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Full length article

IV labetalol and oral nifedipine in acute control of severe hypertension in pregnancy–A randomized controlled trial

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ABSTRACT

Objective: To compare the efficacy of intravenous labetalol with oral nifedipine in the treatment of severe hypertension in pregnancy with blood pressure ≥160/110 mm Hg.

Design, setting and participants: We conducted a parallel double-blinded randomized controlled trial between December 2014 to December 2016 in 120 antenatal women of gestational age >28 weeks, admitted with severe hypertension of blood pressure ≥160/110 mm Hg to maternity ward at a tertiary hospital.

The labetalol group received 20 mg initially followed by escalating doses of 40 mg, 80 mg, 80 mg and 80 mg (5 doses) every 15 min to a maximum of 300 mg. Nifedipine group received 10 mg initially followed by repeated doses of 20 mg every 15 min (total 5 doses) to a maximum of 90 mg. Vital signs were recorded every 15 min.

-The time taken and the number of doses required to achieve the target blood pressure (150/100 mmHg). Survival analysis was used to compare the efficacy of treatment regimens.

Results: Sixty women were randomised to each group and none were lost to follow-up. None of the patients in nifedipine group required labetalol, whereas three patients in labetalol group achieved target BP only after receiving nifedipine was administered after the maximum dose of labetalol.The mean time taken to achieve the target blood pressure in the labetalol group was higher (36.75 min) than in the nifedipine group (27.25 min) [mean difference 9.5 min,p = 0.002]. Nifedipine group required significantly lower doses (1.82 ± 0.83) as compared to labetalol (2.45 ± 1.32) [p = 0.002]. Nifedipine was 1.8 times more likely to achieve target blood pressure (Hazard Ratio = 1.8).

Conclusions: Both intravenous Labetalol and oral Nifedipine were effective in controlling blood pressure. Nifedipine reduced BP more rapidly than Labetalol. Oral Nifedipine may be a better alternative because of its ease of oral administration and a flat dosing regimen.

Introduction

Hypertension is the most common medical disorder of pregnancy and is reported to complicate up to 1 in 10 gestations [1]. The primary concern about elevated blood pressure (BP) relates to the potential harmful effects on both mother and fetus.

Most guidelines recommend labetalol, hydralazine and nifedipine as first line alternatives for the treatment of acute hypertension during pregnancy [2–4]. Hydralazine was previously the preferred drug; however, labetalol and nifedipine have fast emerged as drugs of choice.

Treating pregnant women with moderately high BP with antihypertensive drugs can reduce the chances of developing severe hypertension, but further research is needed to identify the most effective drug [5]. A meta-analysis in 2015 [6], which pooled seven trials (four from developing countries) involving 363 woman–infant pairs with severe hypertension, showed that oral nifedipine was associated with less risk of persistent hypertension and is as efficacious and safe as intravenous labetalol. However, the most important limitation was small number of included trials and small number of participants in

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each of these trials. There is a need for large, adequately powered trials comparing intravenous labetalol and oral nifedipine for treatment of severe hypertension during pregnancy. Therefore we sought to evaluate the efficacy and safety these drugs as treatment of severe hypertension of pregnancy in the context of outcomes which are of importance to both mothers and their babies. Unlike the studies included in the above systematic reviews [5,6] we used a double-blinded double-dummy design for our randomized controlled trial(RCT), to reduce the bias of comparing an intravenous drug with an oral drug.

International guidelines define severe hypertension in pregnancy as systolic blood pressure (SBP) $\geq$ 160 mmHg and/or diastolic BP (DBP) $\geq$ 110 mmHg [7]. According to National High Blood Pressure Education Program (NHBPEP) and NICE guidelines [2,7], the target BP for control of severe hypertension is 150 mmHg systolic and 80–100 mmHg diastolic blood pressure: we chose a target BP of 150/100 mm Hg in our study. This target is in accord with a recent meta-regression analysis of results from 14 trials that suggested that tighter control of maternal mean arterial pressure might contribute to fetal growth restriction, irrespective of the specific agents used [8].

The primary aim of this study is to compare the time taken to achieve a target BP of $\leq$150/100 mmHg between intravenous labetalol with oral nifedipine in treatment of severe hypertension in pregnancy with BP >160 mmHg systolic and/or >110 mm Hg diastolic. Secondary objectives were to assess the efficacy of these drugs in preventing complications of hypertension, maternal and perinatal outcome and to assess adverse effects of the drugs.

Methods

The study is a prospective double-blinded parallel-group RCT. The study took place at a tertiary teaching hospital in India between December 2014 and December 2016. The study was approved by the institutional ethical committee and registered with national clinical trial registry (CTRI/2017/10/009977) (www.ctri.nic.in/)

All antenatal women of gestational age >28weeks with severe hypertension with systolic BP of 160 mmHg or higher and/or diastolic BP of 110 mmHg or higher on two separate occasions, 30 min apart in lateral recumbent position with maternal heart rate(HR) between 60 to 120 beats per minute and re-assuring fetal heart rate were recruited into the study. Patients with history of cardiac disease, bronchial asthma, hematological disorder, allergy to either drug, liver disorders, exposure to any anti-hypertensive medications in the past 24 h, HR <50bpm or >120bpm, or chronic hypertension were excluded from the study.

Out of 160 women approached, 120 with acute severe hypertension were randomized into two groups using computer generated block randomization using blocks of four, 60 received immediate release oral nifedipine and 60 received intravenous labetalol (Fig. 1). Study investigators, attending care teams, subjects and their families were blinded to treatment allocation. Magnesium sulphate prophylaxis was given to all patients in view of severe preeclampsia.

To detect a 20% difference in time interval required to achieve the target BP with significance of 0.05 and 80% power, using previous study by Vermillion et al [9], it was determined that a minimum of 21 participants are required in each group. However as this was a time bound study larger population could be included. Further, previous studies [5,6,10,11] and WHO recommendation 2011 [12], suggest larger samples are needed for definitive conclusion.

A total of sixty patients were randomized to each group. Written informed consent was obtained from all women. Vital signs were recorded every 15 min including pulse rate, respiratory rate, BP, knee jerks, urine output and fetal HR. BP was recorded using a sphygmomanometer, with the BP cuff of width 15 cm. Study medications were placed in sealed envelopes. Each envelope contained 2 packages labelled 'A' and 'B'. Envelope 'A' contained 15 vials of Labetalol for injection (20 mg/4 ml per vial) and 10 placebo, which looked identical to oral nifedipine tablets, or intravenous saline placebo (in similar vials as that of Labetalol) and 10 tablets of 10 mg nifedipine. The drug and placebo combination in Envelope 'A' was allocated to participants according to the randomization schedule. Envelope 'B' contained the opposite regimen and was used if additional treatment was required. The envelopes were opened by the provider (both patient and provider were blinded to the given treatment).

The providers were instructed to administer two tablets from envelope 'A' and to administer 4 ml from vial in envelope 'A' intravenously. After 15 min, if systolic BP was >150 mm Hg and / or diastolic BP was >100 mm Hg, two more tablets and 8 ml of IV solution from envelope 'A' was administered. Similarly, after 15 more minutes, if target BP was not achieved, two more tablets and 16 ml solution were given from envelope 'A'. This was repeated for another two cycles. Crossover to envelope 'B' was required if target BP was not achieved after 5cycles. Drugs in envelope 'B' were administered in the same manner as envelope 'A'. The BP was measured as per standard recommendations using Korotkoff's sound 5 for diastolic BP.

Those randomized to intravenous labetalol received 20 mg initially followed by escalating doses of 40 mg, 80 mg, 80 mg and 80 mg (five doses) every 15 min to a maximum of 300 mg. Once patient has achieved target BP, patient was started on oral labetalol after 2 h. Those randomized to immediate release oral nifedipine, received 10 mg initially followed by repeated doses of 20 mg every 15 min (total five doses) to a maximum of 90 mg. Once target BP was reached, the patient was started on oral nifedipine sustained release (10 mg) tablets. The dosing regimens for each study medication corresponded with the regimens from previous clinical trials [9,13–16].

Frequent maternal and fetal monitoring was undertaken. In the event of non-reassuring fetal or maternal status, the trial treatment schedule was abandoned and appropriate measures, such as open-label antihypertensive treatment instituted. After completion of treatment, women were requested to complete a questionnaire regarding occurrence of side effects such as nausea, vomiting, dizziness, flushing, palpitations, headache, chest pain and shortness of breath. If clinically significant maternal hypotension occurred, the trial treatment was suspended and appropriate measures were suggested for the provider's consideration. All pregnancies were delivered irrespective of the gestation age, due to severe pre-eclampsia, as per the hospital protocol and mode of delivery was decided on a case-to-case basis.

The primary outcome was the time taken, in minutes, to achieve the target BP of systolic 150 mmHg and/or diastolic 100 mmHg. Secondary outcome measures were the number of doses required, adverse effects, maternal and perinatal outcome. Maternal outcome was measured with occurrence of complications such as eclampsia, abruption, HELLP syndrome, pulmonary edema, renal failure, cardiovascular accident and oliguria. Perinatal outcomes were intrauterine death/stillbirth, Apgar scores at 1 and 5 min, neonatal intensive care unit admissions and neonatal deaths.

Statistical analysis was done with SPSS20. We used Survival analysis to compare the primary outcomes. Time-to-event curves were analysed by Cox-proportional hazards regression and a Hazard ratio calculated. Normally distributed continuous data were analysed with Student's *t*-test for numerical data and Chi square test/Fisher's exact test for categorical data. All tests were two-sided and p-value<0.05 was considered significant.

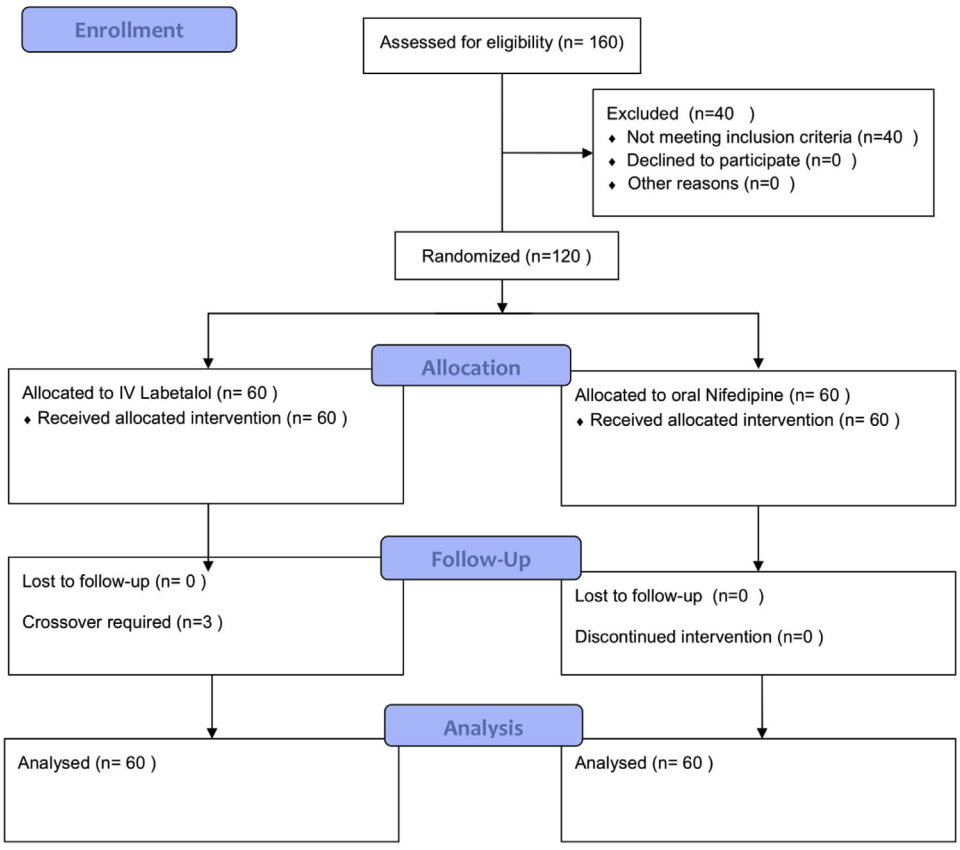

Fig. 1. Consort Flow of patients after enrolment.

Results

The groups were similar with respect to baseline characteristics (Table 1). No women were lost to follow-up. Mean time taken to achieve the target BP for intravenous labetalol was 36.75 (standard deviation [SD] 19.805) and 27.25 (SD12.502) minutes for oral nifedipine. The difference was statistically significant ($p = 0.002$). The Hazard ratio, adjusted for initial systolic and diastolic blood pressures was 1.8 (95%CI 1.23–2.67), indicating nifedipine was 1.8 times more likely to achieve target BP (Figs. 2 and 3). The nifedipine group also required a significantly lower number of doses (1.82 ± 0.83) than labetalol (2.45 ± 1.32) [$p = 0.002$] to reach the target BP [Table 2].

There was no significant difference in the reduction in the systolic BP between the two groups for the first 15 min. However, subsequent readings showed significant reduction in systolic BP for the nifedipine group as compared to the labetalol group. Repeated measures analysis of variance of blood pressure for the first 75 min indicated that both systolic BP and diastolic BP decreased significantly over time in both treatment groups but both systolic BP and diastolic BP decreased significantly more rapidly in nifedipine group (Fig. 2). There was a drop in maternal

Table 1
Baseline characteristics of participants in each study group.

Characteristic	Labetalol n = 60	Nifedipine n = 60
Mean age (years)	22.68	22.48
Parity- primi (number)	43	40
Gestational age		
28–34 weeks	12	10
>34 weeks	48	50
BMI 18.5–24.9	57	56
25–29.9	2	3
>30	1	1
Mean SBP at entry (mm Hg)	173.83	176.0
Mean DBP at entry (mm Hg)	113.33	113.5
Proteinuria	60	60
GDM	3	3
Induction	52	52
Delivery type(number)		
Vaginal	26	25
Caesarean	34	35
Mean heart rate at admission (bpm)	90	90
Mean birth weight (kilograms)	2.494	2.353

BMI-Body Mass Index; SBP-Systolic Blood Pressure; DBP-Diastolic Blood Pressure; GDM- Gestational Diabetes Mellitus; bpm-beats per minute.

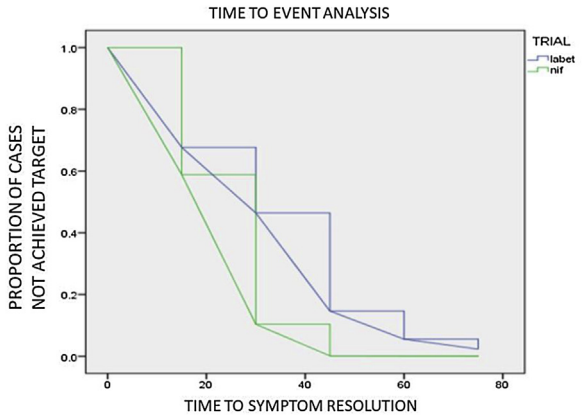

Fig. 2. Survival Analysis with Survival Function (proportion of cases achieving target BP with time).

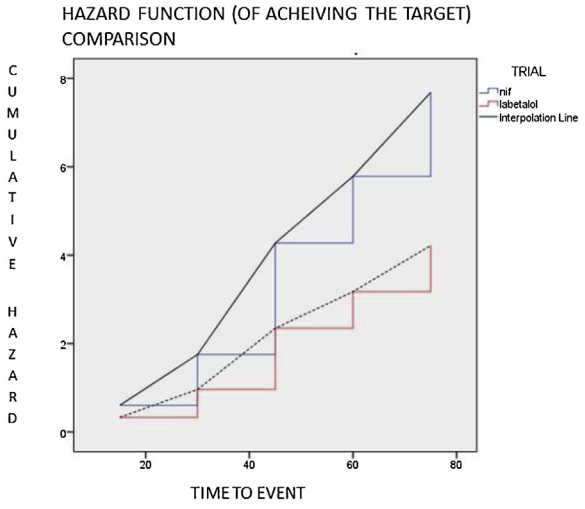

Fig. 3. Hazard function (of acheiving the target) comparison.

HR in labetalol group compared to nifedipine group though the difference was not significant ($p > 0.05$). Mean urine output was significantly higher in nifedipine group ($p < 0.001$) (Table 2) (Fig. 4).

None of the patients in nifedipine group required additional drug using the opposite treatment of labetalol. Three patients in labetalol group achieved target BP only after crossing over to nifedipine.

Few adverse effects were noted in each group (Table 2). Both events of hypotension were transient and asymptomatic. Headache in nifedipine group was mild, relieved with analgesics.

There were more women in labetalol group who had eclampsia, whereas more women in nifedipine group had abruption and HELLP syndrome, although the difference was not statistically significant and numbers were low. The complications occurred after completion of treatment regimen and were managed as per the respective hospital protocols. There were no maternal deaths in either group. Perinatal outcome was measured in terms of stillbirths, APGAR at 5 min, NICU admission and neonatal deaths. No significant difference in outcomes were found between the groups [Table 2].

Discussion

In this double-blinded RCT, pregnant women allocated to oral nifedipine achieved target BP significantly more rapidly and with fewer doses as compared with those receiving intravenous labetalol. A target BP of ≤150/100 mmHg was set, with dosing regimen to be stopped once the goal was achieved followed by maintenance therapy. This target BP is in keeping with Sibai's suggestion to keep systolic BP between 140–155 mmHg and diastolic BP between 90–105 mmHg in severe pre-eclampsia [15].

Our findings were in keeping with the study by Vermillion et al [5] which reported 100% success rate in achieving target BP. In this study, 50 women with BP of systolic>170 mmHg and diastolic >105 mmHg were randomized to either labetalol/nifedipine. It was concluded that both nifedipine and intravenous labetalol are effective; however, nifedipine controls hypertension more rapidly. Vermillion's drug regimen used the same dosing schedule as our study, but with escalation every 20 min, not 15 min. The mean times needed to achieve target BP were 25 and 43.6 min for nifedipine and labetalol groups respectively, compared with mean times of 27.25 and 36.75 min in our study. The longer time needed to achieve target BP in nifedipine group in present study might be attributable to our lower systolic target (150 mmHg) compared to the 160 mmHg target in the study by Vermillion et al [9]. A similar differential effect was also seen in the study by Shekhar et al [16], although this reported longer times taken to achieve the target than our study.

However, Raheem et al [17] found no evidence of a statistically significant difference between nifedipine and labetalol. At enrolment for this study, median diastolic BP in nifedipine group was marginally but statistically significantly higher. The study also used lower doses of nifedipine (10 mg throughout).

The systematic review and meta-analysis by Shekhar et al [6] concluded oral nifedipine to be as efficacious and safe as intravenous labetalol and may be advantageous in low resource settings, but that adequately powered trials were still required. Sridharan et al [18] conducted a network meta-analysis and trial sequential analysis of the RCTs on drugs for severe hypertension. The study concluded a similar efficacy between nifedipine, hydralazine and labetalol in the treatment of severe hypertension in pregnancy, but reported the quality of evidence was low. The pooled analysis by Shi et al [19] showed similar results.

Unlike previous studies, we have calculated Hazard Ratios from time to event analyses, considering the possibility that not all patients would reach the target. The term "hazard" refers to the probability that an individual, under observation in a clinical trial at time t, has an event at that time. We found this analysis to be most suitable for such time to event analysis [20]. The results are as shown in Figs. 2 and 3 and Table2. The outcomes of various studies included in this study in comparison with our study are described in Table 3 [9,16,17,21–26].

Mean urine output in this study was significantly higher in the nifedipine group (66.82 ml/hr vs 55.08 ml/hr)($p = 0.001$). This is comparable to the study by Vermillion et al [9]. In view of presence of preeclampsia-associated intravascular volume depletion and decreased renal perfusion, nifedipine's ability to preserve renal perfusion and urinary output would appear to be beneficial [27].

The most common adverse effects in nifedipine group were headaches, flushing and palpitations, while in labetalol group were nausea and vomiting. Pooled analysis by Shi et al [13] showed that there were no significant adverse effects with the nifedipine and labetalol.

We administered magnesium sulphate to all these patients as per ACOG taskforce guidelines [28]. Hence it is important to consider the possible interaction between antihypertensive agents and magnesium sulphate. However, reassuring evidence regarding the safety of contemporaneous use of both drugs is echoed in a retrospective review by Magee et al [29]. This case–control study of

Table 2
Primary and Secondary outcomes.

Outcome	Randomized to intravenous labetalol N = 60	Randomized to oral nifedipine N = 60	P values and Relative Risks (RR)
Primary outcome Mean time taken to achieve Target BP (in minutes)	36.75 ± 19.80	27.25 ± 12.50	0.002
Hazard Ratio (nifedipine over labetalol)			1.821 (1.238–2.679)
Secondary outcomes Mean number of doses required	2.45 ± 1.32	1.82 ± 0.83	0.002
Crossover required (n)	3	0	0.244
Mean urine output (mL/hour)	55.08	66.82	0.001
Adverse Drug Reactions (ADR) (n)			0.717 (Fischer-Exact)
Total	3	5	RR 0.6(0.15–2.399)
-Hypotension	1	1	
-dizziness	1	0	
-flushing/sweating	0	1	
-palpitations	0	1	
-nausea vomiting	1	0	
-headache	0	2	
Mode of delivery (n)			0.853
Vaginal	26	25	
Caesarean	34	35	
Maternal complications (n)			
Eclampsia	9	5	
Abruption	3	7	
HELLP syndrome	0	2	
Pulmonary Edema	0	1	
Renal failure	0	0	
Postpartum Hemorrhage	2	2	
Number of patients with any one complication	14	15	0.831 RR 1.095 (0.475–2.528)
TOTAL	14	17	
Intrauterine death/still birth	8	8	1.00
APGAR at 5 min			0.284
≤7	5	9	
>7	47	45	
NICU admissions for >7 days	5	4	0.198
Neonatal deaths (n)	4	8	0.233
-Hyaline membrane disease	1	3	
-Birth asphyxia	0	3	
-Sepsis	3	2	

n = number.

162 cases concluded that such practice does not increase the risk of serious magnesium related effects.

Doubts were raised regarding the possible prolongation of labor or uterine atonia and PPH after delivery because of the tocolytic properties of nifedipine. These remain theoretical because there is no supportive data [30]. In our study, a majority of the participants required only 2–3 doses of nifedipine to achieve target BP, therefore were exposed to smaller concentrations of the drug than when used for tocolysis. There was no increase in PPH in nifedipine group. There was no significant difference in the rate of caesarean section in between the groups. Fetal distress was little higher in labetalol group but was insignificant. Incidence of maternal complications was similar in either group ($p < 0.05$) for eclampsia, placental abruption and HELLP syndrome. However, this study is not powered enough to draw conclusion regarding the safety profile of the drugs or the efficacy of the drugs in prevention of complications.

Nifedipine also lowers BP without any apparent reduction in uteroplacental blood flow [31,32] and without any significant FHR abnormalities [33]. Nifedipine may also be preferable because of its ease of oral administration, low cost and a flat dosing regimen. There were no significant differences in maternal and perinatal outcome, which makes nifedipine an ideal or better than equal alternative tolabetalol.

Limitations

The study was not adequately powered to evaluate the safety profile of these drugs conclusively nor does it assess any resurgence of hypertensive crisis. Studies with longer follow-up would be required.

Conclusion

Both intravenous labetalol and oral nifedipine are effective in controlling BP. Nifedipine reduced blood pressure more rapidly and had a favourable effect on urine output. No significant maternal and fetal adverse effects were noted with eitherdrug. Oral

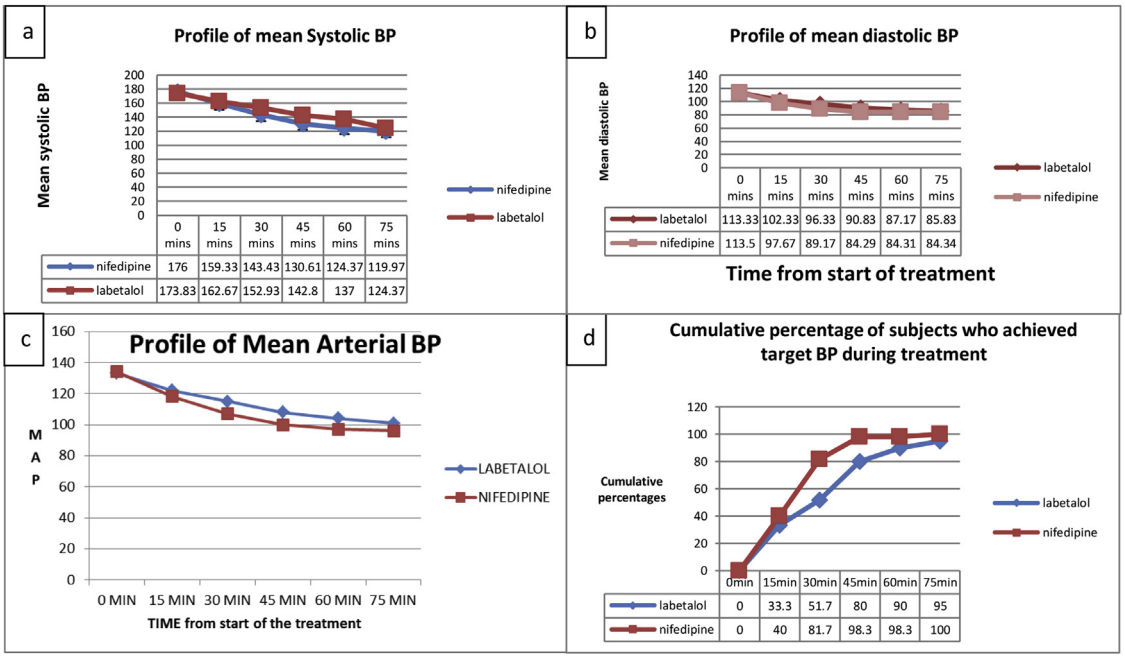

Fig. 4. (a,b,c): The profile of mean systolic (4a), diastolic (4b) and mean arterial pressure (4c) respectively. Fig. 4d shows cumulative percentage of patients achieving target BP during treatment.

Table 3
Primary outcomes of present trial in comparison to previous trials.

Study	Number of patients (n)	Success Rate (%)		Time taken(mins)*			Number of doses		
		L	N	L	N	p-value	L	N	p-value
Our Trial	**120**	**95**	**100**	**36.75 ± 19.8**	**27.25 ± 12.5**	**0.002**	**2.45 ± 1.32**	**1.82 ± 0.833**	**0.002**
Vermillion et al [9]	50	100	100	43.6 ± 25.4	25 ± 13.6	0.002	2.5±1.5	1.5±0.5	0.001
Raheem et al [17]	50	80	80	54 ± 42	46 ± 30	0.45	3 ± 0.6	2 ± 0.9	0.60
Mukherjee et al [21]	60	100	100	38.67 ± 19.43	43 ± 16.74	0.35	1.77 ± 0.63	1.67 ± 0.61	0.534
Shekhar et al [16]	60	83	97	60 ± 38	40 ± 28	0.008	3 ± 0.7	2 ± 0.6	0.08
Lakshmi et al [22] **	100	92	90	NA	NA	NA	1.9 ± 1	3 ± 1.3	<0.05
Dhali et al [23]	100	100	100	48.4 ± 23.5	28.2 ± 11.7	0.001	4.5 ± 1.5	3.5 ± 0.5	0.001
Thalamati et al [24]	100	100	100	44 (20-60)[a]	68(40-85)[a]	0.008	3	2	0.42
Dhananjaya et al [25]	100	100	100	14 ± 6.87	25.7 ± 12.76	<0.05	NA	NA	NA
Das et al [26]	100	88	86	47.2 ± 13.5	45.6 ± 14.5	0.511	–	–	–

N-Nifedipine group; L- Labetalol group; NA- Not Available.
* Time taken to reach the target BP.
** primary outcome in this study was the number of doses required to reduce the Mean Arterial Pressure by 25%.
[a] Range in minutes.

nifedipine may be a better alternative due to its ease of oral administration and a flat dosing regimen.

Potential conflicts of interest

None.

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