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Effects of intravenous nicardipine followed by oral labetalol in combination with nifedipine controlled--release tablet on severe peripartum hypertension

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ABSTRACT

Objectives: To investigate the effects of intravenous nicardipine as initial therapy and oral labetalol combined with nifedipine controlled-release tablet as subsequent treatment of severe peripartum hypertension.

Material and methods: Intravenous nicardipine was delivered as the initial treatment, after the target blood pressure (BP) had been achieved, oral labetalol was used to maintain the target BP. If oral labetalol failed to maintain the target BP, oral labetalol combined with nifedipine controlled-release tablet was used.

Results: A total number of 131 patients were enrolled. The target BP (BP < 140/90 mmHg) was achieved in all patients within 60 minutes by intravenous nicardipine. After receiving labetalol orally, the target BP was maintained in nine patients. However, in 104 patients, we had to combine oral labetalol and nifedipine controlled-release tablet due to re--elevation of their systolic BP to 140–159 mmHg. In 18 patients, we restarted intravenous nicardipine because their systolic BP re-elevated above 160 mm Hg. Among the 104 patients who received oral labetalol and nifedipine controlled-release tablet, the target BP was achieved and maintained in 96 patients, and eight patients had to restart nicardipine. Of the total number of 26 patients in whom intravenous nicardipine was resumed, the target BP was successfully maintained in 22 patients with oral labetalol combined with nifedipine controlled-release tablet.

Conclusions: Intravenous nicardipine rapidly and safely lowered severe peripartum hypertension. As subsequent therapy, oral labetalol combined with nifedipine controlled-release tablet protocol may be applied to effectively maintain a target BP.

Keywords: severe hypertension, peripartum, nicardipine, labetalol, nifedipine controlled-release tablet

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INTRODUCTION

Women with severe peripartum hypertension are at risk of developing acute pulmonary edema and cerebrovascular events, and require urgent antihypertensive therapy [1, 2]. Guidelines and practices therefore recommend that treatment should be initiated as soon as possible, with a target blood pressure achieved in 60 minutes in those women with severely elevated blood pressure (BP) [1, 3].

Nicardipine is a dihydropyridine-type calcium-channel blocker that provides effective treatment in patients with hypertension during pregnancy. Previous studies have reported a safe and rapid effect of intravenous infusion of nicardipine in patients with severe peripartum hypertension [4, 5]. As sequential therapy, oral medications should be administrated after an elevated blood pressure has been brought to and is maintained at a satisfactory level. Although labetalol and nifedipine are widely used antihypertensive agents for hypertension in pregnancy [6–8], their oral administration after intravenous nicardipine has not been fully evaluated.

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Objectives

The aim of this study was two-fold. First, we investigated the effect of intravenous infusion of nicardipine for the treatment of severe peripartum hypertension. Second, we established the effects of oral labetalol combined with nifedipine controlled-release tablets (NCRT) after the target BP was achieved by intravenous nicardipine treatment in the management of severe peripartum hypertension in maternal intensive care units (ICUs).

MATERIAL AND METHODS

This retrospective analysis was conducted from December 2016 to August 2022 in the Chongqing Health Center for Women and Children, Chongqing, China, a tertiary-care hospital with approximately 16,000–20,000 deliveries per year. The study was approved by the Health Center's Ethics Committee, and all patients provided written informed consent.

Study patients

We enrolled all patients who had undergone treatment with intravenous nicardipine due to severe peripartum hypertension at our maternal ICU. Hypertensive disorders in pregnancy were classified into four categories: gestational hypertension (GH), chronic hypertension (CH), pre-eclampsia (PE), and PE superimposed on CH [9, 10]. Severe hypertension was defined as a sustained SBP ≥ 160 mm Hg and/or a DBP ≥ 110 mm Hg [9]. Magnesium sulfate was routinely administrated to prevent eclamptic seizures as per previous recommendations [7, 11]. We excluded patients under 18 years of age for ethical reasons, although severe hypertension may also occur in this age population.

The BP and heart rate (HR) of patients were recorded in the supine position using an IntelliVue MX450 monitor (Philips, Böblingen, Germany). All patients received an indwelling arterial catheter to monitor BP continuously to prevent an abrupt decrease in BP. Because of the difference of BP measured by oscillometry (non–invasive method) and invasive method, the target BP was determined by oscillometry. A triple-lumen central venous line was inserted to allow the administration of medications and the measurement of central venous pressure if needed.

Drug treatment

Nicardipine (Astellas Pharmaceutical Co., Ltd, Shenyang, China) was delivered through a continuous-infusion pump, with details described previously [4]. Briefly, the initial dosage of nicardipine was 2 mg/hour for the patients with an SBP 160–179 mm Hg and 4 mg/hour for those with an SBP ≥ 180 mm Hg. The maintenance dose was adjusted by increasing or decreasing the infusion rate by 0.5–1 mg/hour, with a maximum dosage of 6 mg/hour. All oral medications were withdrawn during the period of intravenous nicardipine treatment. The target of this treatment was to reduce BP to < 140/90 mm Hg [2, 9]. After the target BP had been maintained for at least 5–6 hours, labetalol (Jiangsu Desano Pharmaceutical Co., Ltd, Jiangsu, China) was administered at an initial dose of 200 mg. If the target BP could not be maintained, an additional 100-mg dose was provided up to a maximal dosage of 300 mg three times/day [9, 10]. For nicardipine termination, its dosage was gradually reduced, with an approximate overlap of 2–4 hours. If the target BP could not be maintained and re-elevation to SBP of 140–160 mm Hg occurred, NCRT (Bayer Schering Pharmaceutical Co., Ltd, Guangzhou, China) was administrated at a dose of 30 mg two times/day. If the level of SBP re-elevated to ≥ 160 mm Hg, intravenous nicardipine was re-started. After SBP was lowered to < 140 mm Hg and maintained for at least 5–6 hours, a dosage of oral labetalol at 300 mg three times/day in combination with NCRT at 30 mg two times/day was administered, with a nicardipine administration overlap of approximately 2–4 hours (Fig. 1). All patients were discharged to the Obstetric Department after the target BP had been maintained for at least 72 hours.

Data analysis

The efficacy of nicardipine treatment was evaluated by assessing the number of patients in whom the target BP was reached within 60 min, and the efficacy of labetalol and labetalol + NCRT were evaluated by assessing the number of patients in whom the target BP was maintained until they were transferred out of the maternal ICU. Failure of nicardipine therapy was defined as a persisting SBP ≥ 160 mm Hg and a necessity for multidisciplinary treatment (MDT). Failure of the treatment with labetalol or labetalol + NCRT was defined as nonfulfillment of the target BP, with resumption of intravenous nicardipine. We assessed the safety of labetalol and labetalol + NCRT *vis-à-vis* an SBP < 90 mm Hg or a DBP < 70 mm Hg, and with respect to the incidence of other severe adverse maternal effects, such as acute pulmonary edema, tachycardia, and postpartum hemorrhage as reported in previous studies [12]. Tachycardia was defined as a heart rate > 100 beats per minute (bpm), and bradycardia as a heart rate < 60 bpm. Postpartum hemorrhage was denoted as a post-delivery blood loss > 500 mL [4].

Our statistical results are primarily expressed as means ± ± standard deviation (SD), while some parameters are represented by medians and ranges as needed. The Mann-Whitney test was employed to compare differences in dosage and usage duration of nicardipine infusion. Chi–square test was used to compare efficacy and adverse effects of drugs. A two-sided p value < 0.05 was considered to indicate a statistically significant difference. All statistical analyses were conducted with IBM SPSS software, version 20.0 (IBM Corp., Armonk, NY, USA).

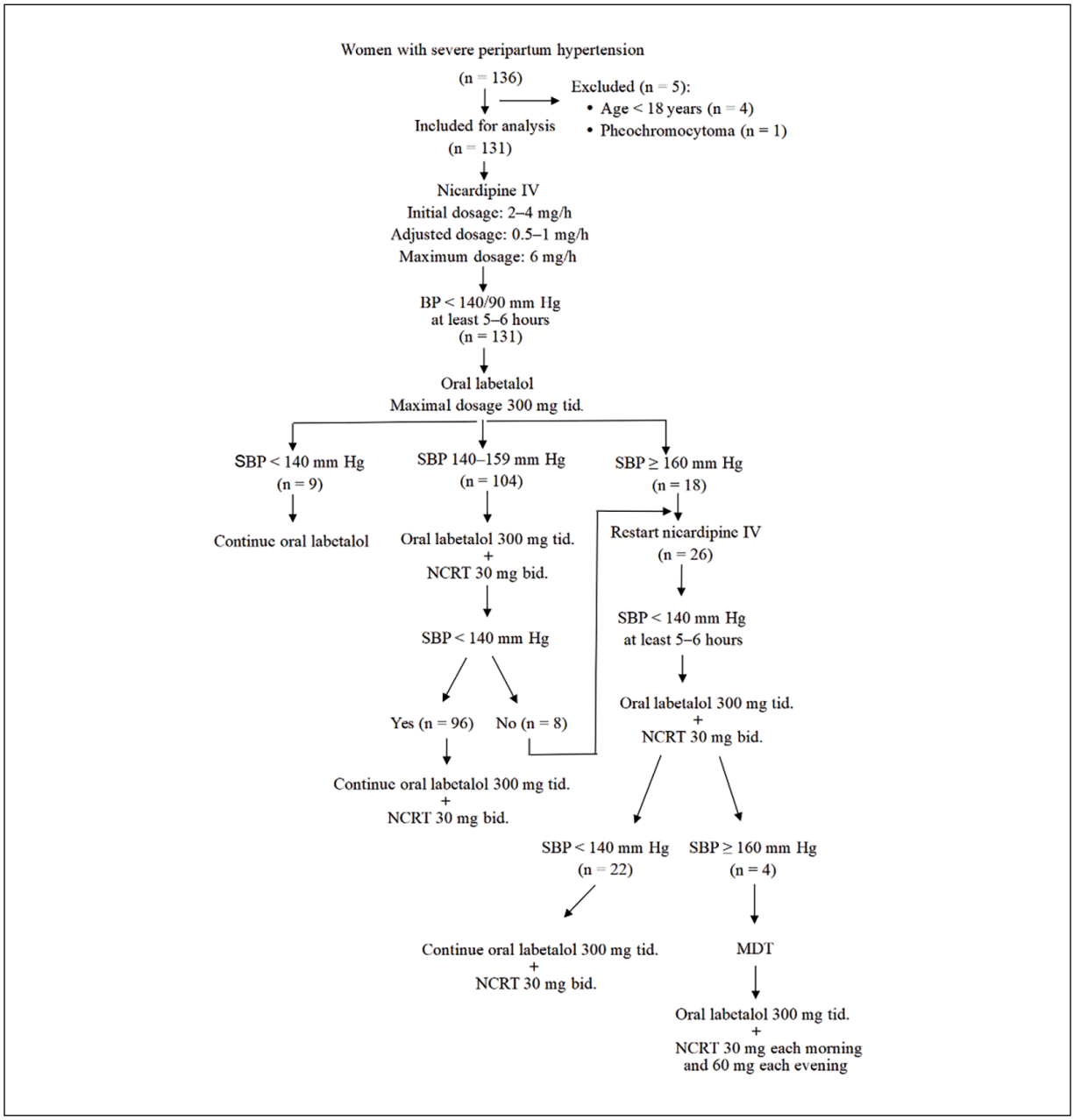

Figure 1. Study flow chart diagram; bid. — twice a day; BP — blood pressure; IV — intravenously; NCRT — nifedipine controlled-release table; MDT — multidisciplinary treatment; SBP — systolic blood pressure; tid. — three times a day

RESULTS

During the study period, a total number of 136 patients were consecutively evaluated. Of these, four patients were excluded for age < 18 years and one patient was excluded for pheochromocytoma. A number of 131 patients who had undergone cesarean section were included. Of these, 83 had an initial SBP ≥ 180 mm Hg and 48 had an initial SBP of 160–179 mm Hg (patient demographic data and baselin characteristics are presented in Tab. 1). All 131 patients received intravenous nicardipine as their initial treatment and the target BP (SBP < 140/90 mm Hg) was achieved in all patients. The time required to reach the target BP was 15.23 ± 10.10 and 28.75 ± 17.75 minutes for the patients with an SBP of 160–179 mm Hg and for those with an SBP ≥ 180 mm Hg, respectively (Tab. 2). The adverse effects of intravenous nicardipine were slight and tolerable (Tab. 3). In one woman (3.13%), fetal demise due to a non-intervention policy. A number of 31 women (96.87%) underwent an emergency cesarean section because of fetal distress (Tab. 4).

All patients were initially administered with oral labetalol after the target BP was achieved and maintained

Table 1. Demographics and baseline characteristics

Parameter	All patients (n = 131)	SBP160–179 mm Hg (n = 48)	SBP ≥ 180 mm Hg (n = 83)
Maternal age [years]	33.92 ± 4.70	34.03 ± 5.01	32.20 ± 4.93
Range	20–54	20–43	22–54
BMI	30.01 ± 4.83	29.90 ± 3.67	30.13 ± 6.01
Range	21.75–50.22	21.75–36.85	22.82–50.22
Weight increase during pregnancy [kg]	16.23 ± 8.91	16.39 ± 6.07	15.45 ± 9.97
Range	2.00–57.50	4.00–31.00	2.00–57.50
Twin pregnancy	16	3	13
Primiparous	64	20	44
Grand multiparous			
2	44	18	26
3	18	8	10
4	5	2	3
Type of hypertension			
PE	89	32	57
CH + PE	42	16	26
CH before pregnancy	14	6	8
CH before 20 weeks of gestation	28	10	18
Proteinuria [g/24 hours]	5.21 ± 4.94	5.10 ± 6.60	5.31 ± 4.04
Range	0.06–24.58	0.14–24.58	0.06–12.05
Symptoms			
Heart rate [bpm]	114.21 ± 3.33	111.00 ± 2.56	122.45 ± 7.83
Range	87–144	87–131	94–144
Headache	26	6	20
Dizziness	20	4	16
Vomiting	7	2	5
Blurred vision	24	6	18
Epigastric pain	4	0	4
Prior antihypertensive treatment	107	28	79
Oral labetalol	14	4	10
Oral nifedipine	12	6	6
Oral labetalol	51	18	33
+ nifedipine	68	24	44
Medical comorbidities			
Gestational diabetes	24	6	18
Thyroid disorders	31	9	22
Multiple sclerosis	3	0	3
Admitted to ICU			
Before delivery		11	21
After delivery		37	62
GA at delivery [weeks]	32.8 (26.3– 40.1)	34.1 (27.5– 40.1)	29.6 (26.3– 38.1)
Type of anesthesia			
General anesthesia	91	22	69
Combined spinal- epidural anesthesia	40	26	14

Data are expressed as mean ± standard deviation or numbers; BMI — body mass index; CH — chronic hypertension; PE — pre-eclampsia; SBP — systolic blood pressure; ICU — intensive care unit; GA — gestational age

Table 2. Antihypertensive effects of nicardipine administered intravenously

Item	SBP 160–179 mm Hg (n = 48)	SBP ≥ 180 mm Hg (n = 83)
Time to target BP [minutes]	15.23 ± 10.10	28.75 ± 17.75[a]
Maximum dose [mg/hour]	4.0	4.8
Minimum dose [mg/hour]	0.4	0.4
Dose at reaching target BP [mg/hour]	1.43 ± 1.11	2.02 ± 1.02[a]
Frequency for nicardipine adjusted [times]	1.50 ± 1.22	1.76 ± 1.25[a]
Range	0–3	0–5
Required additional oral drug to control	0	0
Required additional IV drug to control	0	0
Length of nicardipine using [minutes] Length of stay in ICU [days]	733.43 ± 534.26 4.77 ± 1.46	889.56 ± 744.01[b] 5.30 ± 1.21[a]

Data are expressed as mean ± standard deviation or numbers; BP — blood pressure; ICU — intensive care unit; IV — intravenously; SBP — systolic blood pressure; [a]p < 0.05; [b]p < 0.01

Table 3. Adverse effects of intravenous nicardipine in patients with severe peripartum hypertension

Item	SBP 160–179 mm Hg (n = 48)	SBP ≥ 180 mm Hg (n = 83)	p value
Major side effects	0	0	–
Minor side effects			
Itching	2 (4.17%)	4 (4.82%)	1.000
Racing heartbeat (> 120 bpm)	2 (4.17%)	5 (6.02%)	0.958
Flushing	3 (6.25%)	14 (16.87%)	0.081
Headache	4 (8.33%)	15 (18.07%)	0.127
Loose stool Constipation Stop treatment for side effects	2 (4.17%) 1 (2.08%) 0	4 (4.82%) 2 (2.41%) 0	1.000 1.000 –

bpm — beats per minute; SBP — systolic blood pressure

Table 4. Fetal and neonatal outcomes after pregnant mothers with hypertension were treated with nicardipine

Fetal outcomes	Number/total (%)
Fetal demise	1/32 (3.13%)
Fetal distress followed by emergency cesarean section	31/32 (96.87%)
Fetal distress followed by emergency cesarean section <4 h after starting nicardipine	4/32 (12.50%)
Fetal distress due to maternal hypotension, followed by emergency cesarean section <4 h after starting nicardipine	0
Full course of antenatal corticosteroids	22/32 (68.75%)
Neonatal outcomes	
Umbilical artery pH	7.41 (6.79–7.46)
Base excess	–3.8 (–16–10)
Apgar score at 1 min	7 (0–10)
Apgar score at 5 min	8 (2–10)
Apgar score at 10 min	9 (5–10)

Data are the number (%) or median (range)

by intravenous nicardipine for 5–6 hours. However, an SBP < 140 mm Hg was maintained in only nine (9/131, 6.87%) patients. Labetalol in combination with NCRT was required in 104 (104/131, 79.39%) patients as their SBP re-elevated to 140–159 mm Hg. Intravenous nicardipine was restarted in 18 (18/131, 13.74%) patients due to an SBP ≥ 160 mm Hg. An SBP < 140 mm Hg was achieved and maintained in 96 (96/104, 92.31%) of the 104 patients with an SBP of 140–159 mm Hg by using the labetalol + NCRT protocol. However, the target BP could not be achieved in eight (8/104, 7.69%) patients, and intravenous nicardipine infusion was restarted due to SBP ≥ 160 mm Hg. The target BP was achieved in all 26 patients who needed a restart of intravenous nicardipine administration (26/26,100%); SBP < 140 mm Hg was maintained in 22 (22/26, 84.62%) of the patients by using the labetalol + NCRT protocol; however, the protocol failed in four (4/26, 15.38%) of the patients and MDT was required (Tab. 5). Following the suggestions of the MDT panel, a dose of 300 mg of labetalol three times/day in

Table 5. Antihypertensive effects and adverse maternal outcomes during treatment of oral labetalol and oral labetalol + NCRT

	Oral labetalol			Oral labetalol + NCRT	
	After nicardipine IV (n = 131)	Before nicardipine restarted (n = 104)	p value*	After nicardipine restarted (n = 26)	p value**
Antihypertensive effects					
Maintain SBP < 140 mmHg	9 (9/131, 6.87%)	96 (96/104, 92.31%)	0.000	22 (22/26, 84.62%)	0.000
Have to restart nicardipine IV again	18 (18/131, 13.74%)	8 (8/104, 7.69%)	0.142	0	0.095
Duration from oral medications to restart nicardipine	4 h (2–6 h)	19 h (14–24 h)	0.001	–	
Adverse maternal outcomes					
Major side effects	0	0	–	0	–
Minor side effects					
Bradycardia (< 60 bpm)	2	0	0.582	0	1.000
Tachycardia (> 100 bpm)	0	1	0.908	1	0.367
Hypotension	1	2	0.840	0	1.000
Asthma	0	0	–	0	–
Oliguria (< 25 mL/h for 2 h)	0	1	0.908	0	–
Flushing	3	12	0.004	2	0.411
Headache	4	14	0.003	2	0.571
Palpitations	4	4	1.000	1	1.000
Additional drug required	122	8	0.000	4	0.000
Loose stool	1	4	0.241	0	0.002
Constipation	0	1	0.908	3	
Stop treatment for side effects	0	0	–	0	–

NCRT — nifedipine controlled-release tablet; IV — intravenously; SBP — systolic blood pressure; bpm — beats per minute; *Compared with oral labetalol after nicardipine IV; **Compared with oral labetalol after nicardipine IV

combination of NCRT at 30 mg each morning and 60 mg each evening was given [9], and the target BP was achieved within 48 hours. All adverse effects that occurred during the treatment with labetalol and nifedipine controlled-release tablet in ICU are presented in Table 5.

DISCUSSION

In the present study, we explored the effects of intravenous nicardipine infusion in the treatment of severe peripartum hypertension, and the effects of labetalol or labetalol + NCRT as the subsequent agents for intravenous nicardipine. Our data revealed that the intravenous infusion of nicardipine could lower elevated BP safely and rapidly in the patients with severe peripartum hypertension. Thus, labetalol in combination of NCRT could serve as an effective subsequent protocol to maintain a target BP.

Intravenous nicardipine as a second-line medication for the treatment of severe hypertension during pregnancy has been evaluated in several investigations [4, 5, 13, 14]. Their results showed that nicardipine could be used effectively in pregnant women with severe hypertension. Therefore, intravenous nicardipine has been recommended for the treatment of severe hypertensive disorders in pregnancy. Consistent with previous studies, our data showed that intravenous nicardipine lowered severely elevated BP within 60 minutes, with no serious adverse effects.

Although both oral nifedipine and labetalol are widely used antihypertensive agents for the treatment of hypertension in pregnancy, to our knowledge, few studies have focused on their effects as subsequent medications of intravenous nicardipine in the treatment of severe hypertensive in pregnancy. The results of the present study revealed that the sole use of labetalol failed to effectively maintain the target BP, and the labetalol + NCRT protocol was implemented in the majority of the patients.

Oral labetalol has been confirmed to effectively lower elevated BP in pregnant women with hypertensive diseases [1, 12, 15]. Easterling et al. [12] compared the efficacy of three oral drugs — labetalol, nifedipine retard, and methyldopa — for the management of severe hypertension in pregnancy. Their results showed that the target BP (defined as 120–150 mm Hg for SBP and 70–100 mm Hg for DBP) was achieved within 6 hours in 228 of 295 patients (77%). The target BP was achieved within 3 hours in 212 (72%) of these patients, and only nine (9/295, 3%) patients had to undergo combined antihypertensive drug therapy. In the present study, we found that the majority of the patients needed the combination with nifedipine retard to lower

their elevated BP and achieve the target BP. We hypothesize that the failure of the sole administration of oral labetalol to achieve the target BP was due to two reasons. First, the levels of SBP in the present study were higher than those in the study conducted by Easterling et al. (SBP of 176 ± 18.4 vs 158 ± 11.5 mm Hg). Second, the upper limit of target BP was higher in the study conducted by Easterling et al. than that in the present study (SBP of 150 vs 140 mm Hg).

Nifedipine is a calcium-channel blocker that has been extensively used in pregnancy-related hypertension, as it can control severe hypertension in pregnancy rapidly and effectively [8, 16, 17]. Oral nifedipine has therefore been recommended by most guidelines as the first-line medication for the management of severe pregnant hypertension [6, 9, 11]. Nifedipine-retard is preferable over the normal nifedipine capsule formulation in patients with hypertensive diseases as it effectively reduces BP for ≥ 12 h without precipitous declines [18]. Although nifedipine has been considered to be an effective medication, several adverse effects have been reported, including maternal tachycardia during the treatment period [19–21]. Intriguingly, in the present study we observed a slightly higher heart rate only in two patients after target BP was maintained (102 and 104 bpm, respectively), with two possible reasons for this effect. First, the slow-release formulation of nifedipine has been shown to produce a significant delay in the peak concentrations and a much narrower range of the peak plasma levels, along with a small interindividual variation in the plasma drug levels [22, 23]. Second, the cardiac acceleration caused by nifedipine was compromised due to the adrenergic-blocking effects of labetalol [24, 25].

Although adverse effects including flushing and headache were higher in oral labetalol + NCRT than those in oral labetalol alone, there were slight and tolerable, and no patient needed to interrupt treatment during the period of study.

Limitations

There are some limitations to our study. First, our study population was heterogeneous as we included patients with chronic hypertension, pre-eclampsia, and pre-eclampsia superimposed on chronic hypertension, while all patients manifested severe hypertension and underwent urgent management with IV nicardipine. Second, our study was conducted in ICU settings, and therefore the results need to be confirmed in obstetric departments. Studies with longer follow-up periods are required to confirm our findings.

CONCLUSIONS

In conclusion, we herein provide evidence that infusion of intravenous nicardipine safely and rapidly lowers severely elevated BP in patients with severe peripartum hypertension. As subsequent therapeutic agents, labetalol combined with NCRT can be used to effectively maintain the target BP in patients with severe peripartum hypertension after emergent treatment with intravenous nicardipine. In this study, oral labetalol alone failed to maintain the target BP although it has been previously recommended as the first-line medication for severe hypertension in pregnancy.

Article information and declarations

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Author contributions

ZY: Concept, study design and manuscript writing; LL and YY: Data collection and manuscript writing; QiH, QJ, LiL and GS: Data collection. ZR: Data analysis. All authors contributed to the article. All the authors read and approved the final version of the manuscript.

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Ethics approval

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Ethics Committee of Chongqing Health Centre for Women and Children (No.2018006) on 23 May 2018.

Conflict of interest

The authors declare that they have no competing interests.

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