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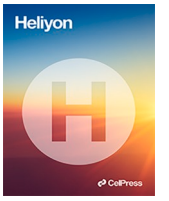

A randomized controlled trial comparing blood pressure reduction in hyperacute phase of spontaneous intracerebral hemorrhage by continuous nicardipine infusion with or without a preceding nicardipine bolus dose

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ABSTRACT

Objectives: To determine whether addition of an intravenous bolus dose before continuous nicardipine infusion would improve blood pressure reduction in the hyperacute phase in patients with spontaneous intracerebral hemorrhage (ICH).
Design: Double-blind randomized controlled trial.
Setting: One academic emergency department (ED) in Bangkok, Thailand.
Participants: Adult patients with spontaneous ICH presented to the ED between June 30, 2022, and July 15, 2023.
Interventions: The bolus group (n = 31) received an intravenous bolus dose of nicardipine before nicardipine continuous infusion, whereas the non-bolus group (n = 31) was given a placebo and nicardipine continuous infusion.
Main outcomes: Systolic blood pressure (SBP) within the first hour (being measured every 5 min), neurological deterioration, and infusion dosage at 60 min were assessed.
Results: Basic characteristic features including the mean baseline SBP were not significantly different between the two groups. At 10 min after treatment initiation, the bolus group had a significant decrease in SBP (32.1 ± 13.6 vs 22.3 ± 18.5 mmHg; p-value = 0.020). Moreover, the target SBP of 180 mmHg could be achieved within 10 min in the bolus group compared with 15 min in the non-bolus group. However, the overall mean SBPs were not significantly different, with 152 ± 12 mmHg in the bolus group compared with 150 ± 15 mmHg in the non-bolus group (p-value = 0.564). None of the patients in both groups had neurological deterioration over the first hour of the treatment. The infusion dosages of nicardipine at 1 h were 6.2 mg/h (5.9, 7.7 mg/h) and 6.8 mg/h (5.9, 8.4 mg/h) in the bolus and non-bolus groups, respectively (p-value = 0.618).
Conclusions: Administering a 1-mg bolus dose of nicardipine before continuous nicardipine infusion notably reduces SBP at 10 min. However, the overall SBP does not exhibit a significant decline during the hyperacute phase of spontaneous intracerebral hemorrhage.

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1. Introduction

Intracerebral hemorrhage (ICH) is the second most common cause of stroke, comprising 10 %–20 % of strokes, has been significantly increasing, and is one of the leading causes of death, especially in developing countries [1,2]. The early phase of ICH is crucial because perihematomal edema, ischemia, and cell necrosis occur instantaneously after bleeding, resulting in neurological damage. Moreover, hematoma expansion, a factor that is directly related to mortality and unfavorable neurological outcomes, mostly occurs in the first 6 h of onset [3–5].

Meanwhile, high blood pressure (BP) correlated with hematoma expansion, and an acute hypertensive response is a pathophysiologic condition that is commonly associated with ICH. The condition is generally more frequent and more severe in patients with chronic hypertension [6,7].

Several organizations have collaboratively released guidelines recommending early BP lowering in patients with ICH and hypertension [8]. Nicardipine, a dihydropyridine calcium ion influx inhibitor, has been reported as the drug of choice to lower BP in the acute phase of ICH [9] due to its several advantages: rapid onset of action of only 5–15 min after intravenous infusion, being able to cross the blood-brain barrier, and having a vasorelaxant effect on cerebrovascular smooth muscles, hence enhancing cerebral blood flow [9–11]. Patients who received nicardipine had less frequent BP variability than those who received non-nicardipine-based agents [12].

BP control in patients with acute ICH is a crucial factor in preventing further brain damage caused by hematoma expansion. Although the continuous infusion of nicardipine has good efficacy in BP control, a more rapid drug action to reduce BP is sometimes needed, especially in patients with extremely high BP [11]. An alternative method for nicardipine administration may be an option.

Few studies have assessed the effect of nicardipine bolus dose before continuous infusion in perioperative hypertension, neurovascular surgery, and severe hypertension [13–16]. This was based on the more rapid action of nicardipine bolus on BP, which is within the first few minutes, compared with 10–15 min of the continuous infusion [16,17]. However, the optimal method of administration of antihypertensive drugs during the hyperacute phase after ICH is still not established [18]. To date, one case report demonstrated the excellent effect of nicardipine bolus in reducing BP, which was given to a patient with a large ICH and intraventricular hemorrhage (IVH) [19]. Another cohort study collected data from patients with ICH who received three different antihypertensive agent boluses including nicardipine without mentioning details of drugs administration [20].

Evidence-based data about nicardipine bolus injection in ICH is still lacking. Therefore, this study aimed to determine the efficacy of an initial bolus dose of nicardipine on BP control prior to continuous infusion in patients with spontaneous ICH. Neurological outcomes throughout the first hour were also studied.

2. Materials and methods

2.1. Study design and setting

This double-blind randomized controlled clinical trial was conducted at an emergency department (ED) of one tertiary hospital in Bangkok, Thailand. The trial was approved by the Institutional Review Board and registered to the Thai Clinical Trails Registry (TCTR20220622004).

2.2. Study population

This study enrolled patients aged ≥18 years who had spontaneous ICH and presented to the ED between June 30, 2022, and July 15, 2023. The patients whose systolic blood pressure (SBP) was greater than 180 mmHg, had a Glasgow coma scale (GCS) of ≥5, and had ICH confirmed by computed tomography (CT) of the brain were included in the study. Patients who were referred from another hospital; had onset of symptoms more than 6 h; intraventricular hemorrhage (IVH) or subarachnoid hemorrhage (SAH); and estimated hematoma volume of >60 mL from imaging study; were pregnant; or had a history of allergic to calcium antagonist medications were excluded. The patients or their legal representatives who refused to participate in the study or had communication barriers were also excluded.

2.3. Patient involvement

Patients or their legal representatives were involved in the plan for results disseminated and reported at the stage of participants' recruitment.

2.4. Sample size

The superior parallel randomized trial was powered to demonstrate the outcome of SBP during the first hour of spontaneous ICH. According to data from previous studies, nicardipine infusion reduced the SBP to 25.1 ± 11.2 mmHg in SAH [21]. The mean ± standard deviation (SD) of SBP in patients who received nicardipine intravenous bolus followed by continuous infusion was 34 ± 8.5 mmHg [22] The hypothesis test was two-tailed with criteria for significance (α) of 0.05. We calculated that 28 patients in each group would provide the trial with 90 % power to detect a difference in the mean SBP of 10 mmHg. Considering the potential missing data or withdrawal, 10 % was added, making the total number of 31 patients required in each group.

2.5. Treatment

All patients suspected of cerebrovascular accidents received treatment according to standard practice. A neurosurgeon was consulted immediately if ICH was detected on the brain CT.

After the stabilization process of medical care, written informed consent was obtained from the patients or their legal representatives. The patients were then randomized by a block of four at a ratio of 1:1 of the bolus group or non-bolus group of nicardipine intravenous administration. The randomization code was generated and kept in opaqued sealed envelopes by the research assistant. The investigators and physicians in charge were blinded to the treatment assignment.

Nurses who were not involved in the study prepared the solution according to the ordinal number in each block (nicardipine 1 mg mixed with normal saline up to 10 mL) and placebo solution (0.9 % NaCl 10 mL without nicardipine) with identical physical appearance as the nicardipine solution. The bolus group received an intravenous bolus dose of nicardipine solution (nicardipine 1 mg mixed with normal saline up to 10 mL). The non-bolus group received a placebo solution (0.9 % NaCl 10 mL without nicardipine). After the bolus injection, both groups had continuous infusions of nicardipine (20 mg of nicardipine in 100 mL of normal saline) at a rate of 5 mg/h.

2.6. Patient monitoring

The conditions of the patients were closely assessed by the physicians and nurses responsible for the treatment throughout the 60 min observation period. Vital signs, including BP were monitored with an automatic BP cuff. The BP level and nicardipine rate were recorded every 5 min after the start of treatment by nurses who were unaware of the group allocation or given medications. GCS scores were serially assessed by experienced emergency physicians and/or neurosurgeons before entering the trial, before nicardipine initiation, and 1 h after drug administration.

The target of the treatment was to keep the SBP below 180 mmHg. If the SBP was greater than 180 mmHg, the dose of nicardipine would be increased by 1 mg/h with a maximum dose of 15 mg/h. On the contrary, if SBP was lower than 120 mmHg, nicardipine would be decreased by 1 mg/h every 5 min until the SBP was $\geq$120 mmHg. If the SBP decreased to lower than 90 mmHg, nicardipine would be discontinued, and norepinephrine would be given (norepinephrine 4 mg in 250 mL of 5 % dextrose in water solution, starting at 0.02–0.1 mcg/kg/min) to raise the SBP up to $\geq$ 90 mmHg. The causes of hypotension were elucidated and reported to the neurosurgeon immediately.

In addition, if a participant had a worsening neurological deterioration (defined as a decline of $\geq$2 points from the baseline GCS), the participant would be withdrawn, and the American Heart Association/American Stroke Association management guideline 2022 would be applied. Repeated brain CT would be performed for a reassessment, and the neurosurgeon immediately renotified.

2.7. Outcomes

The primary outcome of the trial was the first-hour BP reduction by bolus nicardipine injection compared with the non-bolus dose, followed by continuous infusions of nicardipine. The secondary outcomes were neurological deterioration (defined as a decline of $\geq$2 points from the baseline GCS), and the rate of nicardipine infusion at 60 min.

2.8. Data collection

All baseline characteristic data, including age, sex, underlying diseases, symptoms duration, initial vital signs, GCS, blood glucose level, and volume of hematoma were collected.

2.9. Statistical analysis

Data were presented as numbers and percentages for categorical data and mean (SD) or median (interquartile range; IQR) for continuous data. Data were compared using Fisher's exact test or chi-square test and the Wilcoxon rank-sum test or Student's t-tests, as appropriate.

A linear mixed-effects model was used to compare the SBP between the bolus and non-bolus groups at 0, 5,10,15, 20, 25, 30, 35, 40, 45, 50, 55 and 60 min. Data were considered statistically significant when the p-value was $\leq$0.05. All statistical analyses were performed using R version 4.1.1 Foundation for Statistical Computing, Vienna, Austria.

The patients, investigators, physicians, and nurses in charge who took care of the patients and collected data were blinded to the randomization assignment.

3. Results

Of the 73 patients with spontaneous ICH, 11 were excluded due to an interval from onset of >6 h (n = 4), hematoma size >60 mL with IVH (n = 4), hematoma size >60 mL (n = 2), and SAH (n = 1). In total, 62 patients met the inclusion criteria. Among these, 74.2 % were male, with the mean age of 61.6 $\pm$ 11.9 years. Randomization resulted in 31 patients each in the bolus and non-bolus groups. The Consolidated Standards of Reporting Trials (CONSORT) diagram of the study is presented in Fig. 1.

No significant difference in demographic characteristics and findings, including the time from ICH onset to intravenous treatment,

mean SBP, and GCS, was found between the two groups (Table 1).

The time from ICH onset to intravenous treatment was 164.13 ± 70.52 min in the bolus group and 154.84 ± 76.56 min in the non-bolus group (p-value = 0.652). The mean SBP before drug administration were 206.5 ± 20.5 mmHg and 205.8 ± 16.6 mmHg in the bolus and non-bolus groups (p-value = 0.883), respectively. The baseline GCS scores were not different between the two groups (p-value = 0.719).

The target SBP of 180 mmHg could be achieved within 10 min in the bolus group compared with 15 min in the non-bolus group (Fig. 2). The decrease in SBP 10 min after starting nicardipine infusion was significantly higher in the bolus group than in the non-bolus group (32.1 ± 13.6 vs. 22.3 ± 18.5, p-value = 0.020). However, the SBP reduction was not significantly different between the two groups throughout the first hour of treatment (152 ± 12 mmHg in the bolus group vs. 150 ± 15 mmHg in the non-bolus group, p-value = 0.564). The maximal effect of nicardipine on SBP was observed approximately 45 min after drug administration.

No statistically significant differences in GCS scores were found between the bolus and non-bolus groups before drug injection and 1 h after starting treatment (Table 2).

In both groups, the median (IQR) infusion rate of nicardipine to achieve the target SBP was not significantly different: 6.5 (6,8.2) mg/h and 7 (6,9.2) mg/h in the bolus and non-bolus groups, respectively (p-value = 0.471). In addition, the corresponding median (IQR) dose of nicardipine at 1 h between the two groups was not significantly different: 6.2 (5.9,7.7) mg/h and 6.8 (5.9,8.4) mg/h (p-value = 0.618). On the contrary, both groups had nicardipine infusion dosages ranging from 5 to 13 mg/h, resulting in cumulative nicardipine doses of 7.4 ± 2.1 and 8.7 ± 2.9 mg in the bolus and non-bolus groups, respectively (p-value = 0.048, bolus dose not included), in the 1-h study period (Fig. 3).

Adverse events attributed to the studied drug were rare, occurring in only two cases in the non-bolus group whose SBP declined lower than 120 mmHg. The nicardipine dose reduction per protocol was executed. Their SBP returned to greater than 120 mmHg within 15 min without neurological deterioration. No other obvious causes of hypotension were found. Neither of these patients experienced neurological deterioration or other adverse events within the 24-h study period.

74 % of the participants (46 out of 62) in the study experienced hypertensive ICH in common sites, which typically involve the basal ganglia, putamen, and thalamus. Eight of these individuals underwent brain angiography, which did not reveal any abnormalities.

On the other hand, 14 out of 16 participants had hypertensive ICH in less common locations. These cases were further examined using CTA, MRA, and/or MRV. Among these cases, one was found to have an arteriovenous malformation (AVM), one had an enlarged vein, and two were diagnosed with cerebral amyloid angiopathy.

4. Discussion

To our knowledge, this is the first study to assess the effectiveness of a bolus dose of nicardipine in addition to continuous infusion in patients with spontaneous ICH. The result demonstrated the similar effects of bolus and non-bolus doses of nicardipine on SBP reduction in patients with spontaneous ICH during the first hour following the treatment, except at 10 min.

A previous study demonstrated that cardiac surgery with nicardipine 1 mg bolus (SBP decrease of 36 mmHg) showed higher

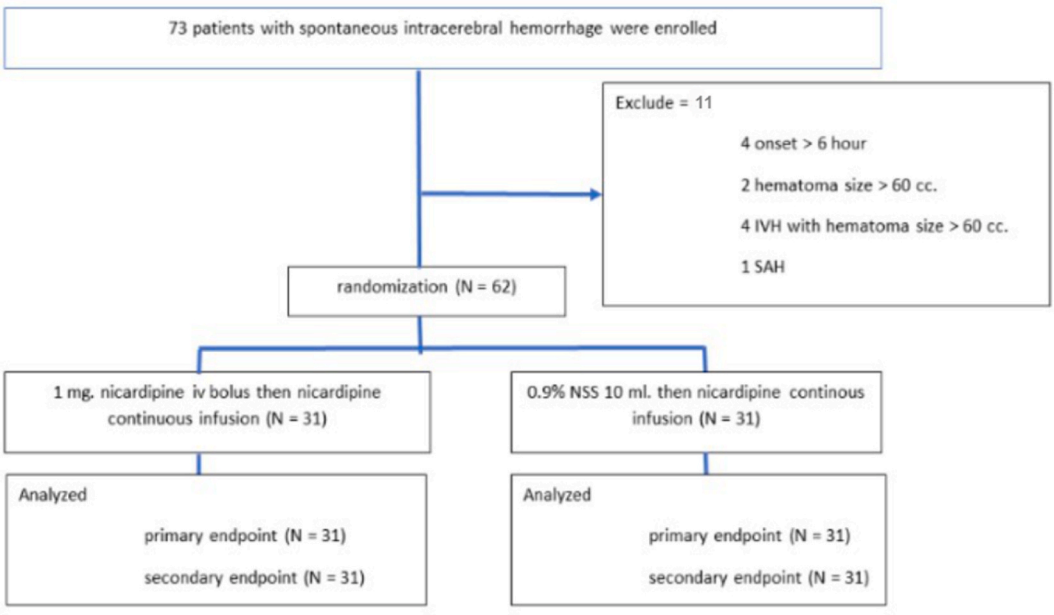

Fig. 1. Consolidated Standards of Reporting Trials (CONSORT) diagram of the trial Abbreviations: IVH, intraventricular hemorrhage; SAH, subarachnoid hemorrhage.

Table 1
Demographic and clinical characteristics of the participants in bolus and non-bolus groups.

	Bolus group N = 31 (%)	Non-bolus group N = 31 (%)
Time from ICH onset to intravenous treatment, mins		
Mean (SD)	164.13 (70.52)	154.84 (76.56)
Age (year)	61,61 ± 11.8	62.8 ± 12.6
Sex, n (%)		
Male	24 (77.4)	22 (71)
Female	7 (22.6)	9 (29)
Underlying disease, n (%)		
Hypertension	17 (54.8)	19 (61.2)
Diabetes mellitus	8 (25.8)	10 (32.3)
Heart disease	5 (16.1)	4 (12.9)
Chronic kidney disease	2 (6.5)	4 (12.9)
Dyslipidemia	6 (19.4)	7 (22.6)
Others[a]	6 (19.4)	4 (12.9)
Initial vital signs, mean (SD)		
Systolic blood pressure, mmHg	208.0 (21.68)	202.8 (18.30)
Respiratory rate, per min	19.0 (2.24)	19.1 (1.99)
Heart rate, beat per min	81.39 (16.86)	82.84 (17.27)
Body temperature, Celsius	36.6 (0.4)	36.7 (0.5)
Plasma glucose, median (IQR)	123 (107,155)	114 (102,143)
Hematoma volume, mean (SD), CC	27.3 (13.9)	29.1 (14.2)

[a] Others included prior undifferentiated stroke, malignancy, and cirrhosis.

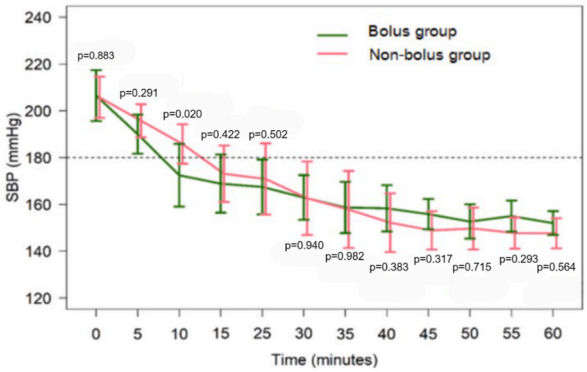

Fig. 2. Mean systolic blood pressure (SBP) during the first hour in bolus and non-bolus groups. *p = p-value (calculated by mixed effect model).

Table 2
Numbers and percentages of the participants according to the Glasgow coma scale (initial and 1 h after drug administration), dose of nicardipine result in target SBP, and dose of nicardipine at 1 h.

	Bolus group (N = 16)	Non-bolus group (N = 16)	p-value
Initial GCS, n (%)			0.719
GCS = 12	2 (6.5)	3 (9.7)	
GCS = 13	2 (6.5)	2 (6.5)	
GCS = 14	5 (16.1)	8 (25.8)	
GCS = 15	22 (71.0)	18 (58.1)	
GCS after 1 h of drug administration, n (%)			0.757
GCS = 12	2 (6.5)	1 (3.2)	
GCS = 13	2 (6.5)	4 (12.9)	
GCS = 14	5 (16.1)	6 (19.4)	
GCS = 15	22 (71.0)	20 (64.5)	
Dose of nicardipine achieved target SBP, mg/hr, Median (IQR)	6.5 (6,8.2)	7 (6,9.2)	0.471
Dose of nicardipine at 1 h, mg/hr, Median (IQR)	6.2 (5.9,7.7)	6.8 (5.9,8.4)	0.618

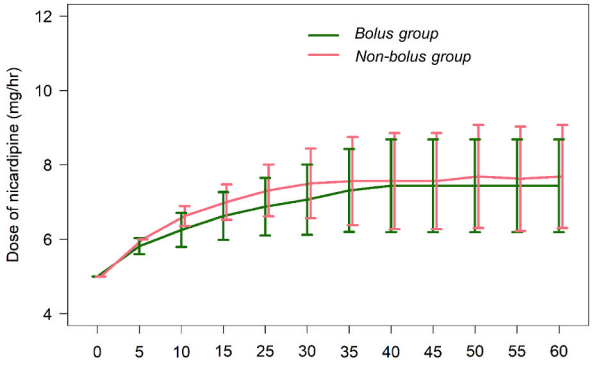

Fig. 3. Dose of nicardipine in patients randomized to receive bolus and non-bolus doses of nicardipine with continuous infusion, excluding bolus injection.

efficacy in SBP reduction in patients with SBP greater than 180 mmHg compared with 0.25 mg or 0.5 mg (SBP decrease of 18 mmHg and 32 mmHg, respectively) [13]. Although a higher dosage of 2 mg could decrease SBP to a greater extent (51 ± 4 mmHg), this might extremely lower SBP, which could negatively affect kidney function and mortality [17,23]. Thus, we decided to give 1 mg of nicardipine to patients with SBP greater than 180 mmHg, in the expectation that BP would not be reduced to lower than 140 mmHg.

Our finding was comparable to those of Ping Tao et al., who followed a similar study design but analyzed different characteristic features of the patients [17]. They assessed the effects of 2 mg of nicardipine given as a bolus dose followed by nicardipine continuous infusion at 2 mg/h compared with only continuous intravenous drip. Their patients had hypertensive emergencies (diastolic blood pressure ≥115 mmHg, severe arrhythmias, atrial fibrillation, cardiogenic shock, or serious congestive heart failure). The results showed equal effectiveness in terms of BP reduction (SBP declined by > 20 mmHg and DBP by < 10 mmHg) within 24 h between the two methods of drug administration. One positive finding from our study was the more rapid achievement of the bolus group. At 10 min after starting treatment, a significantly higher percentage of the patients in the bolus group could achieve the target SBP reduction to ≤180 mmHg compared with the non-bolus group (p-value = 0.020). On the contrary, the non-bolus group took 15 min to achieve the target SBP. Even though the bolus group showed a significantly greater SBP reduction at the early phase, no difference was found in the duration required to reach an SBP of approximately ≤150 mmHg compared with the other group. We were uncertain if the early onset of action, but short duration, of the bolus nicardipine would be clinically meaningful until more data about clinical management, such as in patients who are extremely or critically hypertensive are available.

This study found no difference in the median infusion dose of nicardipine at 1 h or dose for achieving the target SBP. These were inconsistent with the findings of Tao et al., who demonstrated a higher mean infusion dose of 10.9 mg/h at 1 h in the bolus group than 6.9 mg/h in the non-bolus group [17]. The reason for this inconsistency is unclear, however, the different bolus and initial infusion dosages of nicardipine, target BPs, and patients' characteristics potentially contributed to this discrepancy. Nicardipine has a rapid onset, offset of action [24], with a dose-dependent linear effect on BP. The higher injection dose could lower the SBP greatly; as a result, a rapid and larger infusion dose would be needed to maintain the target SBP. However, the infusion dose in the non-bolus group at 1 h in the present study was comparable with that in the mentioned study (6.9 mg/h) and other investigations (7.8 and 5.4 mg/h) [22,25].

Although the infusion rate when the target SBP was reached and at 1 h was not different, data showed that the total infusion dose of nicardipine was lower with an initial 1 mg bolus injection compared with continuous infusion alone. The 1 mg bolus injection in our study reduced SBP without creating a greater BP variation, in terms of mean SD difference between the groups (12.7 ± 3.4 vs. 14.2 ± 4.6, p-value = 0.149), which could result in unfavorable outcomes [26].

The majority of the study participants were male which might influence the outcome of the study according to Koga M et al. [27]. They reported that male individuals required more nicardipine for blood pressure control in acute spontaneous ICH. However, the gender distribution was not significantly different between the bolus and non-bolus groups. This balanced representation minimizes the potential impact of gender on nicardipine dosing in our study.

Most of the patients in our study could, within 1 h, achieve recommended target SBP according to the AHA2022 guideline [18]. No patients in this study had neurological deterioration. The GCS scores of both groups at 1 h after treatment were also comparable. These may be due to our criteria of including patients who have a relatively stable condition without a large or progressive expansile hematoma. The only adverse effect was SBP dropped to <120 mmHg in only two patients in the non-bolus group. The event was transient without any neurologic effects. Few previous studies have also reported this hypotension event with nicardipine either in the bolus group of different doses [13,17] or in the non-bolus group [15]. Cheung et al. reported hypotension in three patients who received 1 mg bolus nicardipine [13]. In another study, one patient in the 2-mg bolus nicardipine group had remarkable hypotension (SBP of 88/68 mmHg) [17]. By contrast, Kim et al. encountered transient hypotension in one patient with SAH who received nicardipine infusion at 2.5 mg/h [15]. The hypotension cases in all previous studies were improved after the discontinuation of nicardipine or dose reduction, as in the present study.

4.1. Strength and limitation

This study has some limitations. First, the recruitment was limited to patients with a limited volume of ICH, not including IVH and SAH, which would not represent all patients with ICH. Second, the small sample size may have caused insignificant outcomes between the groups. Patients who might take any antihypertensive agents before being recruited into the trial were not excluded from the analysis. This could affect their BP during the study period. Furthermore, the 1-h observation period and dose of nicardipine bolus could be criticized. These must be considered in our primary endpoint to determine which method was the most effective. Only GCS was used to assess patients' neurological status, and follow-up CT was not reported, which would be more accurate in neurological evaluation. Moreover, as a single-center study, an external validation is essential.

Nevertheless, our study had some points. To our knowledge, this was the first RCT of bolus nicardipine in spontaneous ICH. Second, although the overall effectiveness of both methods of intravenous nicardipine administration was comparable at 1 h after treatment, a more rapid BP decline in bolus nicardipine might be useful for extremely high BP spontaneous ICH. RCT and linear mixed effect model were used to maximize the reliability of the study.

5. Conclusion

In this study, no significant difference in BP lowering during the first hour between patients who received a 1-mg bolus dose of nicardipine before continuous infusion and those who received only nicardipine continuous infusion; except at 10-min. The rate of neurologic deterioration and the dosages at 60 min to keep SBP $<$180 mmHg were not different between the two groups.

Ethics approval and consent to participate

Ethical approval was obtained from the institutional review board (IRB) of Faculty of Medicine Vajira Hospital, Bangkok, Thailand: (171/2562) and conformed to the Good Clinical Practice Guideline and the Declaration of Helsinki. The study was registered to Thai Clinical Trails Registry: TCTR20220622004. Written informed consent was obtained from patients or their relatives after medical treatment and stabilization were done before randomization.

Consent for publication

Not applicable.

Data availability statement

The data will be made available upon reasonable request.

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CRediT authorship contribution statement

Adisak Nithimathachoke: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Supatpinee Tiensawang:** Writing – original draft, Validation, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Natradee Deechot:** Writing – original draft, Methodology, Investigation, Conceptualization. **Chawin Sutaparak:** Supervision, Project administration, Methodology, Conceptualization. **Kitiporn Sriamornrattanakul:** Supervision, Project administration, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of abbreviations

BP blood pressure

CT	computed tomography
ED	emergency department
GCS	Glasgow coma scale
ICH	Intracerebral hemorrhage
IQR	Interquartile range
IVH	Intraventricular hemorrhage
SAH	subarachnoid hemorrhage
SBP	Systolic blood pressure
SD	standard deviation

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e22812.

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