N = 39) | p value |
|-----------------------------|-----------------------|--------------------------------------------------------|---------|-----------------------|--------------------------------------------------------|---------|
| Age, median (IQR), years    | 76.0 (69.0–82.0)      | 79.4 (67.8–87.0)                                      | 0.17    | 76.0 (69.0–81.5)      | 85.0 (75.8–91.2)                                      | 0.02    |
| Male sex, no. (%)           | 14 (56.0%)            | 11 (55.0%)                                            | 0.95†   | 12 (52.2%)            | 8 (50.0%)                                             | 0.89†   |
| Systolic blood pressure, mean ± SD, mmHg | 208.6 ± 34.5 | 193.0 ± 27.9                                          | 0.12¶   | 207.9 ± 32.6          | 196.1 ± 29.7                                          | 0.26¶   |
| Heart rate, mean ± SD, beats/min | 115.4 ± 25.4 | 105.7 ± 17.0                                          | 0.15¶   | 117.0 ± 25.9          | 104.1 ± 17.6                                          | 0.09¶   |
| Laboratory values           |                       |                                                       |         |                       |                                                       |         |
| Serum hemoglobin, mean ± SD, g/dL | 12.7 ± 2.2 | 10.5 ± 2.0                                            | < 0.01¶ | 12.9 ± 2.2            | 10.8 ± 1.6                                            | < 0.01¶ |
| Serum creatinine, median (IQR), mg/dL | 1.01 (0.82–1.64) | 1.62 (1.04–7.17)                                      | 0.08    | 0.96                  | 1.24                                                  | 0.19    |
| Serum sodium, median (IQR), mmol/L | 140 (137–142) | 140 (137–142)                                         | 0.84    | 140                   | 141                                                   | 0.88    |
| Troponin T, median (IQR), ng/mL | 0.06 (0.03–0.07) | 0.07 (0.04–0.09)                                      | 0.18    | 0.05                  | 0.07                                                 | 0.18    |
| Cardiac ultrasononography   |                       |                                                       |         |                       |                                                       |         |
| Left ventricular ejection fraction (%) | (N = 22) | (N = 15)                                              | 0.24    | (N = 20)              | (N = 11)                                              | 0.20    |
| Reduced ejection fraction (≤ 40) | 8 (36.4%) | 3 (20.0%)                                             |         | 8 (40.0%)             | 2 (18.2%)                                             |         |
| Condition                              | All patients (N = 45) | Excluding patients on renal replacement therapy (N = 39) | p-value |
|---------------------------------------|-----------------------|--------------------------------------------------------|---------|
| Chronic heart failure, no. (%)        | 4 (16.0%)             | 4 (17.4%)                                              | 0.45    |
|                                       | 2 (10.0%)             | 2 (12.5%)                                              |         |
| Diabetes, no. (%)                     | 13 (52.0%)            | 11 (47.8%)                                             | 0.64†   |
|                                       | 9 (45.0%)             | 6 (37.5%)                                              |         |
| Hypertension, no. (%)                 | 19 (76.0%)            | 17 (73.9%)                                             | 0.36    |
|                                       | 17 (85.0%)            | 13 (81.3%)                                             |         |
| Hyperlipidemia, no. (%)               | 6 (24.0%)             | 6 (26.1%)                                              | 0.60    |
|                                       | 5 (25.0%)             | 2 (12.5%)                                              |         |
| Atrial fibrillation, no. (%)          | 2 (8.0%)              | 2 (8.7%)                                               | 0.30    |
|                                       |                       | 0                                                       |         |
| Renal failure, no. (%)                | 7 (28.0%)             | 5 (21.7%)                                              | 0.80†   |
|                                       | 6 (30.0%)             | 2 (12.5%)                                              |         |
| Ischemic heart disease, no. (%)       | 3 (12.0%)             | 3 (13.0%)                                              | 0.13    |
|                                       | 6 (30.0%)             | 5 (31.3%)                                              |         |
| Cancer, no. (%)                       | 2 (8.0%)              | 2 (8.7%)                                               | 0.30    |
|                                       |                       | 0                                                       |         |
| Cerebral vascular disease, no. (%)    | 1 (4.0%)              | 1 (4.3%)                                               | 0.42    |
|                                       | 2 (10.0%)             | 2 (12.5%)                                              |         |
| Medications on admission              |                       |                                                       |         |
| ACE-I, no. (%)                        | 1 (4.0%)              | 1 (4.3%)                                               | 0.42    |
|                                       | 2 (10.0%)             | 2 (12.5%)                                              |         |
| ARB, no. (%)                          | 11 (44.0%)            | 10 (43.5%)                                             | 0.69†   |
|                                       | 10 (50.0%)            | 6 (37.5%)                                              |         |
| Amlodipine, no. (%)                   | 4 (16.0%)             | 3 (13.0%)                                              | 0.13    |
|                                       | 7 (35.0%)             | 5 (31.3%)                                              |         |
| Aldosterone antagonist, no. (%)       | 3 (12.0%)             | 3 (13.0%)                                              | 0.55    |
|                                       | 3 (15.0%)             | 3 (18.8%)                                              |         |
| Beta-blocker, no. (%)                 | 4 (16.0%)             | 3 (13.0%)                                              | 0.35    |
|                                       | 5 (25.0%)             | 5 (31.3%)                                              |         |
| Loop diuretic, no. (%)                | 10 (40.0%)            | 9 (39.1%)                                              | 0.29†   |
|                                       | 5 (25.0%)             | 5 (31.3%)                                              |         |
| Digoxin, no. (%)                      | 1 (4.0%)              | 1 (4.3%)                                               | 0.56    |
|                                       | 0                     | 0                                                       |         |
| Aspirin, no. (%)                      | 5 (20.0%)             | 5 (21.7%)                                              | 0.48    |
|                                       | 5 (25.0%)             | 4 (25.0%)                                              |         |
| Anti-arrhythmic, no. (%)              | 3 (12.0%)             | 2 (8.7%)                                               | 0.39    |
|                                       | 1 (5.0%)              | 0                                                       |         |
| Statin, no. (%)                       | 6 (24.0%)             | 6 (26.1%)                                              | 0.52    |
|                                       | 4 (20.0%)             | 1 (6.3%)                                               |         |
| Warfarin, no. (%)                     | 2 (8.0%)              | 2 (8.7%)                                               | 0.30    |
|                                       |                       | 0                                                       |         |
All patients
(N = 45)

Excluding patients on renal replacement therapy
(N = 39)

| Variable                  | Nitroglycerin (N = 25) | Nicardipine (N = 20) | p value | Nitroglycerin (N = 23) | Nicardipine (N = 16) | p value |
|---------------------------|-----------------------|----------------------|---------|-----------------------|----------------------|---------|
| Maximum dose (µg/kg/min)  | 0.68 ± 0.37           | 3.25 ± 1.25          | -       | 0.61 (0.35–0.87)      | 3.00 ± 1.16          | -       |
| Nitroglycerin spray (%)   | 5 (20.0%)             | 0                    | < 0.05  | 5 (21.7%)             | 0                     | 0.06    |
| Nicardipine IV (%)        | 14 (56.0%)            | 17 (85.0%)           | < 0.05† | 13 (56.5%)            | 14 (87.5%)           | < 0.05† |
| PPV (%)                   | 18 (72.0%)            | 17 (85.0%)           | 0.25    | 16 (69.6%)            | 13 (81.3%)           | 0.33    |
| Diuretics (%)             | 9 (36.0%)             | 9 (45.0%)            | 0.54†   | 9 (39.1%)             | 8 (50.0%)            | 0.50†   |
| hANP (%)                  | 3 (12.0%)             | 1 (5.0%)             | 0.39    | 3 (13.0%)             | 1 (6.3%)             | 0.45    |
| Renal replacement therapy (%) | 2 (8.0%)           | 4 (20.0%)           | 0.23    | -                     | -                    | -       |

Continuous variables are expressed as the mean ± SD for normally distributed variables or median (interquartile range [IQR]) for non-normally distributed variables. Comparisons between groups were performed using the Mann–Whitney U test for continuous variables and Fisher’s exact test for categorical variables unless otherwise indicated.

No patients received direct oral anticoagulants, hydralazine, or nitrates.

ACE-I, angiotensin-converting enzyme antagonist; ARB, angiotensin II receptor blocker

†: χ² test, ¶: Student’s t-test

Table 2
Treatments after admission
Continuous variables are expressed as the mean ± SD for normally distributed variables and median (interquartile range [IQR]) for non-normally distributed variables. Comparisons between groups were performed using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables unless otherwise indicated.

IV, intravenous; PPV, positive pressure ventilation; hANP, human atrial natriuretic peptide

†: $\chi^2$ test

| Variable                                                                 | All patients (N = 45) | Excluding patients on renal replacement therapy (N = 39) |
|--------------------------------------------------------------------------|------------------------|----------------------------------------------------------|
|                                                                          | Nitroglycerin (N = 25) | Nicardipine (N = 20)                                     | Nitroglycerin (N = 23) | Nicardipine (N = 16) |
|                                                                          |                        | p value                                                  |                        | p value |
| BPC time, median (IQR), hour                                            | 1.0 (1.0–3.0)          | 0.5 (0.5–1.0)                                            | 1.0 (1.0–3.5)          | 0.5 (0.5–1.0)        | < 0.01 | < 0.01 |
| PPV time, median (IQR), hour                                            | 30.0 (9.0–50.6)        | 18.5 (11.0–36.0)                                         | 30.0 (11.6–52.6)       | 18.5 (11.0–36.0)     | 0.76   | 0.62   |
| Duration of the continuous infusion anti-hypertensive agents, median (IQR), hour | 65.5 (32.5–127.5)      | 31.0 (18.5–61.0)                                         | 65.5 (33.0–114.3)      | 34.3 (18.5–64.4)     | < 0.05 | < 0.05 |
| Contra, no. (%)                                                         | 10 (40.0%)             | 0%                                                       | 9 (39.1%)              | 0                    | < 0.01 | < 0.01 |
| Length of hospital stay, median (IQR), days                            | 19.0 (10.0–33.0)       | 8.0 (5.0–12.3)                                           | 19.0 (10.0–33.5)       | 7.0 (4.75–12.3)      | < 0.01 | < 0.01 |
| Body weight change, kg                                                  | 5.2 ± 2.9              | 4.5 ± 2.7                                                | 4.2 (2.9–6.2)          | 4.5 (3.3–5.4)        | 0.44¶ | 0.66   |

Continuous variables are expressed as the mean ± SD for normally distributed variables and median (interquartile range [IQR]) for non-normally distributed variables. Comparisons between groups were performed using the Mann–Whitney U test for continuous variables and Fisher's exact test for categorical variables unless otherwise indicated.
Regarding outcomes, the nicardipine group exhibited a shorter time to optimal blood pressure control (1.0 [1.0–3.0] h vs. 0.5 [0.5–1.0] h, p < 0.01) and a shorter duration of the continuous infusion of anti-hypertensive agents (65.5 [32.5–127.5] h vs. 31.0 [18.5–61.0] h, p < 0.05) compared with the nitroglycerin group. There were no differences between the two groups in the duration of positive pressure ventilation (nitroglycerin vs. nicardipine: 30.0 [9.0–50.6] h vs. 18.5 [11.0–36.0] h, p = 0.76). In total, 40.0% of patients in the nitroglycerin group required additional treatment with nicardipine, whereas no patients in the nicardipine group required additional nitroglycerin therapy (p < 0.01). The nicardipine group displayed a shorter length of hospital stay than the nitroglycerin group (19.0 [10.0–33.0] days vs. 8.0 [5.0–12.3] days, p < 0.01) (Fig. 1A). The nicardipine group exhibited a larger change in body weight than the nitroglycerin group (-5.2 ± 2.9 kg vs. -4.5 ± 2.7 kg, p = 0.44), although this difference was not significant.

We performed a subgroup analysis of 39 patients (23 patients in the nitroglycerin group and 16 patients in the nicardipine group) after excluding six patients who received renal replacement therapy. Compared with those in the nicardipine group, patients treated with nitroglycerin tended to be younger (76.0 [69.0–81.5] years vs. 85.0 [75.8–91.2] years, p < 0.05), and they were more likely to be men (12 [52.2%] vs. 8 [50.0%], p = 0.89), albeit without statistical significance. Other baseline characteristics were similar between the two groups (Table 1). Regarding laboratory variables (serum hemoglobin, serum creatinine, serum sodium, serum) on arrival, serum hemoglobin levels were higher in the nitroglycerin group than in the nicardipine group (12.9 ± 2.2 g/dL vs. 10.8 ± 1.6 g/dL, p < 0.05), whereas serum creatinine, serum sodium, and cardiac troponin T levels were similar between the two groups (Table 1). There were no differences between the two groups regarding medication usage and medical history (Table 1). We examined the left ventricular ejection fraction using cardiac ultrasonography for 37 patients. Eleven patients (24.4%) displayed a reduced left ventricular ejection fraction (nitroglycerin [22] vs. nicardipine [15]: 8 [36.4%] vs. 3 [20.0%], p = 0.24, Table 1).

After excluding patients who received renal replacement therapy, the nicardipine group had a shorter time to optimal blood pressure control than the nitroglycerin group (1.0 [1.0–3.5] h vs. 0.5 [0.5–1.0] h, p < 0.01). The nicardipine group also displayed a shorter duration of the continuous infusion of anti-hypertensive agents than the nitroglycerin group (65.5 [33.0–114.3] h vs. 34.3 [18.5–64.4] h, p < 0.05). There was no difference in the duration of positive pressure ventilation between the groups (nitroglycerin vs. nicardipine: 30.0 [11.6–52.6] h vs. 18.5 [11.0–36.0] h, p = 0.62). Moreover, 39.1% of patients in the nitroglycerin group required additional treatment with nicardipine, whereas no patients in the nicardipine group required additional nitroglycerin (p < 0.01). In addition, the nicardipine group exhibited a shorter length of hospital stay than the nitroglycerin group (19.0 [10.0–33.5] days vs. 7.0 [4.8–12.3] days, p < 0.01) (Fig. 1B). No significant difference in body weight change was noted between the groups (nitroglycerin vs. nicardipine: -4.2 [2.9–6.2] kg vs. -4.5 [3.3–5.4] kg, p = 0.66).
Discussion

We conducted a retrospective, observational study comparing the effectiveness of nicardipine and nitroglycerin among patients with hypertensive AHFS. The results demonstrated that compared with nitroglycerin, nicardipine was associated with a shorter time to optimal blood pressure control, a shorter duration of the continuous infusion of anti-hypertensive agents, and a shorter length of hospital stay and did not require adjunctive nitroglycerin administration. After excluding patients receiving renal replacement therapy, the time to optimal blood pressure control, duration of the continuous infusion of anti-hypertensive agents, and length of hospital stay remained shorter in the nicardipine group than in the nitroglycerin group.

Our results indicated that nicardipine is more effective for treating hypertensive AHFS than nitroglycerin. According to the Frank–Starling law, cardiac output is critically dependent on afterload\(^2\). In hypertensive AHFS, excessive fluid influx into a relatively small functional circulatory space causes hypertension\(^6,7\). Theoretically, the treatment goals for hypertensive AHFS include reducing preload by dilating venous beds and reducing afterload via arterial dilation. Our results suggest that nicardipine may resolve the pathological changes earlier than nitroglycerin in patients with hypertensive AHFS. Similar to nicardipine, the calcium channel blocker clevidipine was reported as a novel anti-hypertensive agent for treating hypertensive AHFS\(^25\). Prior research demonstrated that clevidipine more rapidly reduced blood pressure and provided symptom relief than conventional therapies, including nitroglycerin. In this report, nicardipine exhibited similar effects on blood pressure but not symptoms, although only a small number of patients received nicardipine. Calcium channel blockers may be more effective than nitrates for treating hypertensive AHFS. However, further research is needed to clarify which calcium channel blocker is most suitable for the treatment of hypertensive AHFS.

In our study, no patient who received nicardipine required adjunctive anti-hypertensive therapy, compared with 38% of patients in the nitroglycerin group. Because nitroglycerin induces resistance within 1 day\(^2\), this result may reflect resistance to this drug. Although nicardipine induces hypotension and phlebitis as adverse effects, no patients who received nicardipine exhibited these adverse effects in our study. Nicardipine also appears to be more tolerable than nitroglycerin as a continuous anti-hypertensive agent for patients with hypertensive AHFS.

Body weight tended to be reduced to a greater extent in the nicardipine group than in the nitroglycerin group in our study, although this difference was not statistically significant. Nicardipine dilates renal arteries, resulting in increased renal blood flow\(^32,33\). This effect would reduce fluid accumulation in patients with AHFS. Nicardipine acts on coronary arteries to decrease arterial resistance, thereby increasing blood flow and reducing the generation of lactate in the left ventricle\(^33,34\). A similar effect may also be induced by high-dose nitroglycerin. These results provide additional evidence that nicardipine may be more beneficial for the treatment of hypertensive AHFS than nitroglycerin.

Additionally, only six patients (13.3%) had a history of chronic heart failure, whereas 11 patients (24.4%) presented with reduced left ventricular ejection fraction. This finding may indicate that nicardipine would
be more effective for AHFS in patients with preserved ejection fraction than in patients with reduced ejection fraction because vascular failure is the primary cause of heart failure with preserved ejection fraction.

The main limitations of this study included its single-center, retrospective, and observational design. Because of the limited sample size, we cannot definitively conclude that nicardipine is superior to nitroglycerin for treating hypertensive AHFS. Furthermore, half of the patients with acute hypertensive AHFS display reduced left ventricular ejection fraction in general [35], whereas the left ventricular ejection fraction was reduced in only 29.7% of patients in this study. Thus, our results may include potential selection bias. We cannot discuss the long-term effects of nicardipine because this was a short-term study. Thus, further studies are needed to clarify the long-term efficacy of nicardipine, including assessments of the mortality and recurrence of AHFS.

Conclusions

We performed a single-center, retrospective, observational study comparing the effectiveness of nicardipine and nitroglycerin for the treatment of hypertensive AHFS. Nicardipine reduced the time to optimal blood pressure control, duration of the continuous infusion of anti-hypertensive agents, and length of hospital stay compared with the effects of nitroglycerin. No patient who received nicardipine required additional nitroglycerin to control blood pressure. Thus, nicardipine appears to be beneficial for treating hypertensive AHFS.

Abbreviations

AHFS: acute heart failure syndromes, SBP: systolic blood pressure, hANP: human atrial natriuretic peptide, SD: standard deviation, IQR: interquartile range

Declarations

Ethics approval and consent to participate

This study protocol was approved by the University of Miyazaki Hospital’s ethics committee (0-0646). All patients provided informed consent for their participation in this study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets generated and analyzed during the current study are not publicly available because this availability was not included in the study protocol approved by the institutional review board but are available from the corresponding author on reasonable request.
Competing interest

The authors declare that they have no competing interests.

Funding

None.

Authors’ contributions

TK, TA, and HO designed the concept of the study. TK and TA acquired the data. TK and TA analyzed the data. All authors interpreted the data. TK and TA wrote the draft, and TA and HO edited the manuscript. All authors read and approved the final manuscript.

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