Original article

Factors related to the occurrence of phlebitis in acute phase stroke patients receiving intravenous nicardipine hydrochloride as antihypertensive therapy

Yasuko YOKOI, Takako MINAGAWA, Ayako TAMURA

Tokushima University of Graduate School, Institute of Biomedical sciences

Abstract

This study investigated the incidence of phlebitis associated with continuous nicardipine infusion in patients with acute-phase stroke. To identify patient factors related to the occurrence of phlebitis, and considering blood pressure values during nicardipine administration, we retrospectively investigated the nursing and medical records of 301 patients who were hospitalized for stroke. Of these, 92 patients met the inclusion criteria and had data showing whether phlebitis had occurred. We confirmed that phlebitis occurred in 38 patients (41.3%). Factors found to be significantly related to phlebitis onset were Glasgow Coma Scale (GCS)-verbal (V; p = .020) and -motor (M; p = .007), level of consciousness (total GCS score [(p = .009)]), nicardipine administration time (p = .001), nicardipine dose (p = .000), mean nicardipine rate of administration (p = .000), nicardipine dilution rate (p = .000), mean arterial blood pressure at first insertion (p = .030), and difference in the diastolic blood pressure at first insertion (p = .032). Multiple logistic regression analysis indicated that nicardipine administration time (odds ratio: 1.042, 95% confidence interval: 1.023–1.062, p = .000) was a related factor. Results also suggested that a decreased level of consciousness after the stroke onset (V3 or below and M5 or below) is related to phlebitis occurrence. Patients with stroke having a lower level of consciousness (total GCS score of 12 or below), who are being administered continuous nicardipine infusion, may require more frequent and careful infusion management and needle insertion site observation. Because phlebitis onset occurs after 24 h of continuous infusion, peripheral insertion site catheter replacement should be performed within 24 h.

Keyword: stroke, nicardipine, Phlebitis, Factors

Introduction

Hypertension is the most remarkable risk factor common to all types of strokes (Yagita, 2017). The target systolic blood pressure (SBP) following the event depends on the type of stroke. In patients following cerebral infarction, the target for SBP is slightly increased at 220 mmHg. In contrast, the target SBP following a subarachnoid hemorrhage is 160 mmHg or below and that for patients following cerebral hemorrhage is 140 mmHg or below (Stroke Guideline Committee, The Japan Stroke Society, 2017). Intravenous drugs used to rapidly lower blood pressure during the hyperacute phase include nicardipine hydrochloride (nicardipine) and diltiazem, which are both Ca channel antagonists, as well as nitroglycerin, a nitric acid medication. These drugs are generally administered with very low dose intravenous infusions (Taguchi, 2017; Urabe, Shimada,

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& Kawai, 2019, p. 609). Nicardipine can be administered to patients for whom oral ingestion is impossible. Nicardipine has a recognized specific action on the cerebral vascular smooth muscle (Urabe, Shimada, & Kawai, 2019, p. 588), causes little cardiac depression, and can have its dosage easily adjusted (Hypertension Treatment Guideline Preparation Society, The Japanese Society of Hypertension, 2019). It can be used for patients with any type of stroke (Urabe et al., 2019, p. 588). Nicardipine is the first-line agent in approximately 60% of the medical facilities in Japan for patients with cerebral hemorrhage requiring strong hypotensive medication (Koga et al., 2009).

Clinically, patients experience pain, reddening, and induration around the venous catheter insertion site (Matsuda & Takeda, 2006), as well as pain associated with repeated catheter insertions (Rickard et al., 2012) because the rate of occurrence of phlebitis in such patients is high. These complications markedly reduce the patient's quality of life (QOL) and can make it difficult to continue treatment or prolong the hospital stay, warranting adequate measures. In studies that were limited to patients with acute stroke as original reports and research reports, excluding the proceedings, two reports (Narishige et al., 2012; Kawada et al., 2016) examined the cause of phlebitis due to nicardipine administration. In addition, there were three reports (Miyagi, Nishiyama, & Kohamoto, 2010; Nakai, Kawata, Ohta, Yamazaki, & Miyamoto, 2018; Tsuchida et al., 2018) that examined the incidence of phlebitis due to efforts to prevent the development of phlebitis, and there was no sufficient comparison. In particular, SBP must be well controlled in patients with stroke (Stroke Guideline Committee, The Japan Stroke Society, 2017). Despite this, there have been no reports focusing on blood pressure during the use of nicardipine nor any studies referring to the relationship with consciousness.

Therefore, this study focused on phlebitis associated with the continuous infusion of nicardipine in patients with acute-phase stroke. This study aimed to clarify the factors related to the onset of phlebitis in patients with acute stroke, including the circulatory dynamics and consciousness level during nicardipine administration, and to seek suggestions for nursing to improve the patient's QOL by reducing the onset of phlebitis.

Definition of terms

Phlebitis: In this report, phlebitis refers to the appearance of at least one of the following: pain, reddening (rubefaction), swelling, or induration at the needle insertion site for continuous nicardipine infusion, resulting in a nurse determining that replacement is necessary.

Catheter: In this report, the catheter was a peripheral venous catheter used for continuous intravenous administration of nicardipine.

Study Methods

1. Design

Retrospective correlation validation study

2. Subjects

Patients hospitalized at Hospital A for stroke (cerebral infarction, cerebral hemorrhage, subarachnoid hemorrhage) and who underwent hypotensive treatment with nicardipine were included.

1) Exclusion criteria

Patients were excluded who did not have detailed records available on nicardipine administration (start/finish time and dose), were under 40 years or over 90 years of age, were administered nicardipine via a central vein, provided a do not attempt resuscitation order, or did not consent to the study.

2) Discontinuation/dropout criteria

The patients discontinued the study when they (or their legal representative) requested it, they were lost to follow-up because of hospital transfer or for similar reasons, it was determined after beginning the study that the subject was ineligible, or a major deviation from the study protocol was noted, and it was determined that the subject's data could not be evaluated.

3. Nicardipine continuous infusion method used at Hospital A

At Hospital A, nicardipine continuous infusion was performed by inserting a syringe full of undiluted nicardipine into an ultra-low dose continuous infusion pump and administering it through a bypass to the main intravenous

line for physiological saline solution, thereby diluting it within the catheter. The ward staff were instructed to not administer any drugs other than nicardipine through the nicardipine line.

4. Study period

We investigated the nursing records (medical records) of patients hospitalized between February 2018 and March 2019.

5. Study parameters

1) Basic attributes

We gathered data on age, sex, medical history, disease type, treatment method, presence or absence of paralysis, peripheral venous indwelling catheter insertion site, and indwelling needle gauge from the patients' medical records.

2) Determining the presence of phlebitis

Phlebitis was determined to be present if the patient's medical records stated that pain, reddening (rubefaction), swelling, or induration was noted at the insertion site used for continuous nicardipine infusion or when continuous nicardipine infusion ended, and catheter replacement was performed.

3) Parameters considered to possibly be related factors extracted from medical records

Data on the level of consciousness during hospitalization (Glasgow Coma Scale (GCS)), body mass index (BMI), triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, blood glucose, C-reactive protein (CRP), rate of nicardipine administration, main infusion rate of administration, and systolic and diastolic blood pressure (DBP) during continuous nicardipine infusion. We calculated the following parameters using the obtained information: time of administration, dose, and mean administration rate of nicardipine, mean dilution rate of nicardipine in the catheter, mean arterial blood pressure (MAP), and difference in blood pressure.

4) Method of calculating nicardipine administration time, dose, mean rate of administration, and mean dilution rate of nicardipine in the catheter

The nicardipine administration time was cumulatively calculated as the time from initiation of continuous nicardipine after the admission of the patient to the stroke care unit of Hospital A, until administration was stopped. The dose was cumulatively calculated as the dose from starting administration to stopping administration, after converting the hourly continuous nicardipine infusion dose from the set flow rate (ml/h) of the ultra-low dose infusion pump. The mean administration rate was obtained by dividing the cumulative doses of nicardipine administered intravenously for 1 h, which is converted from the set flow rate (ml/h) of a micro-volumetric infusion pump, by the time of nicardipine administration. The mean dilution rate of nicardipine in the catheter was calculated per hour (main route set flow rate (ml/h) + nicardipine set flow rate (ml/h)) / nicardipine set flow rate (ml/h), and the mean value from starting to stopping administration was calculated.

5) Method of calculating blood pressure and blood pressure differences

The SBP, DBP, and MAP during continuous nicardipine infusion were calculated as the mean blood pressure from starting to stopping administration. MAP was calculated as (SBP – DBP) / 3 + DBP. The differences in the following parameters during the catheter insertion were calculated: the maximum and minimum SBP, the maximum and minimum DBP, and the maximum and minimum MAP.

6. Analysis methods

We tabulated the data on basic attributes as well as the number of times cannulae were replaced and the presence or absence of phlebitis. We then divided the patients into a non-phlebitis group and a phlebitis group and used the Mann–Whitney U test to analyze age, level of consciousness [total GCS score, eye-opening (E), best verbal response (V), best motor response (M)], BMI, triglycerides, HDL-C, LDL-C, blood glucose and CRP, nicardipine administration time, nicardipine dosage, SBP at first insertion, DBP, mean blood pressure, SBP difference at first insertion, DBP difference, mean blood pressure difference. A chi-squared test was used to analyze age, sex, level of consciousness (GCS; total score), history of hypertension, BMI, triglycerides, HDL-C, LDL-C, blood glucose, CRP, and disease type. When 20% or

more of the cells with an expected frequency of less than 5 were present in all cells, analysis was performed using Fisher's exact test. Patients were divided into three groups: a non-phlebitis group, single episode of phlebitis group, and multiple episodes of phlebitis group, and the Kruskal–Wallis test was used to analyze age, level of consciousness (GCS score and E, V, M), BMI, triglycerides, HDL-C, LDL-C, blood glucose, and CRP. In univariate analysis, multiple logistic regression analysis was performed with factors for which a significant difference was noted as the explanatory variables and the presence or absence of phlebitis as the dependent variable. We calculated the odds ratio for phlebitis and the 95% confidence interval (CI). The statistical analysis software used was IBM SPSS statistics Ver. 24, and the level of significance was set at below 5%.

7. Ethical considerations

This study was screened by the Medical Clinical Study Institutional Review Board (IRB) of Tokushima University Hospital (approval no.: 3170). In accordance with the rules of the IRB, by publicly displaying information showing the study purpose, methods, data storage methods, privacy protection, and inquiry point for questions or for refusing participation in the study on the hospital website, we were not required to obtain consent from each subject. If subjects did not agree to participate in the study, their data were excluded from the analysis.

Study subject codes were used for the data so that individuals could not be identified, and the data were stored in a lockable cabinet. Data were completely destroyed after the storage period ended and not used for any purpose other than this study.

Results

A total of 301 patients were hospitalized during the study period. Disease type was cerebral infarction for 181 patients (60.1%), cerebral hemorrhage for 75 patients (24.9%), and subarachnoid hemorrhage for 45 patients (15.0%). Of the 301 patients, 100 patients met the inclusion criteria. Of these, our study included 92 patients from whose medical records we were able to confirm the presence or absence of phlebitis. A total of 179 nicardipine administration catheters were used, with 1–9 catheters used per patient.

1. Outline of study subjects (Table 1), The number of catheter replacements during the onset of phlebitis (Table 2)

The median subject age was 70.5 (61.8–79.0) years. There were 49 men (53.3%) and 43 women (46.7%). The median level of consciousness (total GCS score) was 14 (11–15), and the median BMI was 22.4 (19.8–26.8). A history of hypertension was confirmed in 47 patients (51.1%). Disease type was cerebral infarction in 37 patients (40.2%), cerebral hemorrhage in 38 patients (41.3%), and subarachnoid hemorrhage in 17 patients (18.5%). The most common treatment method was conservative treatment for cerebral infarction (18 cases; 48.6%), as well as for cerebral hemorrhage (33 cases; 86.8%), whereas curative surgery was the most common treatment for subarachnoid hemorrhage (16 cases; 94.1%).

Catheters were replaced 1–8 times, with a median frequency of 2 times. Catheters were replaced once for most patients (15 cases; 39.5%), followed by twice (12 cases; 31.6%).

2. Investigation of phlebitis incidence rates and related factors

1) Phlebitis incidence rate

Of the 179 continuous nicardipine infusion catheters, phlebitis occurred in 70 catheters (39.1%) and did not occur in 109 catheters (60.9%).

2) Comparison of patient backgrounds by the presence/absence of phlebitis onset and frequency (Table 3; Table 4)

Patients were divided into a non-phlebitis group ($n = 54$) and a phlebitis group ($n = 38$), and univariate analysis was performed for each parameter. The items that showed a significant tendency were consciousness level ($p = .033$) and disease type ($p = .006$). The difference in frequency due to adjusted residue was examined for the two items. In the mild group with a consciousness level GCS score of 13–15, the incidence of non-phlebitis was significantly higher (adjusted residue 2.1) and the incidence of phlebitis was significantly lower (adjusted residue −2.1). In the moderate/severe group with a

Table 1. Outline of study subjects

n = 92

	number (%)
Age	
40–49	7 (7.6)
50–59	12 (13.0)
60–69	24 (26.1)
70–79	27 (29.3)
80–89	22 (23.9)
Median [Quartile]	70.5 [61.8-79.0]
Sex	
Male	49 (53.3)
Female	43 (46.7)
Consciousness level GCS (total GCS score)	
Median [Quartile]	14 [11-15]
BMI	
Median [Quartile]	22.4 [19.8-26.8]
Medical history (multiple answers)	
Hypertension	47 (51.1)
Stroke	19 (20.7)
Cardiovascular disease	14 (15.2)
Diabetes	13 (14.1)
None	14 (15.2)
disease type	
Cerebral infarction	37 (40.2)
Cerebral hemorrhage	38 (41.3)
Subarachnoid hemorrhage	17 (18.5)
Treatment method	
Cerebral infarction (*n* = 37)	
Conservative treatment	18 (48.6)
t-PAℓt Endovascular repair	9 (24.3)
Endovascular repair	8 (21.6)
t-PA or Intraarterial urokinase injection	2 (5.4)
Cerebral hemorrhage (*n* = 38)	
Conservative treatment	33 (86.8)
Hematoma removal (endoscopic or open surgery)	5 (13.2)
Subarachnoid hemorrhage (*n* = 17)	
Curative surgery (Endovascular repair and Craniotomy)	16 (94.1)
Elective treatment	1 (5.9)

Table 2. The number of catheter replacement during the onset of phlebitis

n = 38

Catheter replacement count	Cases (%)
1 time	15 (39.5)
2 times	12 (31.6)
3 times	4 (10.5)
4 times	5 (13.2)
5 times	0 (0.0)
6 times	0 (0.0)
7 times	1 (2.6)
8 times	1 (2.6)

consciousness level GCS total score of 12 or less, phlebitis was significantly more common (adjusted residue 2.1) and non-phlebitis was not significantly developed (adjusted residue –2.1). By type of disease, cerebral infarction was significantly more common in non-phlebitis (adjusted residue 3.1) and significantly less in phlebitis (adjusted residue –3.1). There was no difference in frequency between cerebral hemorrhage and subarachnoid hemorrhage. No significant differences were noted for age, sex, history of hypertension, BMI, triglycerides, HDL-C, LDL-C, blood glucose, or CRP. Comparison of phlebitis incidence rates revealed significant differences for level of consciousness [GCS (V) and (M), and total score; $p = .020$, $p = .007$, $p = .009$].

3) Nicardipine usage status and blood pressure status by phlebitis frequency (Table 5)

The median total nicardipine administration time was 62.2 (42.9–92.4) h in the phlebitis group, which was significantly longer than for the non-phlebitis group, which was 9.3 (4.7–25.2) h ($p = .000$). The median nicardipine dose was 248.8 (142.0–501.9) ml in the phlebitis group, which was significantly higher than in the non-phlebitis group at 90.8 (57.4–131.8) ml ($p = .000$). The MAP at first insertion had a median of 95.4 (90.1–100.8) mmHg in the phlebitis onset group, which was significantly lower than the median value of the group without the onset of phlebitis (100.4: 94.1–107.9 mmHg) ($p = .030$). The difference in the DBP at first insertion had a median of 41.0 (34.3–52.8) mmHg in the phlebitis onset group, which was significantly different from the median of 35.5 (25.3–44.5) mmHg for the group without the onset of phlebitis ($p = .032$). During the initial catheterization, no significant difference was observed in SBP, DBP, as well as the differences in SBP and MAP ($p = .193$, $p = .053$, $p = .061$, $p = .181$).

4) Insertion site per catheter (Table 6) and nicardipine usage per catheter (Table 7)

No significant differences were noted in the insertion site, presence or absence of paralysis, or indwelling needle gauge per catheter.

The median nicardipine administration time per catheter was 23.75 (13.02–35.04) h in the phlebitis group, which was significantly longer than the 11.92 (4.87–26.05) h recorded for the non-phlebitis group ($p = .001$). The median nicardipine dose was 72.35 (38.06–153.73)

Table 3. Patient backgrounds by presence/absence of phlebitis onset

		non–phlebitis group (%)	phlebitis group (%)	*p*-value
Age (years) *n* = 92				
	Median [Quartile]	71.0 [61.3–80.5]	69.0 [60.5–78.0]	.498[a]
	40–60s	24 (26.1)	19 (20.7)	.515[b]
	70–80s	30 (32.5)	19 (20.7)	
Sex *n* = 92				
	Male	32 (34.8)	17 (18.5)	.211[b]
	Female	22 (23.9)	21 (22.8)	
level of consciousness GCS *n* = 92				
	E Median [Quartile]	4.0 [4.0–4.0]	4.0 [3.0–4.0]	.090[a]
	V Median [Quartile]	5.0 [3.8–5.0]	4.0 [1.0–5.0]	.056[a]
	M Median [Quartile]	6.0 [6.0–6.0]	6.0 [5.0–6.0]	.060[a]
	total GCS score Median [Quartile]	14.0 [12.3–15.0]	13.0 [10.0–15.0]	.099[a]
	13–15	40 (43.4)	20 (21.8)	.033[b]
	12 or below	14 (15.2)	18 (19.6)	
History of hupertension *n* = 92				
	Yes	29 (31.5)	18 (19.6)	.549[b]
	No	25 (27.2)	20 (21.7)	
BMI *n* = 92				
	Median [Quartile]	22.1 [19.6–26.1]	23.3 [20.3–27.9]	.234[a]
	18.5–24.9	30 (32.6)	17 (18.5)	.307[b]
	18.5–24.9 outside	24 (26.1)	21 (22.8)	
Triglycerides (mg/dL) *n* = 84				
	Median [Quartile]	107 [77–134]	91 [65–150]	.412[a]
	Male 40–234, Female 30–117	41 (48.8)	30 (35.7)	.438[b]
	Male 40–234, Female 30–117 outside	9 (10.7)	4 (4.8)	
HDL-C (mg/dL) *n* = 84				
	Median [Quartile]	61 [52–69]	60 [48–72]	.739[a]
	Male 38–90, Female 48–103	44 (52.4)	29 (34.5)	.751[c]
	Male 38–90, Female 48–103 outside	6 (7.1)	5 (6.0)	
LDL-C (mg/dL) *n* = 85				
	Median [Quartile]	112 [99–139]	113 [97–133]	.572[a]
	65–163	45 (52.9)	29 (34.1)	.748[c]
	65–163 outside	6 (7.1)	5 (5.9)	
Blood glucose(mg/dL) *n* = 90				
	Median [Quartile]	136 [115–179]	138 [117–161]	.899[a]
	73–109	8 (8.9)	5 (5.5)	.767[b]
	73–109 outside	44 (48.9)	33 (36.7)	
CRP(mg/dL) *n* = 91				
	Median [Quartile]	0.12 [0.06–0.19]	0.1 [0.06-0.3]	.846[a]
	0.00–0.14	33 (36.2)	22 (24.2)	.674[b]
	0.00–0.14 outside	20 (22.0)	16 (17.6)	
Disease type *n* = 92				
	Cerebral infarction	29 (31.2)	8 (8.6)	.006[b]
	Cerebral hemorrhage	18 (19.4)	20 (21.5)	
	Subarachnoid hemorrhage	7 (7.5)	10 (11.8)	

a) Mann-Whitney U test
b) Chi-squared test
c) Fisher's exact test

ml in the phlebitis group, which was significantly higher than the 24.60 (8.80–62.80) ml recorded for the non-phlebitis group ($p = .000$). The median value for the mean rate of administration for nicardipine was 2.79

Table 4. Patient backgrounds by presence/absence of phlebitis frequency

		non-phlebitis group	single episode of phlebitis group	multiple episodes of phlebitis group	*p*-value
Age(years) *n* = 92					
	Median [Quartile]	71.0 [61.3–80.5]	67.5 [56.8–78.5]	71.5 [68.0–77.5]	.726
Consciousness level GCS *n* = 92					
	E Median [Quartile]	4.0 [4.0–4.0]	4.0 [3.0–4.0]	4.0 [3.0–4.0]	.138
	V Median [Quartile]	5.0 [3.8–5.0]	5.0 [2.5–5.0]	2.5 [1.0–4.0]	.020 *
	M Median [Quartile]	6.0 [6.0–6.0]	6.0 [5.8–6.0]	5.0 [4.3–6.0]	.007 ** *
	total GCS score Median [Quartile]	14.0 [12.3–15.0]	15.0 [11.5–15.0]	11.5 [10.0–13.8]	.009 * *
BMI *n* = 92					
	Median [Quartile]	22.1 [19.6–26.1]	23.4 [21.2–29.7]	22.3 [19.3–26.8]	.289
Triglycerides (mg/dL) *n* = 84					
	Median [Quartile]	107 [77–134]	88 [60–102]	103 [65–174]	.416
HDL-C(mg/dL) *n* = 84					
	Median [Quartile]	61 [52–69]	64 [50–72]	67 [48–72]	.945
LDL-C (mg/dL) *n* = 85					
	Median [Quartile]	112 [99–139]	116 [105–133]	106 [92–127]	.739
Blood glucose (mg/dL) *n* = 90					
	Median [Quartile]	136 [115–179]	126 [114–150.8]	157.5 [120.5–173]	.267
CRP (mg/dL) *n* = 91					
	Median [Quartile]	0.12 [0.06–0.19]	0.11 [0.06–0.23]	0.11 [0.05–0.49]	.969

Kruskal-Wallis test *<.05, **<.01

(16.8–5.73) ml/h for the phlebitis group, which was significantly faster than the 0.34 (0.68–2.21) ml/h recorded for the non-phlebitis group (p = .000). The median value for the mean nicardipine dilution rate within the line was 7.74 (4.04–12.99)-fold, which was significantly more concentrated than the 14.41 (8.98–24.79)-fold recorded for the non-phlebitis group (p = .000).

5) Investigation of factors related to the occurrence of phlebitis (Table 8)

Based on the results of the univariate analysis (Tables 4, 5, and 6), we used factors with significant differences as explanatory variables, that is, categories of verbal response (V) and motor response (M) on the GCS, both of which are used to describe the level of consciousness, the total GCS score, disease type, nicardipine administration time, nicardipine dose, MAP at first insertion, and difference in the DBP at first insertion. Multiple logistic regression analysis was performed with the likelihood ratio forward stepwise method using the presence or

Table 5. Nicardipine usage status and blood pressure status by phlebitis frequency

n = 92

	non-phlebitis group	phlebitis group	*p*-value
Nicardipine administration time (hour)			.000
Median [Quartile]	9.3 [4.7–25.2]	62.2 [42.9–92.4]	
Nicardipine dose (ml)			.000
Median [Quartile]	90.8 [57.4–131.8]	248.8 [142.0–501.9]	
SBP at first insertion (mmHg)		.	.193
Median [Quartile]	136.5 [131.3–152.7]	134.4 [130.3–137.8]	
DBP at first insertion (mmHg)			.053
Median [Quartile]	82.9 [75.4–89.5]	78.2 [70.7–85.0]	
MAP at first insertion (mmHg)			.030
Median [Quartile]	100.4 [94.1–107.9]	95.4 [90.1–100.8]	
Difference in the SBP at first insertion (mmHg)			.061
Median [Quartile]	58.5 [48.3–73.5]	65.0 [60.0–85.5]	
Difference in the DBP at first insertion (mmHg)			.032
Median [Quartile]	35.5 [25.3–44.5]	41.0 [34.3–52.8]	
Difference in the MAP at first insertion (mmHg)			.181
Median [Quartile]	42.7 [30.3–48.2]	45.0 [36.6–56.4]	

a) Mann-Whitney U test

Table 6. Insertion site per catheters

n = 179

	non-phlebitis group (%)	phlebitis group (%)	*p*-value
Peripheral venous indwelling catheter insertion site			.504[a]
Upper limb	107 (59.8)	67 (37.4)	
Lower limb	2 (1.1)	2 (1.1)	
unkown	0 (0.0)	1 (0.6)	
Presence or absence of paralysis			.216[b]
Paralysus side	29 (16.2)	13 (7.3)	
Absence and Non-paralyzes side	80 (44.7)	57 (31.8)	
Indwelling needle gauge			.787[b]
20G	9 (5.0)	4 (2.2)	
22G	70 (39.1)	46 (25.7)	
24G	27 (15.1)	19 (10.6)	
unknown	3 (1.7)	1 (0.6)	

a) Fisher's exact test
b) Chi-squared test

Table 7. Nicardipine usage per catheters

n = 179

	non-phlebitis group (%)	phlebitis group (%)	*p*-value
Nicardipine administration time (hour)			
Median [Quartile]	11.92 [4.87–26.05]	23.75 [13.02–35.04]	.001
Nicardipine dose (ml)			
Median [Quartile]	24.60 [8.80–62.80]	72.35 [38.06–153.73]	.000
mean rate of administration of nicardipine (ml/h)			
Median [Quartile]	0.34 [0.68–2.21]	2.79 [16.8–5.73]	.000
Mean dilution rate of nicardipine			
Median [Quartile]	14.41 [8.98–24.79]	7.74 [4.04–12.99]	.000

Mann-Whitney U test

Table 8. Multiple logistic regression analysis

	odds ratio	the 95% confidence interval	*p*-value
Nicardipine administration time (hour)	1.042	1.023–1.062	.000

absence of phlebitis as the dependent variable. Results indicated that the odds ratio of phlebitis onset for nicardipine onset time was 1.042 (95% CI: 1.023–1.062). The Hosmer–Lemeshow test result was $p = 0.003$. While the regression formula did not match, the percentage of correct classifications was found to be 80.0%.

Discussion

1) Outline of study subjects

The breakdown of phlebitis rates among patients with an emergency admission for stroke during the study period was roughly the same as those reported by Ushio, Taneda, and Yamada (2013). The median age of the subjects was 70.5 years and included 53% male subjects and 47% female subjects. These results correlated with trends reported by Toyota (2010), indicating that our subject sample was representative of the standard population. Our breakdown by stroke type was 40.2% cerebral infarction, 41.3% cerebral hemorrhage, and 18.5% subarachnoid hemorrhage. This differed from the standard population as there was a low proportion of patients with cerebral infarction but high proportion of patients with cerebral hemorrhage and subarachnoid hemorrhage. Our subjects comprised patients who were administered nicardipine as hypotensive

therapy. This could be the reason why there were naturally more patients with cerebral hemorrhage and subarachnoid hemorrhage, who required more aggressive hypotensive therapy than patients with cerebral infarction.

2) Phlebitis incidence rate

The phlebitis incidence rate in this study was 39.1%. Previously reported phlebitis incidence rates ranged from 25.7% to 34.1% (Kawada et al., 2016; Miyazu et al., 2017). Thus, our results were slightly higher, possibly because the subjects enrolled in this study were all patients with stroke, whereas no such criterion was placed on patients in previous studies. Our result was clearly higher than the recommended phlebitis incidence rate of 5% or below, as recommended by the Intravenous Nurses Society (USA) (1998). Ochi, Kakehi, Tanaka, Toyoda, and Ishihara (2015) performed a blood vessel irritation experiment on rabbits, and they showed that phlebitis is a pharmacologic action of nicardipine, which strongly stimulates the peripheral vascular endothelial cells. No studies have investigated this phenomenon in human subjects. Basic research is required to investigate the pathophysiology of this effect.

3) Factors related to the occurrence of phlebitis

Our results indicated that phlebitis was unlikely to occur in the more conscious patients (total GCS score: 13–15), the "mild" group, whereas in the less conscious patients, (total GCS score: 12 or below) the "moderate/severe" group, phlebitis was more likely to occur ($p = .033$). Our results showed that the level of consciousness GCS-V was significantly lower in the single onset phlebitis group than in the multiple onset phlebitis group ($p = .020$). Our results demonstrated that scores were also significantly lower for GCS-M ($p = .007$), and significantly lower results were noted for the level of consciousness (total GCS score; $p = .009$). The GCS is a globally-recognized standard for determining the level of consciousness based on eye-opening, verbal responses, and motor responses as reactions to stimulation that can be used to accurately evaluate the patient's level of consciousness (Hickey, 2009). GCS-V and -M are believed to correspond to the patient's physical and mental activity. This appears to be why we noted a correlation between the level of consciousness and the occurrence of phlebitis. Gorski et al. (2016) emphasized the importance of patient education, involving instructing patients to report any pain or discomfort at the insertion site and appropriate management of infusions. The inability to effectively educate or communicate with patients having stroke, who often have diminished consciousness, could be affecting phlebitis onset in such patients. Nogueira et al. (2017) reported that lower phlebitis incidence rates were associated with higher ratios of nursing hours provided to patients compared with the nursing hours required by patients. Gorski et al. (2016) indicated the need to regularly evaluate signs of phlebitis using standardized tools. To prevent phlebitis in patients with stroke having a decreased level of consciousness, infusions must be appropriately managed and the insertion site needs to be more frequently and carefully inspected.

Multivariate analysis indicated that the nicardipine administration time was a significantly related factor (95% CI: 1.023–1.062). Thus, our results indicated that administering nicardipine at high doses, over prolonged periods of time, and at fast rates was associated with significant differences in phlebitis rates. This is in line with studies that have also indicated that administration at highly concentrated doses (Kawada et al., 2016; Miyazu et al., 2017) and rapid administration at massive doses (Narishige et al., 2012) are risk factors for phlebitis. The median nicardipine dilution rate in our study was 7.74-fold for the phlebitis group. Despite administering nicardipine at the recommended concentration according to the package insert (0.01%–0.02%, 5–10-fold) and within the recommended dose concentration, phlebitis occurred at high rates. Phlebitis, therefore, cannot be prevented even if nicardipine is administered at the concentration recommended on the package insert.

In terms of blood pressure during the use of nicardipine, there was no significant difference in the initial SBP and the difference in the SBP at first insertion. However, MAP at first insertion had a median of 95.4 mmHg in the phlebitis onset group, which was significantly lower than the median of 100.4 mmHg for the group without the onset of phlebitis ($p = .030$). In addition, differences in the DBP at first insertion had a median of 41.0 mmHg for the phlebitis onset group, which was significantly different from a median of 35.5 mmHg for the group without the onset of phlebitis ($p = .032$). Management of blood pressure during

an acute-phase stroke includes adjustment for the flow rate of nicardipine based on SBP; therefore, there were no significant differences in values associated with SBP. However, a significant difference appeared in MAP and differences in the DBP. This appears to have been because blood pressure is strictly managed during the stroke acute phase to prevent the condition from worsening. Therefore, the high concentration administration of nicardipine over long periods of time and at fast rates of administration as described in this study are necessary to protect patients' lives. We must emphasize the importance of not making changes in nicardipine administration concentrations, time, or rate focusing on phlebitis to the detriment of blood pressure management.

We propose reducing the administration time per catheter as a method of intervention to reduce the incidence of phlebitis. For normal fluid infusions, there is no need to replace the peripheral catheter more than every 72–96 h to reduce the risk of phlebitis (O'Grady et al., 2011). However, we believe that patient QOL should be prioritized when managing the administration of nicardipine, which is associated with a high incidence of phlebitis. Consistent with a previous study, which recommended replacement at the insertion site every 24 h (Miyazu et al., 2017), we found that phlebitis occurred after a median of 23.75 h of nicardipine administration in the phlebitis group, which is a much shorter interval than 72–96 h. Considering the nicardipine-related phlebitis frequency and resulting patient discomfort, we propose cannula replacement less than 24 h during continuous infusion of the drug.

Study limitations and future issues

In this study, we investigated factors related to the occurrence of phlebitis associated with continuous nicardipine infusion in patients with stroke. The limitations of this study include the fact that it was a retrospective study based on patient medical records and only targeted at patients in whom phlebitis was confirmed, meaning that we were unable to confirm the presence or absence of phlebitis in all patients. Further examination is necessary for the onset of phlebitis and differences in the judgments made by nurses who perform the assessment.

Although we were able to clarify factors related to phlebitis in patients with stroke, further research is required on whether the incidence of phlebitis can be reduced by nursing intervention.

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