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Full Length Article

Optimal treatment for women with acute hypertension in pregnancy; a randomized trial comparing intravenous labetalol versus nicardipine

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ABSTRACT

Objectives: Blood pressure control in severe hypertension of pregnancy is crucial for mother and neonate. In absence of evidence, guidelines recommend either intravenous labetalol or nicardipine. We compared the effectiveness and safety of these two drugs in women with severe hypertension in pregnancy.

Study design: We performed an open label randomized controlled trial. Women with a singleton pregnancy complicated by severe hypertension (systolic ≥ 160 mmHg and/or diastolic ≥ 110 mmHg) requiring intravenous antihypertensive treatment were randomized to intravenous labetalol or intravenous nicardipine. The primary outcome was a composite adverse neonatal outcome defined as severe Respiratory Distress Syndrome (RDS), Broncho Pulmonary Dysplasia (BPD), Intraventricular Hemorrhage (IVH) IIB or worse, Necrotizing Enterocolitis (NEC), or perinatal death defined as fetal death or neonatal death before discharge from the neonatal intensive care unit (NICU).

Based on a power analysis, we estimated that 472 women (236 per group) needed to be included to detect a difference of 15% in the primary outcome with 90% power. The study was halted prematurely at 30 inclusions because of slow recruitment and trial fatigue.

Results: Between August 2018 and April 2022, we randomized 30 women of which 16 were allocated to intravenous nicardipine and 14 to intravenous labetalol. The composite adverse neonatal outcome was not significantly different between the two groups (25 % versus 43 % OR 0.28 (95 % CI 0.05–1.43), p = 0.12)). Respiratory distress syndrome occurred more often in the labetalol group than in the nicardipine group (42.9 % versus 12.5 %). Neonatal hypoglycemia occurred more often in the nicardipine group than in the labetalol group (31 % versus 7 %). Time until blood pressure control was faster in women treated with nicardipine than in women treated with labetalol (45 (15–150 min vs. 120 (60–127,5) min).

Conclusion: In our prematurely halted small RCT, we were unable to provide evidence for the optimal choice of treatment for severe hypertension to improve neonatal outcome and/or to obtain faster blood pressure control. Differences in Respiratory distress syndrome and neonatal hypoglycemia between the groups might be the result of coincidental finding due to the small groups included in the study. A larger randomized trial would be needed

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to determine the safest and most efficacious (intravenous) therapy for severe hypertension in pregnancy. This study emphasizes the challenges of conducting a RCT for the optimal treatment for these women.

1. Introduction

Hypertensive disorders of pregnancy (HDP) are the most common complications in pregnancy with short- and long-term risks for mother and neonate [1–3]. Adequate blood pressure control during pregnancy, during delivery and postpartum is of paramount importance for maternal and neonatal safety [4–6]. There is consensus that women with severe hypertension should receive antihypertensive drugs to lower their blood pressure, but evidence to support the first choice of intravenous antihypertensive drug is lacking [4–7]. A review on the subject concluded, "until better evidence is available, the choice of antihypertensive should depend on the clinician's experience and familiarity with a particular drug, and on what is known about adverse effects" [7]. National guidelines mention multiple options, reflecting the lack of a uniform evidence [5,6].

Therefore, in this study we studied the clinical effectiveness and safety of two different intravenous treatment regimens for acute hypertension in pregnancy, i.e. labetalol and nicardipine. The choice to compare labetalol and nicardipine was based on literature regarding treatment effectiveness comparing labetalol and a calcium-channel blocker [7–18].

Labetalol intravenously has been adopted internationally as antihypertensive agent of choice in severe hypertension in pregnancy, because of its safety profile and minimal maternal side effects. However, neonatal side effects including bradycardia and hypoglycaemia have been recognised at high dosages [4,16]. Moreover, beta-blockers should be used with caution in patients with bronchoconstrictive disorders, compromised myocardial function, or bradycardia.

Intravenous nicardipine, a calcium-channel blocker, may be an attractive alternative since it has a high efficacy to lower maternal blood pressure, and a controllable effect due to a fast onset of action and a short elimination half-life (2 to 5 min). Reflex tachycardia seems to be the most troublesome side effect [16]. A recent case-series among over 800 pregnant women with severe hypertension in pregnancy showed the effectiveness and safety of nicardipine and the authors suggested to consider nicardipine as first-line treatment [18].

The expected faster and more controllable blood pressure regulation using intravenous nicardipine as compared to oral nifedipine, also a calcium-channel blocker, might result in less side-effects. Data from one trial (60 women) suggested that intravenous nifedipine caused a greater decrease in blood pressure than intravenous labetalol [10]. However, there are insufficient data for reliable conclusions about the comparative effects of labetalol intravenously and nicardipine intravenously. Therefore, we performed this randomized controlled trial to evaluate whether nicardipine improves neonatal outcome, due to a quicker blood pressure regulation with minimal side effects.

2. Methods

2.1. Design and setting

We performed an open label randomized controlled trial that recruited from August 2018 until April 2022 in a secondary care hospital, Haaglanden Medical Center in The Hague and a tertiary care hospital, Amsterdam UMC location VUmc, The Netherlands, respectively. The study was approved by the Medical Research Ethics Committee (no. 2017.295). All participants gave written informed consent prior to randomization. The trial was prospectively registered in the EudraCT Registry, number: 2015—005811-34 on May 7th, 2018.

2.2. Participants

Women with a singleton pregnancy, ≥24 weeks of gestation, and a first episode of severe hypertension defined as a systolic blood pressure ≥ 160 mmHg and/or diastolic blood pressure ≥ 110 mmHg with an indication for intravenous antihypertensive treatment were recruited for participation.

Exclusion criteria were maternal age < 18 years, inability to understand Dutch or English language, major fetal abnormalities, clinically relevant pulmonary edema (defined as pulmonary failure or distress requiring > 10 L of oxygen supplementation and/or pulse oximetry < 94 %), or an allergy or contra-indication for labetalol or nicardipine.

For the informed consent, potential participants were counselled by GCP trained research nurses/midwives or physicians for participation in the trial. After women provided informed consent to participate in the study, randomization took place by a web-based central randomization system and women were allocated to either labetalol or nicardipine. Allocation was executed by an algorithm in computer software ALEA Clinicals. Randomization was stratified for gestational age (<34 or ≥ 34) weeks and for participating center. As the study was not blinded, both the participant and the treating physician were aware to which group a participant was allocated.

2.3. Interventions

Participants were randomly allocated in a 1:1 ratio to receive either intravenous labetalol or nicardipine. Blood pressure was measured using a manual, validate meter using Korotkoff V. Blood pressure control aimed to keep the systolic blood pressure between 130 and 155 mmHg and a diastolic blood pressure between 85 and 105 mmHg. Blood pressure was checked every 15 min and noted at 15, 30, 60 and 120 min after the start of the study medication. After stabilization, blood pressure was checked every four hours.

Women allocated for intravenous labetalol: starting with 20 mg/hr, if blood pressure targets were not achieved within 30 min after initiating therapy, dosage was increased with incremental steps of 20 mg/hr every 30 min with a maximum dose of 2400 mg/day. Women allocated for intravenous nicardipine: starting with 1 mg/hr, if blood pressure targets were not achieved within 15 min, dosage was incrementally increased with 1 mg/hr steps every 15 min with a maximum dose of 10 mg/hr.

The clinician decided if the response was inadequate if blood pressure was above the range of 130 and 155 mmHg for systolic blood pressure and 85 and 105 mmHg for diastolic blood pressure. Moreover, if the maximal dose of the allocated study medication was reached, participants switched to the other study arm, with discontinuation of the medication of the assigned study arm.

During treatment, fetal condition was monitored using fetal heart rate monitoring until adequate blood pressure control was reached, and thereafter at least once daily. In case of a new episode of severe hypertension with an indication for intravenous antihypertensive treatment, the study medication was resumed according to the protocol as described above.

2.4. Outcomes

The primary outcome measure was a composite adverse fetal and neonatal outcome, defined as severe Respiratory Distress Syndrome (RDS), Broncho Pulmonary Dysplasia (BPD), Intraventricular Hemorrhage (IVH) IIB or worse, Necrotizing Enterocolitis (NEC), or perinatal death defined as fetal death or neonatal death before discharge from the neonatal intensive care unit (NICU). We expected that improvement of

hypertensive treatment would ensure better maternal blood pressure control, with possibly a subsequent prolonged pregnancy and as a result improved neonatal outcome.

Secondary maternal outcomes were a composite outcome that included eclamptic seizures, cerebral hemorrhage, liver hematoma or rupture, pulmonary edema, admission to the intensive care for ventilation or necessity for intra-arterial monitoring, or maternal death. Other outcomes were inadequate control of blood pressure with the necessity to switch to other antihypertensive medication arm (i.e. therapy resistance), time interval required to achieve the target blood pressure, number of incremental dosages needed for blood pressure control, mode of delivery and time from inclusion until delivery and side effects. The time to blood pressure target was assessed when both systolic and diastolic have to be within the defined target.

Perinatal outcomes were preterm birth rate < 34 and < 37 weeks gestational age, bradycardia (intrauterine or postnatal), asphyxia (defined as umbilical artery pH<7.10). Secondary neonatal outcomes were hypoglycemia, admission to the NICU, days of NICU admission, as well as the individual outcomes of the composite neonatal outcome.

2.5. Statistical analysis

Based on a power analysis, we estimated that 472 women (236 per group) needed to be included to detect a difference of 15 % in the primary outcome with 90 % power.

Data analysis was performed according to the intention-to-treat principle. Categorical variables were analyzed with a Pearson chi-square or Fisher's exact test when appropriate and expressed as a number with percentage of the total allocation arm. Continuous variables are presented as mean with standard deviation or as median with interquartile range, when respectively normally and not normally distributed. An independent samples *T*-test was used for normally distributed data, if not normally distributed the Mann-Whitney test was used. To account for within-subject variation in blood-pressure values, the difference between blood pressure values at 60 versus 0 min was calculated and compared between the two arms with a *t*-test. P-values < 0.05 were considered statistically significant.

3. Results

The study was terminated before target sample size was reached, because of slow inclusion rate and trial fatigue. A total of 30 women were randomized of whom 14 women were assigned to labetalol and 16 women to nicardipine (Table 1).

Table 1
Baseline characteristics.

	labetalol (n = 14)	nicardipine (n = 16)
Maternal age at study inclusion (years)	31.4 ± 4.6	31.7 ± 5.3
BMI prepregnancy (kg/m^2)	26.1 [25.1–28.7]	29.0 [24.2–32.7]
Nulliparous	10 (71.4)	9 (56.3)
Chronic hypertension	4 (28.6)	7 (43.8)
Systolic blood pressure at booking visit (mmHg)	134.3 ± 31.0	120.9 ± 16.0
Diastolic blood pressure at booking visit (mmHg)	80.0 [67.5–93.8]	78.0 [68.0–82.0]
Gestational age at inclusion (weeks)	31.0 [26.6–36.1]	31.5 [29.9–38.4]
Systolic blood pressure at study inclusion (mmHg)	172.6 ± 11.8	172.3 ± 11.2
Diastolic blood pressure at study inclusion (mmHg)	110.0 [104.5–110.5]	110.0 [103.0–110.0]
Women using oral antihypertensive medication in the last 24 hrs before starting study medication (%)	11 (78.6)	12 (75)

Data are described as mean ± SD, median with [IQR] or number (%) as appropriate.

Overall, baseline characteristics were comparable in the two arms, except for occurrence of chronic hypertension (44 % in the nicardipine group versus 28.6 % in the labetalol group, Table 1).

Although the rate of composite neonatal outcome was more favorable in the nicardipine group versus the labetalol group, this difference was not statistically significant (25 % versus 43 % (p = 0.12), see Table 2). Respiratory distress syndrome occurred 3.5 times more often in the labetalol group than in the nicardipine group (42.9 % versus 12.5 %, p = 0.04). We performed a post hoc analysis to correct for gestational age at randomization, but the regression model became overdispersed, and therefore uninterpretable. However, in the stratum of gestational age below 34 weeks, 4/5 neonates in the labetalol group developed RDS, compared to 2/8 in the nicardipine group.

The median number of days admitted on NICU level 3 was higher in neonates born after maternal treatment with labetalol (26.0 [9.0–48.0]) compared to treatment with nicardipine (8.0 [4.0–13.5]).

Time until blood pressure control was not statistically different in women treated with labetalol than in women treated with nicardipine group. Nicardipine reduced blood pressure with an additional 4.7 mmHg (95 % CI: −18.7–11.4) in systolic blood pressure, and 5.2 mmHg (95 % CI: −14.1–3.7) for diastolic blood pressure (Fig. 2). The time to control blood pressure appeared to be faster for women treated with nicardipine (p = 0.05, Table 3). Visual inspection showed that women treated with intravenous labetalol had a higher baseline systolic and diastolic blood pressure than women treated with intravenous nicardipine. In the nicardipine group, lower diastolic blood pressures were reached.

During the time of the study there was one case of fetal death in the labetalol group and one case of neonatal death before discharge in the

Table 2
Neonatal outcome.

	labetalol (n = 14)	nicardipine (n = 16)	
Composite adverse neonatal outcome*	6 (42.9)	4 (25.0)	OR 0.28 (95 % CI 0.05–1.43)
Respiratory distress syndrome	6 (42.9)	2 (12.5)	OR 0.13 (95 % CI 0.02–0.86)
Bronchopulmonary dysplasia	1 (7.1)	0 (0.0)	
Intraventricular haemorrhage	0 (0.0)	1 (6.3)	
Necrotising enterocolitis	0 (0.0)	1 (6.3)	
Fetal death	1 (7.1)	0 (0.0)	
Neonatal death before discharge	0 (0.0)	1 (6.3)	
Admission to the NICU	8 (57.1)	9 (56.3)	OR 0.80 (95 % CI 0.18–3.57)
Number of days admitted at the NICU	26.0 [9.0–48.0]	8.0 [4.0–13.5]	
Apgar score after 5 min	8.3 [7.3—9.8]	9.0 [9.0–10.0]	
Neonatal hypotension	2 (14.3)	0 (0.0)	
Neonatal hypoglycemia	1 (7.1)	5 (31.3)	OR 4.50 (95 %CI 0.44–46.17)
Neonatal bradycardia	2 (14.3)	0 (0.0)	
pH<7.10	2 (14.3)	0 (0.0)	
Composite adverse neonatal outcome* using IV medication at delivery	2/8	2/10	OR −0.13 (95 % CI −0.72–0.45)

Data are depicted as median with [IQR] or number (n, %) as appropriate with denominator corrected for missings. *Composite adverse neonatal outcome is defined as at least one of the following complications: respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular haemorrhage, necrotising enterocolitis, fetal death or neonatal death before discharge.

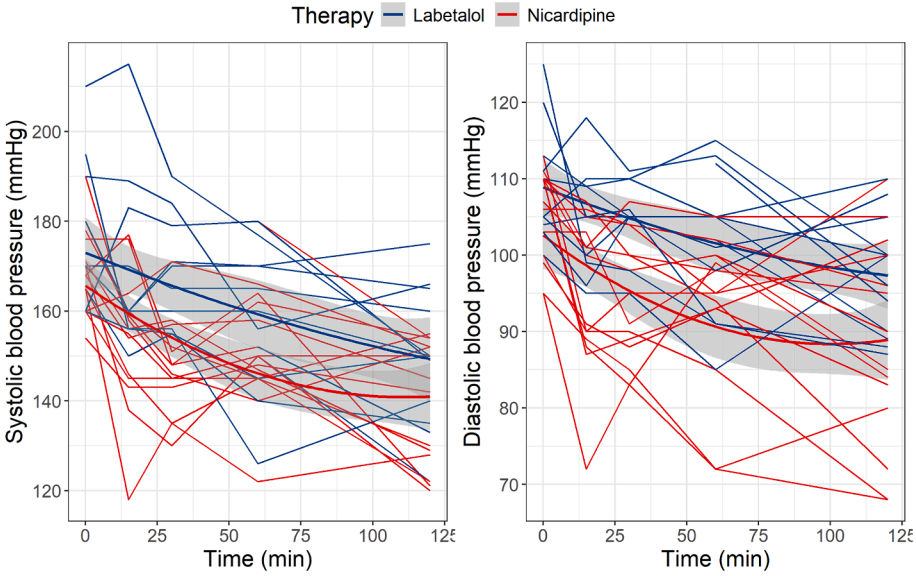

Fig. 2. Systolic and diastolic blood pressure after start treatment with labetalol and nicardipine over time (in min) with grey line mean and 95 % CI per treatment group.

Table 3
Obstetric and maternal outcome.

	labetalol (n = 14)	nicardipine (n = 16)
Composite adverse maternal outcome*	1 (7.1)	0 (0.0)
Time until blood pressure control (minutes)	120 [60–127.5]	45 [15–150]
Inadequate blood pressure control with necessity to switch medication	1 (7.1)	0 (0.0)
Side effects		
Gastro-intestinal discomfort	0 (0.0)	1 (6.3)
Reflex tachycardia	0 (0.0)	2 (12.5)
Headache	0 (0.0)	2 (12.5)
Hypotension with CTG abnormalities	1 (7.1)	0 (0.0)
Gestational age at delivery (weeks)	32.1 [24.4–40.4]	32.0 [27.1–39.1]
Time start treatment to delivery (weeks)	0.43 [0.14–0.71]	0.28 [0.07–0.93]

Data are depicted as median with [IQR] or number (%) as appropriate. *Composite adverse maternal outcome is defined as at least one of the following complications: eclampsia, cerebral haemorrhage, liver hematoma or rupture, lung edema, admission to ICU for ventilation or intra-arterial monitoring, or maternal death.

nicardipine group. In the single case of fetal death, it was decided not to preform active obstetric management because of severe fetal growth restriction with divergent Doppler ultrasound after the parents were counseled about postnatal viability. The neonate who died before discharge was born at a gestational age of 29 weeks and died of multi-organ failure with necrotizing enterocolitis (NEC).

In the labetalol group one woman needed to switch over to nicardipine because of therapy resistance with maximal dosage of labetalol. After the start of nicardipine she reached blood pressure control within 15 min of therapy with the lowest dosage.

A third woman allocated to receive labetalol experienced severe hypotension, combined with CTG abnormalities that both normalized after decreasing the medication dosage. In the nicardipine group some women experienced mild side-effects, i.e. gastro-intestinal discomfort, headaches and reflex tachycardia. (Table 3). Neither of these women experienced any palpitations and no intervention to decrease the heart rate was needed. The time until blood pressure control was faster in women treated with nicardipine than labetalol ((Table 3).

4. Discussion

In this small RCT, for neonatal outcomes we found no evidence for the optimal choice of treatment for women with severe hypertension treated with nicardipine versus labetalol. We were unable to confirm whether blood pressure control was reached faster for women treated with nicardipine versus labetalol.

In our study, respiratory distress syndrome and number of days admitted to the NICU were significantly more common in neonates of women who were treated with labetalol compared to nicardipine. Previously, Nooij et al. concluded in a retrospective cohort study that "neonates born from women treated with labetalol suffered from respiratory symptoms more often [16]." Combined with our results, this warrants more research into a potentially favorable safety profile for nicardipine for the treatment of severe hypertension in pregnancy. These adverse neonatal outcome might be coincidental findings due to small sample size. More data might answer the mechanism of earlier premature birth, as in our trial the mean gestational age at delivery was only on average 2 days different for women treated with labetalol and nicardipine or lower gestational weight.

The median number of days on NICU was different between both groups and might again indicate a more favorable effect of nicardipine. Also, it might be explained by a non-significant trend in worse neonatal outcome including RDS in the labetalol group.

We found no evidence for a different time until blood pressure control for both treatment groups. In contrast, Elatrous et al [10] found in a RCT treating 30 women with severe hypertension in pregnancy with labetalol and 30 with nicardipine for 1 h a similar length of time to achieve the blood pressure goal (12 vs. 11 min, respectively using a very strict time-based protocol). Signs of fetal distress as defined by abnormal fetal tracings were not observed by reduction of blood pressure [18,19]. In a large case-series study including more than 800 women on the use of nicardipine for treating severe antepartum hypertension in pregnancy, nicardipine successfully reduced blood pressure in 100 %, and 77 % reached successful treatment within 2 h without fetal distress [18]. These data therefore also warrant more research into effectiveness of intravenous nicardipine versus labetalol for the treatment of severe hypertension in pregnancy.

Unexpectedly, neonatal hypoglycemia was reported more frequently in the nicardipine group, although the difference was not significant. Bateman et al. conducted a study using a cohort of 2,292,116 completed

pregnancies [20]. They concluded that neonatal hypoglycemia is more common when a neonate is exposed to a beta-blocker late in pregnancy compared to no exposure at all (adjusted OR 1.68; 95 %-CI, 1.50–1.89) [20]. The fact that in our study only 7 % of the neonates experienced hypoglycemia, instead of 15 % when using labetalol as described before, is most likely due to chance by small number of participants. The same can be stated about neonatal bradycardia after maternal labetalol use. An effect of using oral medication before starting intravenous medication might influence the neonatal effect of hypoglycemia. However, four women used labetalol as oral medication in the last 24 h before starting intravenous labetalol versus five women used nicardipine as oral medication in the last 24 h before starting intravenous nicardipine. This warrants further studies to describe the risk of hypoglycemia after the use of nicardipine, as this check might be necessary also for labetalol.

Regarding side-effects it must be stated that both gastro-intestinal discomfort and headaches can also be a symptom of pre-eclampsia and are not necessarily a side-effect. Nij Bijvank et al. concluded that the prevalence of headaches and nausea and vomiting decreased after starting with nicardipine [18]. This suggests that these symptoms are more often caused by preeclampsia instead of nicardipine itself. Nevertheless, these side-effects are consistent with the case-control study performed by Nooij et al. [16].

5. Limitations and strengths

The study was underpowered to answer the hypothesis, as patients were recruited in only two hospitals in The Netherlands. A large, national RCT might answer the question about the effectiveness and safety of antihypertensive treatment in pregnancies complicated by severe hypertension. A Canadian study described a prevalence of severe high blood pressure (>110 mmHg) in 2.3 women per 1,000 deliveries [21]. A national study would potentially identify 360 women yearly. Of those, a large percentage would be treated adequately with oral medication. It is therefore questionable of this RCT for intravenous therapy is feasible and might not better be placed in a RCT of any, oral and intravenous, anti-hypertensive treatment for women with severe hypertension in pregnancy. Moreover, using the iv medication during delivery might affect the neonatal outcome. The numbers of participants are too small to draw a conclusion as other factors, such as gestational age at delivery might also influence the results.

Another limitation was the dosage increases in the nicardipine protocol. At the start of the study, dosage increasements after 15 min were protocol because of the shorter half-time and sooner effect. [15,20,22]. The current guidelines suggest increasing nicardipine after 30 min instead of 15 min [5]. Besides that, no severe adverse effects were observed including fetal distress. In addition, total 23 women used oral antihypertensive medication before starting intravenous study medication and the length of treatment overall was short might induce a maternal and neonatal adverse effect.

Being underpowered, the results of this RCT should be cautiously interpreted. More evidence to confirm whether nicardipine might decrease neonatal complications would be welcomed. However, we question whether this will be feasible because of the infrequent need of intravenous treatment in women with PIH or PE. The pro-active treatment in early stages of the disorder may prevent the need for intravenous treatment, something already stated by Magee et al. in the CHIPS study [23]. However, the choice of intravenous antihypertensive treatment including nicardipine could be preferred over labetalol since the latter has more contraindications (i.e. congestive heart failure, asthma and bradycardia) than nicardipine [10]. Nicardipine might be less costly due to the price per used concentration and because the data from this study suggest that a faster and more relevant aimed blood pressure control is achieved with nicardipine. Precautions should be made when using nicardipine in women with liver function disorders because it is metabolized by the liver [4].

6. Conclusion

We were unable to provide evidence for the optimal choice of treatment for severe hypertension to improve neonatal outcome and/or to obtain faster blood pressure control. This study emphasizes the challenges of conducting a RCT for the optimal treatment for women with severe hypertension during pregnancy. Additional evidence to confirm these findings is eagerly awaited.

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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