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ORIGINAL RESEARCH ARTICLE

Nicardipine for treating severe antepartum hypertension during pregnancy: Nine years of experience in more than 800 women

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Abstract

Introduction: Women with severe hypertension during pregnancy require prompt stabilization with a combination of magnesium sulfate and rapidly acting intravenously administered antihypertensives. It remains unknown which antihypertensive is best suited for pregnancy. The present study evaluated the intravenous use of the calcium antagonist, nicardipine.

Material and Methods: This multicenter, retrospective case series included all pregnant women beyond 20 weeks of gestation with severe antepartum hypertension that were treated with intravenous nicardipine. Primary outcome measures: successful treatment, time to successful treatment, and maternal safety. Severe hypertension was defined as systolic blood pressure (SBP) of 160 mm Hg or more and/or diastolic blood pressure (DBP) of 110 mm Hg or more.

Results: This study included 830 women. After 1 h of treatment, two-thirds of the women had SBP below 160 mm Hg and DBP below 100 mm Hg. In three out of four women, the mean arterial pressure was below 120 mm Hg. Within 2 h of treatment, 77.4% of women achieved successful treatment. In all cases, nicardipine was eventually effective. Within the first 2 h, 42.7% of women experienced temporary low DBP (ie below 70 mm Hg) without clinical consequences for the mother or fetus. In all cases, the low DBP resolved after discontinuing or reducing the dosage of nicardipine. One case of fetal distress was attributable to maternal hypotension, and a cesarean section was performed at more than 2 h after initiating therapy. During treatment, headache, nausea, and vomiting decreased significantly.

Conclusions: To date, this was the largest case-series study on the use of nicardipine for treating severe antepartum hypertension in pregnancy. We found that nicardipine could effectively and safely treat this condition. Based on its high success rate and

Abbreviations: bpm, beats per minute; DBP, diastolic blood pressure; MAP, mean arterial pressure; MC, medical center; SBP, systolic blood pressure.

acceptable safety profile, nicardipine should be considered a first-line treatment in women with severe hypertension in pregnancy.

KEYWORDS
antihypertensive medication, maternal morbidity, neonatal morbidity, nicardipine, pre-eclampsia, severe hypertension

1 | INTRODUCTION

Pre-eclampsia and other hypertensive disorders are responsible for 14% of all maternal deaths worldwide, so these conditions comprise the second leading direct cause of maternal mortality.[1] Women with pre-eclampsia and their (unborn) children are at increased risk of developing serious morbidity.[2] Among women with antepartum severe hypertension, the incidence of maternal adverse events exceeds 25%.[3] The general consensus recommends that persistent severe hypertension must be treated to reduce maternal mortality and morbidity.[4–6] The administration of magnesium sulfate reduces the risk of eclampsia by more than half, and it probably reduces maternal mortality, but it has not shown a clear effect on serious maternal morbidity.[7] A worldwide World Health Organization survey highlighted the fact that additional measures are needed.[8] In addition to magnesium sulfate, antihypertensive medication is mandatory to lower blood pressure and stabilize the patient. After stabilization, it must be determined whether to induce delivery or to postpone delivery for antenatal corticosteroid treatment, when indicated. The ideal antihypertensive drug would lower blood pressure within a short period, would have a short half-life (to facilitate titration), and would be safe for the fetus, the neonate, and the mother.

To date, the antihypertensive drugs that have been investigated most in clinical trials and systematic reviews are: (di)hydralazine, calcium antagonists (mostly nifedipine), labetalol, and ketanserin. Previous Cochrane systematic reviews on this subject have come to the same conclusion: until better evidence is available, the best choice of drug should be based on the experience of the clinician.[9–11] Drugs that should be avoided include ketanserin, diazoxide, nimodipine, and chlorpromazine. Drugs that can be used include calcium antagonists, labetalol, or (di)hydralazine.[9–11] Currently, labetalol and calcium antagonists are the most promising antihypertensives for treating severe hypertension in pregnancy.

In 2004, a prospective randomized trial was conducted to compare dihydralazine and ketanserin.[12] That trial was prematurely stopped because of the high rate of severe adverse effects with dihydralazine and persistent hypertension with ketanserin. In cases of persistent hypertension, nicardipine was used as a rescue medication, and in all cases, it successfully lowered blood pressure to adequate levels.[13] Based on those promising results, nicardipine became the first-line treatment option in the two hospitals that participated in this observational study. Subsequently, a review and meta-analysis confirmed that nicardipine was highly effective and safe for treating severe hypertension in pregnancy, and that it could be a better alternative than other available treatment options.[14,15]

Key message

Nicardipine is safe for treating severe hypertension in pregnancy; it reduces blood pressure rapidly and effectively.

The primary goal of the present observational study was to confirm our hypothesis that nicardipine would be effective and safe for treating severe antepartum hypertension in pregnancy.

2 | MATERIAL AND METHODS

2.1 | Trial design and participants

This multicenter, retrospective case series focused on routine clinical care. We identified eligible patients based on the nicardipine hospital pharmacy distribution list from two tertiary care hospitals in the Netherlands: the Isala Women's and Children's Hospital and the Erasmus Medical Center (MC). Data were collected from medical charts on patients treated from January 2006 to January 2015. The data were registered in an electronic database (SPSS 24.0). Eligible patients included all pregnant women beyond 20 weeks of gestation that had severe hypertension and were treated with intravenous nicardipine. Severe hypertension was defined as systolic blood pressure (SBP) of 160 mm Hg or more and/or diastolic blood pressure (DBP) of 110 mm Hg or more, measured at two separate times, 30 min apart, with a standard sphygmomanometer, based on phase V Korotkoff sounds. Patients were diagnosed with pregnancy-induced hypertension or pre-eclampsia (hypertension combined with de novo proteinuria of at least 300 mg/24 h). Patients were included, irrespective of previous or concomitant use of other oral antihypertensive medication.

2.2 | Intervention and outcome assessment

Nicardipine was administered by continuous infusion through a venous line. Nicardipine was continued as long as indicated, and for as long as the fetal and/or maternal condition did not warrant discontinuation, as judged by the attending obstetrician. During treatment, blood pressure was measured every 15 min, with a standard sphygmomanometer or an automated blood pressure device, or continuously, with an intra-arterial catheter in the radial artery. Mean arterial pressure (MAP) was calculated as: MAP = 1/3 (SBP–DBP) + DBP.

Patients were treated at the obstetric high dependency units of both participating hospitals.

At the Isala Women's and Children's Hospital, the starting dose of nicardipine was 1 mg/h. All patients received a loading dose of 500 mL colloids (a 6% hetastarch solution), at 1 h before starting nicardipine. The nicardipine dosage was increased every 15 min, by 0.5–1 mg/h, to a maximum of 10 mg/h infusion, or until the blood pressure reached the targeted level. In the Erasmus MC, nicardipine was started immediately, without a preload, at a starting dose of 1–3 mg/h. The dosage was increased every 15 min, by 0.5–1 mg/h, to a maximum of 10 mg/h, or until the blood pressure reached the targeted level. According to Dutch National Guidelines, all patients received a loading dose of 4 g magnesium sulfate over 20 min, followed by a maintenance dose of 1 g/h for seizure prophylaxis.[16]

Fetal viability was set at 26 weeks of gestation and/or an estimated fetal weight of 500 g or greater. All women admitted between 25^{+5} and 34 weeks of gestation received antenatal corticosteroids to facilitate fetal lung maturation. Antenatal corticosteroids were administered in two intramuscular doses of 12 mg betamethasone each, 24 h apart.

2.3 | Outcomes

Primary outcomes:

- Successful treatment, defined as reaching the target SBP of less than 160 mm Hg and DBP of less than 100 mm Hg
- Treatment duration (minutes), which started at nicardipine administration and ended when successful treatment was achieved
- Maternal safety, defined as avoidance of low blood pressure (DBP <70 mm Hg) and the absence of maternal adverse effects that required therapy discontinuation within the first 2 h of treatment

Secondary outcomes:

- Maternal hemodynamic parameters, measured 1 h after nicardipine initiation
- Maternal adverse effects during treatment, including headache, nausea, and vomiting, pulmonary edema, low calcium levels, reflex tachycardia (increases of more than 20 beats per minute [bpm]), bradycardia (below 40 bpm), or eclampsia
- Cesarean deliveries, based on fetal indications, as a result of maternal hypotension
- Apgar score, umbilical artery pH, and excess base in the maternal–fetal acid–base balance.

Pulmonary edema was defined as the presence of typical signs of pulmonary edema on a CT scan or chest X-ray and/or three or more clinical parameters of pulmonary edema (dyspnea, basal crepitations, oxygen saturation <95%, arterial oxygen content <10 kPa, need for supplemental oxygen and/or administration of diuretics).

2.4 | Statistical analyses

Categorical data are presented as the number (%) and groups were compared with the chi-squared test. Skewed data are presented as the median (minimum–maximum) and/or interquartile range, and groups were compared with the Mann–Whitney *U* test. Normally distributed data are presented as the mean (standard deviation) and groups were compared with the independent samples *t* test. Univariate logistic regression was performed to test associations between variables. Statistical analyses were performed with SPSS version 24 (IBM). Finally, all study results were compared between the two participating hospitals.

2.5 | Ethical approval

This study was reviewed and approved by the Medical Ethics Committees of the Erasmus MC (reference number MEC-2011-144 on May 10, 2011) and the Isala Women's and Children's Hospital.

3 | RESULTS

In total, 1042 pregnant women were treated with nicardipine during the study period, according to the hospital pharmacy distribution lists. We excluded 114 women from the study, because their blood pressure lowered without medication or they were mentioned twice on the list. Intravenous nicardipine administration was started in 928 patients. We excluded 98 women, because SBP and DBP were below 160 and 110 mm Hg, respectively, when the nicardipine infusion started, or they were transferred to another hospital, or nicardipine had been started in another hospital. One woman received nicardipine before 20 weeks of gestation. Finally, a total of 830 patients were included in this study. Table 1 shows the baseline demographics and clinical characteristics of all participants.

Data on primary outcomes are shown in Table 2. Data were missing on treatment success for 27 women. Nicardipine was effective in 100% of 803 women, and of these, 77.4% reached successful treatment within 2 h. Low DBP occurred temporarily within the first 2 h in 42.7% of women. In 21.5% of women, nicardipine was discontinued after successful treatment was achieved, because of maternal adverse effects.

The mean gestational age at delivery was 33 weeks (range 21–42 weeks). Vaginal deliveries were achieved in 338 women, and 485 women underwent cesarean sections.

At 1 h after nicardipine initiation, nicardipine resulted in significant reductions in SBP, DBP, and MAP (Table 3). The SBP was less than 160 mm Hg in nearly two out of three women. The MAP was below 120 mm Hg in three out of four women. In some women (11.5%), the maternal heart rate increased significantly, and reflex tachycardia occurred. Conversely, in other women (20.6%), the maternal heart rate decreased.

TABLE 1 Baseline demographic and clinical characteristics of pregnant women with hypertension that were treated with nicardipine

Characteristic	Category	Total, *N* (%)	Isala Zwolle	Erasmus MC	*p* value[a]
		830	362	468	
Gravidity	1	417 (50.2%)	203 (56.1%)	214 (45.7%)	0.003
	≥2	413 (49.8%)	159 (43.9%)	254 (54.3%)	
Parity	0	534 (64.3%)	250 (69.1%)	284 (60.7%)	0.012
	≥1	296 (35.7%)	112 (30.9%)	184 (39.3%)	
Age (years); *n* = 830		31 (18–57)	30 (18–46)	31 (18–57)	0.007
Pre-pregnancy BMI, *n* = 522 (308 missing)		25.6 (18–55)	25.9 (18–50)	25.3 (18–55)	0.185
General history	None	429 (51.7%)	224 (61.9%)	205 (43.8%)	<0.001
	PEH	130 (16.3%)	52 (14.4%)	78 (16.7%)	0.366
	Kidney disease	30 (3.8%)	12 (3.3%)	18 (3.8%)	0.684
	Diabetes	25 (3.1%)	10 (2.8%)	15 (3.2%)	0.711
	Cardiac disease	16 (1,9%)	2 (0.6%)	14 (3%)	0.011
Ethnicity	Caucasian	524 (70.8%)	292 (80.7%)	232 (49.6%)	<0.001
	Asian	37 (5%)	9 (2.5%)	28 (6%)	0.015
	African	110 (1.4%)	17 (4.7%)	93 (19.9%)	<0.001
	Mediterranean	59 (7.9%)	4 (1.1%)	55 (11.8%)	<0.001
GA at admission (weeks), *n* = 823		31.6 (20.3–42.1)	34.7 (21.1–2.1)	30.4 (20.3–1.6)	<0.001
SBP at t = 0 (mm Hg), *n* = 826		170 (140–270)	170 (150–240)	172 (140–270)	<0.001
DBP at t = 0 (mm Hg) *n* = 826		105 (80–145)	105 (80–131)	105 (80–145)	0.248
MAP at t = 0; *n* = 826		127 (107–177)	127 (107–163)	127 (107–177)	0.002

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; GA, gestational age; MAP, mean arterial blood pressure; PEH, pre-existing hypertension; SBP, systolic blood pressure.

[a]Evaluation of the mean differences between groups.

TABLE 2 Clinical outcomes in women with hypertension during pregnancy that were treated with nicardipine

Outcome	Definition	Summary statistics
Successful treatment	SBP <160 and DBP <100 mm Hg	803 (100%)
Successful treatment <2 h		621/802 (77.4%)
Time to successful treatment (min)		76.5 (5–3175)
Low blood pressure	DBP <70 mm Hg	349/818 (42.7%)
Discontinuation, because of maternal adverse effects	Hypotension	90/830 (10.8%)
	Low calcium	18/830 (2.2%)
	Tachycardia	4/830 (0.5%)
	Bradycardia	8/830 (1%)
	Other	58/830 (7%)

Note: Data are the number (%) or median (range).
Abbreviations: DBP, diastolic blood pressure; SBP, systolic blood pressure.

Nicardipine treatment reduced the occurrences of headache, nausea, and vomiting (Table 4). The incidence of pulmonary edema increased, and the median serum calcium decreased. One patient developed bradycardia, which immediately stopped after nicardipine was discontinued.

In one woman (0.1%), fetal distress due to maternal hypotension resulted in a cesarean section. In 46 women, fetal demise occurred because of pregnancy termination or a non-intervention policy (Table 5).

The success rate for nicardipine was 100% in both hospitals (Table 6), and the times to success were comparable. We noted no clinically relevant differences in hemodynamic parameters at 1 h after treatment initiation between the two hospitals. However, low DBP occurred significantly more frequently at Erasmus MC (47%) compared with Isala Women's and Children's Hospital (36%). Consequently, nicardipine was discontinued more frequently at Erasmus MC than at Isala Women's and Children's Hospital.

4 | DISCUSSION

This study showed that intravenous nicardipine successfully reduced blood pressure in all women. A previous study also showed successful treatment in all patients (*n* = 27), when they used nicardipine as an escape medication for other treatment options (ketanserin or dihydralazine).[13] A previous review confirmed that nicardipine had a high success rate (91%) for treating severe hypertension in pregnancy.[14] Both SBP and DBP were significantly reduced in all patients. Our definition of treatment success was based on previous evidence that the risk of stroke increased when

TABLE 3 Hemodynamic parameters in pregnant women with hypertension, at 1 h after starting nicardipine

Parameter	Before nicardipine, $n = 826$	After 1 h, $n = 800$	p value[a]
SBP (mm Hg)	170 (140–270)	152 (86–288)	<0.001
DBP (mm Hg)	105 (80–145)	91 (34–130)	<0.001
MAP (mm Hg)	127 (107–177)	112 (51–161)	<0.001
Maternal heart rate (bpm)	81 (47–144)	90 (40–149)	<0.001
Reflex tachycardia		92 (11.5%)	
Decrease in heart rate		117 (20.6%)	
SBP <160 mm Hg		507 (63.4%)	
MAP <120 mm Hg		608 (75.8%)	

Note: Data are the mean (interquartile range) or the number (%).

Abbreviations: bpm, beats per minute; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; SBP, systolic blood pressure.

[a]Evaluation of the mean differences between groups with 95% confidence intervals (two-sample *t* test).

TABLE 4 Maternal adverse effects in pregnant women during nicardipine treatment for hypertension

Adverse effects	Before nicardipine	During nicardipine	p value[a]
Headache	354/827 (42.7%)	113/742 (15.2%)	<0.001
Nausea and vomiting	224/828 (27%)	39/742 (5.3%)	<0.001
Pulmonary edema[b]	4/830 (0.5%)	14/830 (1.7%)	0.027
Calcium (mmol/L) corrected for serum albumin (g/L)	2.26 (1.65–2.95) 0.18	2.14 (1.34–2.48) 0.2	<0.001
Tachycardia		73/742 (9.8%)	
Bradycardia		1/742 (0.1%)	
Eclampsia	4/830 (0.5%)	1/830 (0.1%)	0.200

Note: Data are the number (%) or median (range).

[a]Evaluation of the mean differences between groups with 95% confidence intervals (two-sample *t* test).

[b]Pulmonary edema was defined as the presence of typical signs of pulmonary edema on CT or chest X-ray images and/or three or more of the following clinical signs: dyspnea, basal crepitations, oxygen saturation <95%, arterial oxygen content <10 kPa, need for supplemental oxygen and/or administration of diuretics.

TABLE 5 Fetal and neonatal outcomes after pregnant mothers with hypertension were treated with nicardipine

Fetal outcomes	Number/total (%)
Fetal demise	46/815 (5.6%)
Fetal distress followed by emergency cesarean section	297/830 (35.8%)
Fetal distress followed by emergency cesarean section <4 h after starting nicardipine	22/830 (2.7%)
Fetal distress due to maternal hypotension, followed by emergency cesarean section <4 h after starting nicardipine	1/830 (0.1%)
Full course of antenatal corticosteroids	292/403 (72.5%)
Neonatal outcomes	
Umbilical artery pH	7.25 (6.70–7.43)
Base excess	−4.0 (−35 to 10)
Apgar score at 1 min	7 (0–10)
Apgar score at 5 min	8 (1–10)
Apgar score at 10 min	9 (5–10)

Note: Data are the number (%) or median (range).

TABLE 6 Comparisons between the two participating hospitals (Isala Zwolle and Erasmus MC) for outcomes in pregnant mothers with hypertension treated with nicardipine

Primary outcomes	Definition	Isala Zwolle	Erasmus MC	*p* value[a]
Successful treatment	SBP <160 and DBP <100 mm Hg	362 (100%)	468 (100%)	–
Time to successful treatment (min)		79 (5–1678)	75 (5–3175)	0.594
Hypotension; *N* = 818	DBP <70 mm Hg	130 (36.3%)	219 (46.8%)	0.001
	DBP <60 mm Hg	35 (9.8%)	74 (15.8%)	0.008
Maternal adverse effects that led to nicardipine discontinuation	Hypotension	28 (7.7%)	62 (13.2%)	0.013
	Low calcium	18 (4.9%)	0 (0%)	<0.001
	Tachycardia	1 (0.3%)	3 (0.6%)	0.465
	Other	21 (5.8%)	37 (7.9%)	–
Secondary outcomes				
Hemodynamics after 1 h				
SBP (mm Hg)		151 (92–205)	153 (86–288)	0.0428
DBP (mm Hg)		95 (54–125)	90 (34–130)	<0.001
MAP (mm Hg)		113 (70–147)	111 (51–161)	0.013
Maternal heart rate (bpm), *N* = 569		89 (40–143)	91 (48–150)	0.067
Increase MHR >20 bpm		44 (15.9%)	48 (16.4%)	0.858
Decrease MHR <20 bpm		56 (20.2%)	61 (20.9%)	0.842
SBP <160 mm Hg		226 (64.4%)	281 (62.6%)	0.599
MAP <120 mm Hg		263 (74.9%)	345 (76.5%)	0.576
Maternal adverse effects				
Headache		58 (16%)	55 (11.8%)	0.075
Nausea and vomiting		15 (4.1%)	24 (5.1%)	0.506
Pulmonary edema		4 (1.1%)	10 (2.1%)	0.252
Calcium (corrected for serum albumin)		2.1 (1.34–2.41)	2.17 (1.44–2.48)	<0.001
Tachycardia		44 (12.2%)	29 (6.2%)	0.003
Bradycardia		3 (0.8%)	3 (0.6%)	0.752
Fetal outcome				
Full course of antenatal corticosteroids		94 (73.4%)	198 (72%)	0.764

Note: Data are the number (%) or median (range).

Abbreviations: bpm, beats per minute; DBP, diastolic blood pressure; MAP, mean arterial blood pressure; MHR, median heart rate; SBP, systolic blood pressure.

[a]Evaluation of the mean differences between groups with 95% confidence intervals (two-sample *t* test).

SBP was 160 mm Hg or more and a consensus that DBP should be below 100 mm Hg.[17]

Previous studies showed that the desired blood pressure could be reached within a short time after initiating nicardipine. In one study, target blood pressures were reached within 23 min in 70% of patients, and within 130 min in 91% of patients.[14] Hanff et al showed that target blood pressures were reached within a median of 23 min.[13] Our data confirmed those findings. No data were available on the times to target blood pressures for other antihypertensives.

In our opinion, the intravenous route was preferable for achieving rapid blood pressure control. The California Maternal Quality Care Collaborative advised that, for severe hypertension, treatment should start within 1 h, to reduce blood pressure as soon as possible.

The high nicardipine success rate was comparable to the success rates of the more commonly prescribed calcium antagonist nifedipine (84%) and (di)hydralazine (88%), and higher than those achieved with labetalol (80%)[11] and ketanserin (73%–79%).[18,19] A previous systematic review and meta-analysis showed that the rates of achieving target blood pressures were not significantly different for diazoxide, nicardipine, nifedipine, hydralazine, and other agents.[20] Another meta-analysis showed comparable success rates with nicardipine and labetalol, but nicardipine was more often associated with headache, tachycardia, and nausea, and labetalol was more often associated with hypotension.[15] It is difficult to draw definitive conclusions about the effectiveness of different treatment options because of inconsistent results among studies and the different definitions for successful treatment. However, no previous study has shown 100% successful treatment and significant blood pressure reductions in all

patients. Nicardipine is licensed for treating acute severe hypertension and postoperative hypertension. For those indications, it has shown potent, rapid blood pressure reductions with intravenous administration.[21] Here, we showed that, in pregnancy, nicardipine also potently and rapidly reduced blood pressure.

The high success rate and short time to success had some disadvantages. We found a high rate of maternal low blood pressure during nicardipine treatment. In 90 of 349 women, treatment had to be (temporarily) stopped because of low blood pressure. However, after stopping or reducing the dosage, the blood pressure resolved within minutes, in all cases, without compromising the maternal or fetal condition. Therefore, in this case series, only one case of clinically relevant hypotension occurred during nicardipine treatment. After an emergency cesarean section, a healthy neonate was born.

Pharmacokinetic data showed that nicardipine had a short half-life (2–5 min).[21] The short half-life is a plausible explanation for why low blood pressure rapidly resolved after a dosage reduction. With longer intravenous infusions (24–48 h), the half-life increased (from 1 to 2 h). In our experience, this longer half-life did not result in an increase in low blood pressure occurrences because, in most women, blood pressure stabilized after 24–48 h or the infant was delivered. Other potential causes of maternal hypotension include epidural/spinal anesthesia during labor, a cesarean section, or co-medication. In addition, the concomitant use of calcium antagonists and magnesium sulfate may have a synergistic effect on blood pressure. Previous case reports found that neuromuscular blockade and hypotension occurred with nifedipine combined with magnesium sulfate, but they found no causal explanation.[22,23] Two other studies found that magnesium sulfate combined with nicardipine had no adverse reactions.[13,24] The concomitant use of magnesium sulfate and calcium antagonists should be monitored carefully.

The two hospitals we studied had distinct outcomes. A logistic regression analysis showed that a higher starting dosage (>1 mg/h) did not predict low blood pressure. However, the preload with colloid fluid might explain the lower incidence of low blood pressure in the Isala Women's and Children's Hospital. Currently, a preload is standard in both hospitals.

Pulmonary edema associated with pre-eclampsia has a multifactorial origin. The factors that appear to play a role include fluid overload, reduced plasma oncotic pressure, increased capillary permeability, and increased pulmonary capillary hydrostatic pressures, caused by elevated cardiac afterload.[25] Studies have shown that nicardipine significantly decreased systemic vascular resistance (afterload) and increased cardiac output and ejection fraction.[21,26] Accordingly, one might expect nicardipine to have a protective effect on pulmonary edema, consistent with the low incidence of pulmonary edema (1.7%) observed in our population, compared with previous studies (3%–10%).[2] However, we found that the incidence of pulmonary edema increased during the nicardipine infusion. In considering potential causes, we ruled out several factors. In our population, none of the patients with pre-existing cardiac disease developed pulmonary edema. Volume overload was an unlikely factor, because most cases occurred in the Erasmus MC, and so, they did not receive a fluid preload. A logistic regression analysis showed that differences in demographic characteristics between the two cohorts were not associated with pulmonary edema, nor was the use of co-medication (labetalol, nifedipine, magnesium sulfate). The treatment-to-delivery interval was not significantly different between groups with and without pulmonary edema (3.5 days vs 3 days, respectively, $p = 0.427$). Therefore, the pre-delivery management did not increase the risk of developing pulmonary edema. However, another logistic regression analysis showed that gestational age at admission was a significant predictor of pulmonary edema. Women that developed pulmonary edema had an earlier gestational age (median 29 weeks) compared with women without pulmonary edema (median 32 weeks, $p < 0.001$). Therefore, a potential explanation could be that the pathophysiology was different between women with early-onset and late-onset pre-eclampsia, as mentioned previously.[27] Early-onset pre-eclampsia may be initiated by compromised maternal cardiovascular adaptations, which can increase the risk of pulmonary edema.

During treatment, serum calcium declined and, in some women, the nicardipine infusion was stopped because of low serum calcium, although no maternal symptoms occurred. In our study population, low serum calcium was most likely caused by hypermagnesemia, which suppresses parathyroid hormone secretion.[28] Hypocalcemia induced by nicardipine has not been described previously. Hence, when symptomatic hypocalcemia occurs (spasm, tetany, seizures, decreased cardiac function, prolonged QT interval) during the magnesium sulfate infusion, we advise to (temporarily) stop the magnesium sulfate infusion and correct calcium levels with intravenous calcium therapy. It might not be necessary to stop the nicardipine infusion, when hypocalcemia occurs.

Reflex tachycardia occurred frequently, and in a few cases (0.5%), it led to therapy discontinuation. However, nicardipine was associated with lower frequencies of other symptoms, like headache, nausea, and vomiting.

Severe bradycardia (10 bpm) occurred in one woman at 10 h after nicardipine was started. The bradycardia resolved after stopping the nicardipine infusion. Bradycardia during a nicardipine infusion has rarely been described in the literature.[29] Direct sinus bradycardia due to nicardipine was described in a rat model.[30] Arima et al concluded that the cause of bradycardia was unclear; potential contributing factors included sympathetic tone depression by epidural anesthesia, hypothermia, and paroxysmal atrial fibrillation.[31] Hence, during a nicardipine infusion, obstetric care units should be equipped with tools for closely monitoring hemodynamic parameters (measurements every 15 min), particularly in the first 24 h after starting nicardipine. These features, combined with the fact that nicardipine must be administered intravenously, make it unsuitable for use in less-than-optimal circumstances and in low-income countries.

Our study had some limitations. It had a retrospective design, lacked a control group, and the treatment required the concomitant use of magnesium sulfate. Although magnesium sulfate may have a synergistic effect on lowering blood pressure, it cannot be withheld

from pregnant women with severe hypertension, because it has preventive effects on eclampsia. Additionally, a control group was not necessary to show treatment effectiveness, because the treatment was 100% effective. The main strengths of our study were the large cohort and the well-defined study population.

5 | CONCLUSION

To date, this study was the largest case series on the use of nicardipine for treating severe antepartum hypertension in pregnancy. We found that nicardipine was highly effective and safe for this indication. Based on its high success rate and acceptable safety profile, nicardipine should be considered a first-line treatment for women with severe hypertension in pregnancy.

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None.

AUTHOR CONTRIBUTIONS

This study was conceived by SNB, MH, JC, SH, ME, and JD. SNB, JD, and ME conducted the statistical analysis and wrote the first draft of the manuscript. MH, JC, and SH contributed significantly to data analysis, interpretation and writing of the manuscript. When compiling the manuscript, EQUATOR reporting guidelines were followed. All authors have read and approved the final version of this manuscript.

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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