Short-Acting Oral Nifedipine versus Intravenous Labetalol for the Control of Severe Hypertension in the Postpartum Period: A Retrospective Cohort Study

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Abstract

Objective This study aimed to compare the effectiveness of oral short-acting (SA) nifedipine with intravenous (IV) labetalol for the treatment of postpartum (PP) severe hypertension.

Study Design We conducted a retrospective cohort study of women who delivered at a tertiary care facility between January and December 2018, had not previously received antihypertensive medication, and required treatment for PP severe hypertension defined as systolic blood pressure (SBP) $\geq$ 160 mm Hg and/or diastolic blood pressure (DBP) $\geq$110 mm Hg. Exposure groups were defined by the receipt of either oral SA nifedipine or IV labetalol. The primary outcome was time (minutes) to BP control (SBP $<$ 160 mm Hg and DBP $<$110 mm Hg). Secondary outcomes included number of doses required to achieve BP control, crossover to the alternative medication, and recurrence of severe range BP after the achievement of BP control. *t*-Tests and Wilcoxon–Mann–Whitney tests were used to analyze continuous variables and chi-square tests or Fisher's exact tests were used to analyze categorical variables. Multivariable linear regression models were conducted for the primary outcome, controlling for potential confounders in a sequential fashion across three models. A Kaplan–Meier plot was also created.

Results Of the 99 women included, 74 received oral SA nifedipine and 25 received IV labetalol. There was no significant difference in minutes to initial BP control between groups (30.5 minutes [interquartile range, IQR: 20.0–45.0] vs. 25.0 minutes [IQR: 14.0–50.0]; $p = 0.82$) or in the rate of recurrent severe BP. However, patients who received nifedipine required fewer doses to achieve control ($p < 0.01$) and did not require crossover (0 vs. 12%, $p = 0.01$).

Keywords

- blood pressure
- postpartum
- severe hypertension
- nifedipine
- labetalol

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Conclusion Both oral SA nifedipine and IV labetalol are effective options for treating PP severe hypertension. An initial choice of nifedipine was associated with a lower requirement for subsequent doses of medication and no need for crossover to an alternative antihypertensive medication.

Key Points

- Nifedipine and labetalol effectively treat PP severe HTN.
- Nifedipine requires fewer doses to treat PP severe HTN.
- Both have low recurrence rates of severe HTN.

Hypertensive disorders of pregnancy are a leading cause of maternal morbidity and mortality worldwide, with more than 50% of hypertensive-related stroke and 50% of eclamptic seizures occurring in the postpartum (PP) period.[1] Similar to a hypertensive emergency in a pregnant individual, the primary goal during a PP hypertensive emergency is to reduce BP safely and rapidly to limit preventable complications (e.g., eclampsia, stroke, death), and the American College of Obstetricians and Gynecologists (ACOG) emphasizes the importance of treating severe range blood pressure (BP) emergently within 30 to 60 minutes.[2] However, despite a desperate need, data from prospective studies examining treatment strategies for PP hypertensive emergency are lacking. In the absence of PP-specific data, current treatment protocols for PP hypertensive emergency are extrapolated from clinical trials examining the treatment of hypertensive emergency in pregnancy and recommend the use of either oral short-acting (SA) nifedipine or intravenous (IV) labetalol.

Importantly, the pathophysiology of PP hypertension, which is often driven by fluid shifts from the extravascular to intravascular space, loss of pregnancy-associated vasodilation, and IV fluid administration,[3] may differ from the antepartum mechanisms that drive hypertension. Thus, the two medication classes that are safe and effective for the treatment of a hypertensive emergency in pregnancy may not be equally effective at rapidly treating PP severe-range hypertension.[4,5] The objectives of this study were to examine which SA antihypertensive (oral SA nifedipine or IV labetalol) better treats a PP hypertensive emergency, as defined by: (1) shorter time in minutes to achieve therapeutic BP, (2) lower number of doses required to achieve therapeutic BP, (3) lower incidence of crossover to the alternative antihypertensive medication to achieve therapeutic BP, and (4) lower incidence of recurrent severe-range hypertension after achievement of therapeutic BP.

Materials and Methods

Study Cohort

This was a retrospective cohort study of women aged ≥ 18 years who gave birth between January 1 and December 31, 2018 at the Columbia University Irving Medical Center and were prescribed one of two SA antihypertensives (oral SA nifedipine or IV labetalol) for the treatment of PP severe hypertension. Severe hypertension was defined as a systolic BP (SBP) ≥ 160 mm Hg and/or diastolic BP (DBP) ≥ 110 mm Hg in the PP period. For this analysis, the PP period consisted of 42 days (6 weeks) beginning on the day of delivery and qualifying severe-range BP values could occur during the delivery hospitalization or a readmission for any indication.

Women were excluded from this analysis if the treatment of their hypertensive emergency went off-protocol or there was no clear documentation of the timing of BP measurement or medication administration (►Fig. 1).

Maternal sociodemographic characteristics and medical and surgical history were extracted from the electronic medical record via chart review. Reported heart rate was the value noted immediately prior to receipt of the first antihypertensive medication dose. Exposure groups were defined according to the initial medication received, and crossover to the other agent was allowed.

Outcomes

The primary outcome was defined as time in minutes required to achieve an initial therapeutic BP (SBP < 160 mm Hg and DBP < 110 mm Hg). Specifically, time to achieve an initial therapeutic BP was measured from the time of administration of the antihypertensive agent until a therapeutic BP was achieved. Secondary outcomes included the total number of doses required to achieve initial therapeutic BP, crossover to the alternative agent, and the recurrence of severe hypertension (defined as at least one severe-range BP measurement after initial BP control was achieved).

Statistical Analyses

Baseline demographic and clinical characteristics were compared between exposure groups. Continuous variables were compared using *t*-tests or Wilcoxon–Mann–Whitney tests, whereas binary and categorical variables were analyzed using chi-square tests or Fisher's exact tests, as appropriate. Normality for continuous variables was assessed using graphical methods. In addition to demographics, the association of outcomes with the two exposure groups was also determined using the methods above. Multivariable linear regression

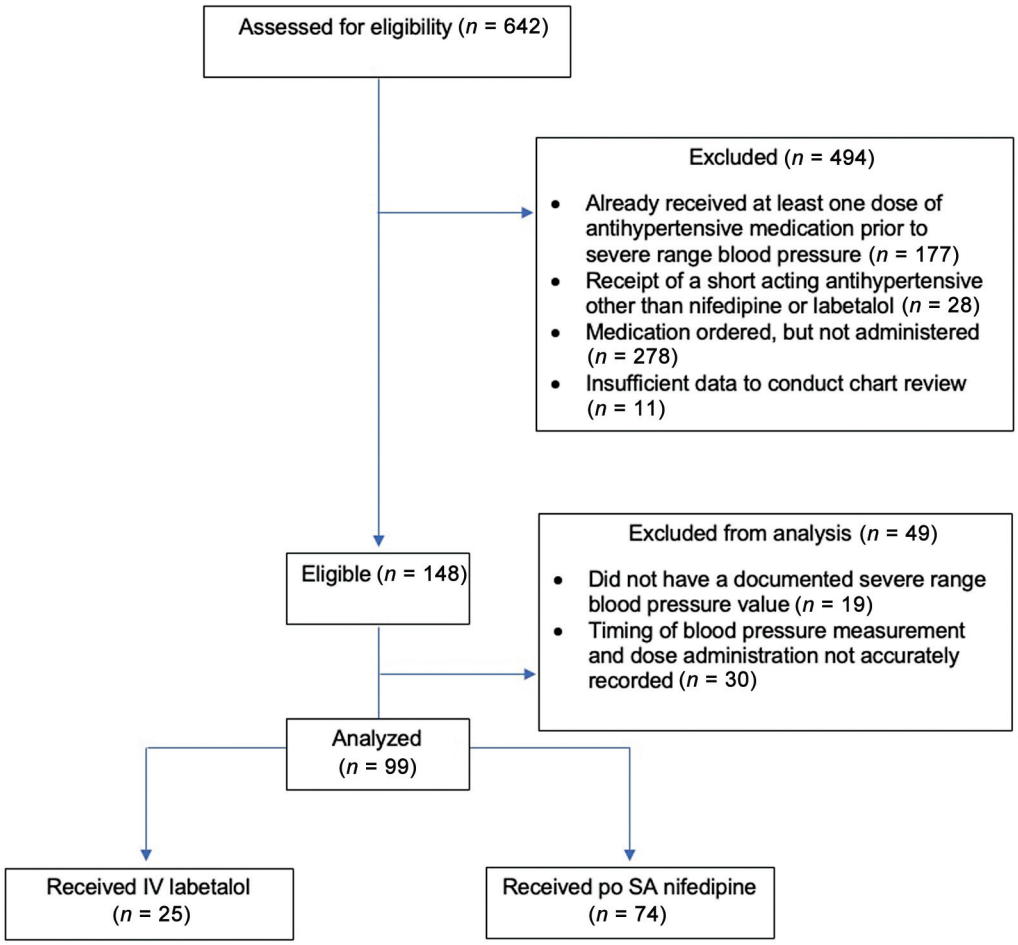

Fig. 1 Flow chart of patients enrolled with postpartum severe hypertension treated with either oral short-acting (oral SA) nifedipine or intravenous (IV) labetalol.

models were conducted for the primary outcome, controlling for potential confounders that were chosen a priori, in a sequential fashion across three models: unadjusted regression (Model 1); a history of chronic and/or gestational hypertension and baseline BP (Model 2); and antihypertensive administration antepartum, self-reported race, gestational age at delivery, insurance (commercial vs. Medicaid), and parity (Model 3). Patients who crossed over to the second medication before achieving BP control were analyzed based on the initial medication they received. In addition, a Kaplan–Meier curve was plotted using the survival plot macros from SAS, with crossovers censored at the time of the last BP measurement taken with the starting medication. Statistical analyses were conducted using SAS version 9.4 (SAS Institute, Inc., Cary, NC), R (R Foundation for Statistical Computing, Vienna, Austria), and RStudio (Posit Software, PBC, Boston, MA).

Two-sided tests were conducted and p-values < 0.05 were considered significant for all analyses. As this was an exploratory study, no adjustment for multiple comparisons was made. This study was approved by the Institutional Review Board at the Columbia University Medical Center, with a waiver of informed consent.

Results

We identified 99 patients with PP severe HTN, 74 were initially treated with nifedipine and 25 with labetalol (►**Fig. 1**). A comparison of baseline characteristics revealed that patients who received labetalol were significantly more likely to have delivered at a later gestational age, have a higher SBP at the time of medication administration, and have public insurance (►**Table 1**).

There was no significant difference in time to achieve initial therapeutic BP for nifedipine (median: 30.5 [interquartile range, IQR: 20.0–45.0]) as compared with labetalol (25.0 [14.0–50.0]; $p = 0.82$) (►**Table 2**). This finding remained consistent after adjustment for potential confounders (►**Table 3**). Time to initial BP control for both nifedipine and labetalol was also assessed using Kaplan–Meier curves and analyzed using the log-rank test and demonstrated no difference in time to event curves between treatment groups when considering crossovers as censored (►**Fig. 2**). We found patients initially treated with nifedipine required significantly fewer doses of medication to reach target BP and were less likely to require crossover to labetalol to achieve BP control. The incidence of recurrent severe

Table 1 Baseline characteristics of patients with postpartum severe hypertension stratified by initial treatment medication received

Characteristics	Overall $n=99$	Nifedipine $n=74$	Labetalol $n=25$	*p*-Value
Age (y)	32 ± 6	33 ± 6	32 ± 6	0.98
Race				0.02
Black	26 (26)	24 (32)	2 (8)	
White	41 (41)	31 (42)	10 (41)	
Asian	2 (2)	2 (3)	0 (0)	
Unknown/not reported	30 (30)	17 (23)	13 (52)	
Ethnicity				0.72
Hispanic/Latina	42 (42)	33 (45)	9 (36)	
Not Hispanic/Latina	34 (34)	24 (32)	10 (40)	
Unknown/not reported	23 (23)	17 (25)	6 (24)	
Medicaid	50 (51)	34 (46)	16 (64)	0.12
Primiparity	50 (51)	37 (50)	13 (52)	0.86
Gestational age at delivery (wk)	38 [35–39]	38 [35–39]	39 [38–40]	0.01
Cesarean delivery	55 (56)	42 (57)	13 (52)	0.68
Chronic hypertension[a]	17 (18)	13 (18)	4 (17)	>0.99
Gestational diabetes mellitus[b]	9 (10)	7 (10)	2 (8)	>0.99
Body mass index (kg/m^2)	31 [28–37]	31 [27–37]	32 [28–36]	0.42
Initial systolic BP (mm Hg)	166 [162–173]	166 [162–172]	172 [165–177]	0.01
Initial diastolic BP (mm Hg)	97 [88–105]	96 [85–105]	100 [92–104]	0.28
Heart rate (bpm)	74 [64–86]	74 [63–87]	75 [66–86]	0.47

Abbreviations: BP, blood pressure; IQR, interquartile range; SD, standard deviation.
Note: Data presented as mean ± standard deviation, median [IQR], or *n* (%).
[a]Information only available on 97 participants.
[b]Information only available on 95 participants.

Table 2 Time to initial blood pressure control and secondary outcomes stratified by initial treatment medication

	Nifedipine $n=74$	Labetalol $n=25$	*p*-Value
Primary outcome			
Time (min) to initial BP control	30.5 [20.0–45.0]	25.0 [14.0–50.0]	0.82
Secondary outcomes			
Number of doses needed to achieve therapeutic BP[a]	1 [1–1]	1 [1–2]	<0.001
Crossover to alternative agent needed for initial BP control	0 (0)	3 (12)	0.01
Recurrence of severe hypertension	23 (31)	5 (20)	0.29

Abbreviation: BP, blood pressure; IQR, interquartile range.
Note: Data presented as median [IQR] or *n* (%).
[a]Crossovers, $n=74$ for nifedipine and $n=22$ for labetalol.

Table 3 Unadjusted and adjusted time to initial blood pressure control when nifedipine was used to treat postpartum severe hypertension compared with labetalol

	Time in minutes (95% CI)	*p*-Value
Unadjusted	−4.7 (−13.9, 4.6)	0.32
Model 2	−5.4 (−15.5, 4.8)	0.30
Model 3	−4.5 (−15.9, 6.9)	0.44

Abbreviation: CI, confidence interval.
Note: Model 2 was adjusted for baseline blood pressure and history of chronic or gestational hypertension. Model 3 was further adjusted for antihypertensive administration antepartum (yes or no), race, gestational age at delivery, and parity.

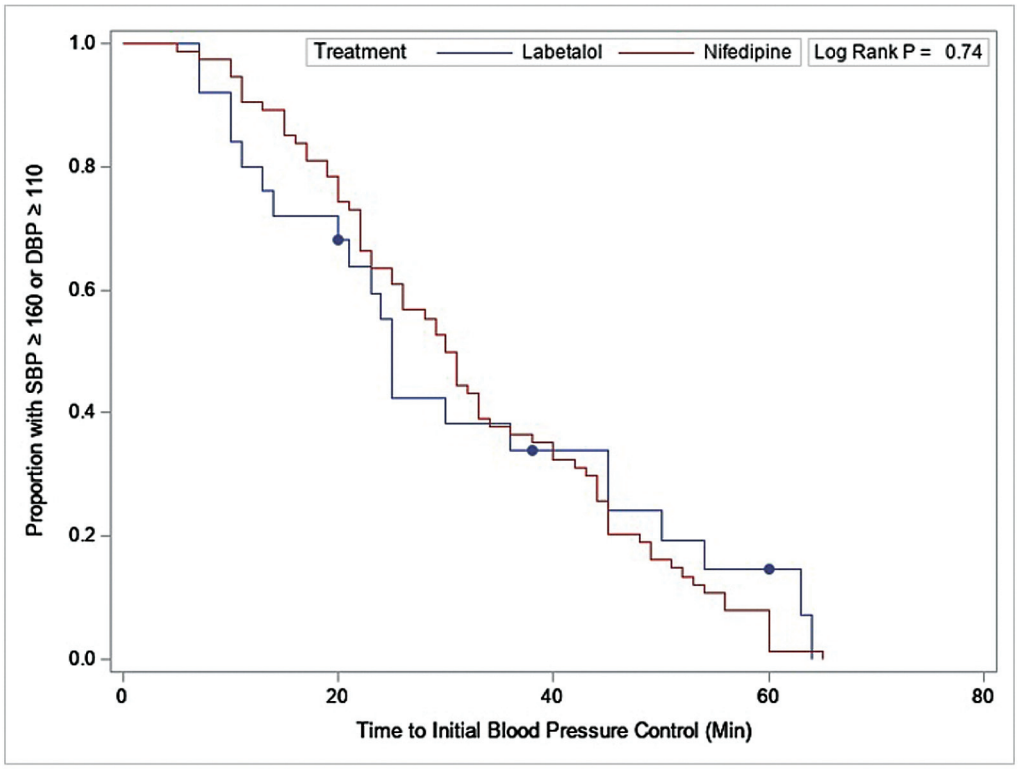

Fig. 2 Kaplan–Meier estimates of the cumulative time to blood pressure control among patients receiving oral short-acting nifedipine compared with those receiving intravenous labetalol. DBP, diastolic blood pressure; SBP, systolic blood pressure.

hypertension (31.1 vs. 20.0%; $p = 0.29$) was high in patients who were treated with either nifedipine or labetalol. Urine output was similar in both groups (►**Supplementary Table S1**, available in the online version). With respect to potential adverse medication effects, hypotension, flushing, palpitations, nausea, and headache were similar between patients treated with either nifedipine or labetalol, and there was no association between having an adverse reaction and the exposure groups (►**Supplementary Table S1**, available in the online version).

Discussion

In our retrospective cohort study of PP severe hypertension, we found that there was no difference in time to the achievement of initial therapeutic BP in individuals who received oral SA nifedipine compared with those who received IV labetalol. Further, our study suggests that patients who received oral SA nifedipine may require fewer doses to achieve a therapeutic BP and are less likely to need to cross over and receive labetalol as an alternative antihypertensive to achieve therapeutic BP. Our findings support the continued use of both oral SA nifedipine and IV labetalol as first-line agents for the treatment of severe PP hypertension. Historically, IV labetalol has been a preferred agent in this setting due to concerns about time to onset of action for an oral medication extrapolated from nonpregnant individuals. The described onset of action is 2 to 5 minutes versus 30 to 60 minutes in nonpregnant patients treated with IV labetalol versus oral SA nifedipine, respectively.[6,7] However, in our study, time to initial BP control was not significantly different between treatment groups. This is consistent with a systematic review that found no clear evidence as to which medication is most effective and should, therefore, be preferentially prescribed.[8]

Our findings that nifedipine may have additional benefits compared with labetalol for the treatment PP severe hypertension are also consistent with those of several other studies performed on patients in the antepartum period with hypertensive emergencies.[9,10] The lower number of doses required to achieve BP control is promising, as increased number of required doses may lead to delayed administration and related suboptimal BP control and adverse events. Furthermore, the need to administer more doses is a strain on nursing resources and also creates additional opportunities for medication administration error. Importantly, the opportunity to use an oral medication has important benefits in the acute setting for patients without IV access as is commonly encountered in PP clinical care, as well as in lower resources settings where qualified staff and equipment needed for administration of IV medications may be more challenging or completely unavailable. Additionally, those with contraindications to labetalol use (asthma, relative bradycardia) benefit from an effective alternative.

In addition to these therapeutic benefits of nifedipine, it offers additional potential benefits for the management of PP hypertension. Our study suggested that patients treated with nifedipine were less likely to need an alternative agent to achieve their target BP. Since many of these patients will

need to transition to a longer-acting medication, use of a single medication has the potential to facilitate this transition. Further work is needed to see if this simplified transition from short- to long-acting medication may have the additional benefit of reducing length of stay.

Although not directly examined in our study, nifedipine has also been shown to increase renal blood flow and improve urine output,[9] specifically in the PP setting.[11] Nifedipine related enhanced urine output is hypothesized to be secondary to the selective renal arteriolar vasodilation, leading to increased renal perfusion. The pathophysiology of PP preeclampsia predisposes patients to intravascular volume depletion, and so a better understanding of mechanisms to optimize renal function in this context warrants further exploration and possible benefits for the management of PP preeclampsia who simultaneously require hypertensive treatment. Additionally, a study by Tolcher et al suggests that nifedipine may also lower cerebral perfusion pressure (CPP), improving autoregulation and potentially preventing neurovascular complications of preeclampsia.[12] Gaining a better understanding of medication profiles and rapidly changing maternal physiology specific to the peripartum period will be instrumental in understanding how to reduce maternal morbidity and mortality in this complex time. Findings from pregnancy may not be generalizable to the PP period.

Limitations and Strengths

Our study has several limitations that invite follow-up studies for further exploration. In accordance with protocol initiatives set out by the ACOG and the Safe Motherhood Initiative, BP measurements should be taken every 10 to 20 minutes after administration of a SA antihypertensive medication. The retrospective nature of our data meant that, despite clinical practice and compliance of hospital protocols with these initiatives, subsequent BP measurements were often not taken as frequently nor recorded as clearly in the electronic medical record as is recommended. Also, our study had a relatively small sample size, and the treatment groups were unbalanced due to local practices, potentially limiting our power to find clinically significant results. An additional limitation of our study is a lack of information about the concurrent use of magnesium sulfate, a commonly used medication in the peripartum period for seizure prophylaxis that has documented antihypertensive effects.[13]

Our study has several strengths. To our knowledge, it is the first to compare oral SA nifedipine and IV labetalol in treating severe hypertension, specifically in the PP period. Several studies have compared the efficacy of antihypertensives in the acute management of hypertensive emergencies in pregnancy.[8,9] The pathophysiology of PP hypertension is thought to be uniquely related to profound fluid shifts in the peripartum period secondary to a rise in intravascular volume related to mobilization of extravascular fluid.[4,5] For this reason, the efficacy of antihypertensives in the PP period may differ. The results of our analysis contribute to a better understanding of pharmacokinetics of these medications unique to the PP period.

Conclusion

A call to action for timely treatment of hypertensive emergencies in the PP period has been established to reduce maternal morbidity and mortality. However, evidence-based guidelines demonstrating optimal drug treatment regimens have yet to be established. Our study is the first to address this knowledge gap in the PP setting. Larger randomized clinical trials are needed to validate these findings and further understand the trajectory of BP reduction from drug administration. Data from this area of research will inform clinical guidance for treatment algorithms for PP hypertensive emergencies. Further, an optimized antihypertensive medication regimen may be associated with improved maternal morbidity outcomes and safety, reduced lengths of maternal hospitalization, and decreased need for readmission in the PP period.

Note

These findings were presented in poster format at the 41st Annual Pregnancy Meeting, Society for Maternal-Fetal Medicine in Virtual Format.

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Conflict of Interest

None declared.

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