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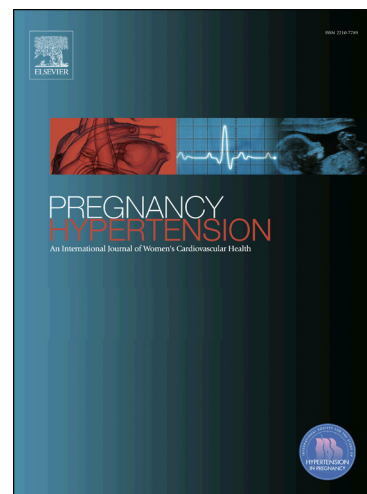
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The Effect Of Labetalol And Nifedipine MR On Blood Pressure In Women With Chronic Hypertension In Pregnancy

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Introduction

Chronic hypertension (CHT) is defined as blood pressure (BP) $\geq 140/90$ mmHg that precedes the pregnancy or is detected < 20 weeks gestation [1]. It is a common medical condition that currently affects approximately 3% of pregnancies [2]. This percentage is likely to increase with increasing maternal age and body mass index (BMI) within the population. Pregnancies complicated by CHT are at increased risk of adverse maternal and fetal outcomes including: superimposed preeclampsia, iatrogenic pre-term delivery and fetal growth restriction (FGR) [3].

Optimal treatment of hypertension in pregnancy remains controversial. Although treating hypertension has been shown to reduce the incidence of severe hypertension by 50% this has not been associated with an improvement in other outcomes such as a reduced risk of pre-eclampsia (PE), FGR or neonatal mortality [4]. Concerns regarding the over treatment of hypertension were raised in a systematic review that reported an association between a reduction in mean arterial pressure (MAP) by 10 mmHg and a decrease in birthweight of 176g [5]. To try to address these issues Magee et al. conducted a large randomized control trial (RCT) investigating whether tight or less tight BP control was associated with better outcomes [6]. The findings of the CHIPS trial have shown that aiming for a target diastolic blood pressure (DBP) of 85 mmHg compared with 100 mmHg was associated with maternal benefits without detrimental effect on perinatal outcome [6].

The range of anti-hypertensive agents available for use in pregnancy is limited due to a lack of safety data on potential teratogenic or fetotoxic effects. Methyldopa had been the drug of choice as a result of many years of use [7]. There are limited head to head studies comparing different antihypertensive agents for the treatment of CHT in pregnancy [8]. Currently the National Institute of Health Care Excellence (NICE) recommends labetalol as the first line drug in the UK for the treatment of CHT [9], with nifedipine and methyldopa as alternative options.

Physiological adaptations to pregnancy alter drug pharmacokinetics. Available data regarding the pharmacokinetics and pharmacodynamics of labetalol and nifedipine in pregnancy are limited; existing studies had small sample sizes and investigated effects in the third trimester only. However, for both drugs clearance appears to be increased in pregnancy [10]. To date there are no studies investigating and comparing the acute BP lowering effects of antihypertensive medication in pregnancy. The optimal drug, dose and dosing interval required to achieve the desired BP targets remains uncertain and variation exists in prescribing regimes due to a paucity of evidence based guidelines.

Nifedipine as a modified release (MR) preparation and labetalol are two of the most commonly prescribed antihypertensive agents in pregnancy. The primary aim of this exploratory study was to describe and compare the BP lowering effects of these two medications on the systolic BP (SBP) and DBP in pregnancies complicated by CHT. We also investigated the effect of each drug on heart rate (HR) and determined whether the use of labetalol or nifedipine resulted in better overall BP control by analysing the time spent in target.

Methods

Recruitment

We performed a single centre exploratory study at a tertiary maternity hospital. Women were recruited from the Manchester Antenatal Vascular Services (MAViS) clinic, which is a dedicated research clinic for pregnant women with pre-existing vascular disease. Women who were on a stable dose of labetalol or nifedipine MR for at least 1 week, with a diagnosis of CHT were offered 24-hour ambulatory blood pressure monitoring (ABPM). Participants were fitted with a SpaceLabs monitor and advised to continue with normal daily activities. BP readings were not revealed to the woman during the monitoring period. The BP was recorded every 30 minutes during the day (08:00-22:00h) and hourly at night (22:00-08:00h). Drug ingestion time, sleep and wake periods were self-reported. Baseline demographics were recorded.

Statistical methods

Initial Data Analysis

Patient demographics were compared and analysed using chi-squared test. The pre-dose levels of SBP and DBP were compared between each treatment using boxplots. The correlation between pre-dose SBP and DBP with dose and gestation, were first explored graphically before being assessed via a one-way ANOVA analysis. The time-series of SBP, DBP and HR were binned in the following way to assess temporal trends. The pre-dose recording was assigned to the first bin. The second, third, fourth and fifth bins contained the first quartile (minus pre-dose values), second, third and fourth quartile of the data over the dosing interval. Due to the varying dosing regimes, time series data is available for 6.4-12.5 hours for labetalol and 8.5-16.4 hours for nifedipine. For each bin a boxplot was created and all boxplots were plotted in chronological order. Only daytime BP and HR readings were used.

Time-series structural model

An indirect response model was used to analyse the SBP, DBP and HR time-series. A schematic of the model together with example simulations can be seen in the Supplementary Material.

Time-series data analysis

The time-series under consideration contains two levels of hierarchy and thus two sources of variability; between patient and within patient (inter-visit). To account for these sources of variability the structural models described above were placed within a mixed-effects framework and analysed in the following way.

For SBP and DBP, the drugs are intended to lower these values and so the inhibitory model was used. For HR we considered both the inhibitory and stimulatory model given that the HR can produce the opposite dynamics to that seen for SBP and DBP. For the SBP and DBP analysis the goodness of fit statistic, $-2 \times \log\text{-likelihood} (-2LL)$, was calculated for the pooled data-set (labetalol and nifedipine) using a step-wise approach. Firstly, without accounting for which visit belonged to which woman, secondly, accounting for visit-to-visit correlations and finally accounting for which drug a woman was prescribed. Finally, where a treatment effect was identified gestation time effect was explored through inclusion of an interaction term (drug and gestation). The likelihood ratio test was used to assess the improvement in model fit after including each piece of extra information.

For the HR analysis we fitted both the inhibitory and stimulatory models to each drug data-set separately, firstly, without accounting for which visit belonged to which woman. The choice of which model to take forward for further analysis was based on certain parameter conditions to ensure the correct dynamics for the given model, see Supplementary Material. If the inhibitory model was found to give the best fit for one drug and the stimulatory model for the other then the data was kept un-pooled. Hence, in that situation only an assessment of which visit belonged to which woman was performed. Analysis of the effect of gestation time was modelled in the same way as for SBP and DBP analysis if a pooled data-set was used via an interaction term between drug and gestation. However, if the data was kept un-pooled then gestation was modelled as an additive covariate.

Further details on parameter estimates with 95% confidence intervals (CI) and model diagnostic plots for the final models can be found in the supplementary material. R v3.1.1 was used for all analyses conducted.

Simulation of time in target: SBP and DBP

The parameter estimates for each woman from the final models were used to simulate SBP and DBP time-series for eight hours. This time-series was then used to calculate the average proportion of time spent in target for each patient during all visits. The following cut offs were used as targets: SBP <140mmHg and DBP 80-99mmHg. To assess the quantitative difference in the distribution of the proportion of time spent in target between each drug for SBP and DBP p-values from the Kolmogorov-Smirnov test were calculated.

Results

Study Participants

A total of 48 women underwent ABPM; 24 on labetalol and 24 on nifedipine MR. Table 1 presents the characteristics and delivery outcomes of the two groups. The majority of women had a diagnosis of essential hypertension (65%). There was no significant difference between the two groups with respect to ethnicity, BMI, gestation and underlying diagnosis. Labetalol was most commonly prescribed as an 8-hourly regime and there were nine different total daily doses. Nifedipine MR was predominantly prescribed 12-hourly and there were eight different total daily doses. Delivery outcomes were compared. Adverse outcomes were classified as: PE, isolated FGR (customised birth-weight <10th centile) or other. The only statistically significant difference was the number of vaginal deliveries achieved.

	Labetalol n=24	Nifedipine n=24	P value
Ethnicity			0.07
White European	14 (58%)	9 (37%)	
African/Caribbean	7 (29%)	5 (21%)	
Other	3 (13%)	10 (42%)	
BMI at booking (kg/m²)	32 ± 7	29 ± 6	0.18
Gestation at ABPM monitoring (weeks)	22.2 ± 6.9	23.2 ± 7.5	0.65
Diagnosis			0.11
Essential HTN	18 (75%)	13 (54%)	
Renal HTN	6 (25%)	10 (42%)	
Other	0 (0%)	1 (4%)	
Total dose mg/ day (median/IQR)	400 (225, 600)	40 (20, 60)	
Women on b.d. dose	8 (33%)	22 (92%)	
Delivery Outcome			
Delivery gestation (weeks)	37.9 (36.7, 38.4)	37.6 (35.4, 38.6)	0.82
Vaginal delivery	12 (50%)	10 (42%)	0.02
Birth weight centile	33 (31)	30 (34)	0.78
Complication	11 (46%)	17 (71%)	0.85

Table 1. Patient demographics and delivery outcome presented as either mean ± sd, N (%) or median (IQR)

Initial Data Analysis

Pre-dose SBP and DBP were compared between the two treatment groups and there was no significant difference in baseline SBP or DBP ($p=0.922$ and $p=0.805$ respectively).

The relationship between the pre-dose SBP and DBP values and the dose taken for the two treatments or gestation was assessed (Figure 1). In this cohort of women no effect of gestation was seen on the pre-dose SBP or DBP. We did however find a statistically significant relationship between pre-dose BP and the dose of nifedipine, with the most hypertensive women scheduled to take the highest doses of nifedipine ($p=0.002$); this relationship was not significant for women taking labetalol.

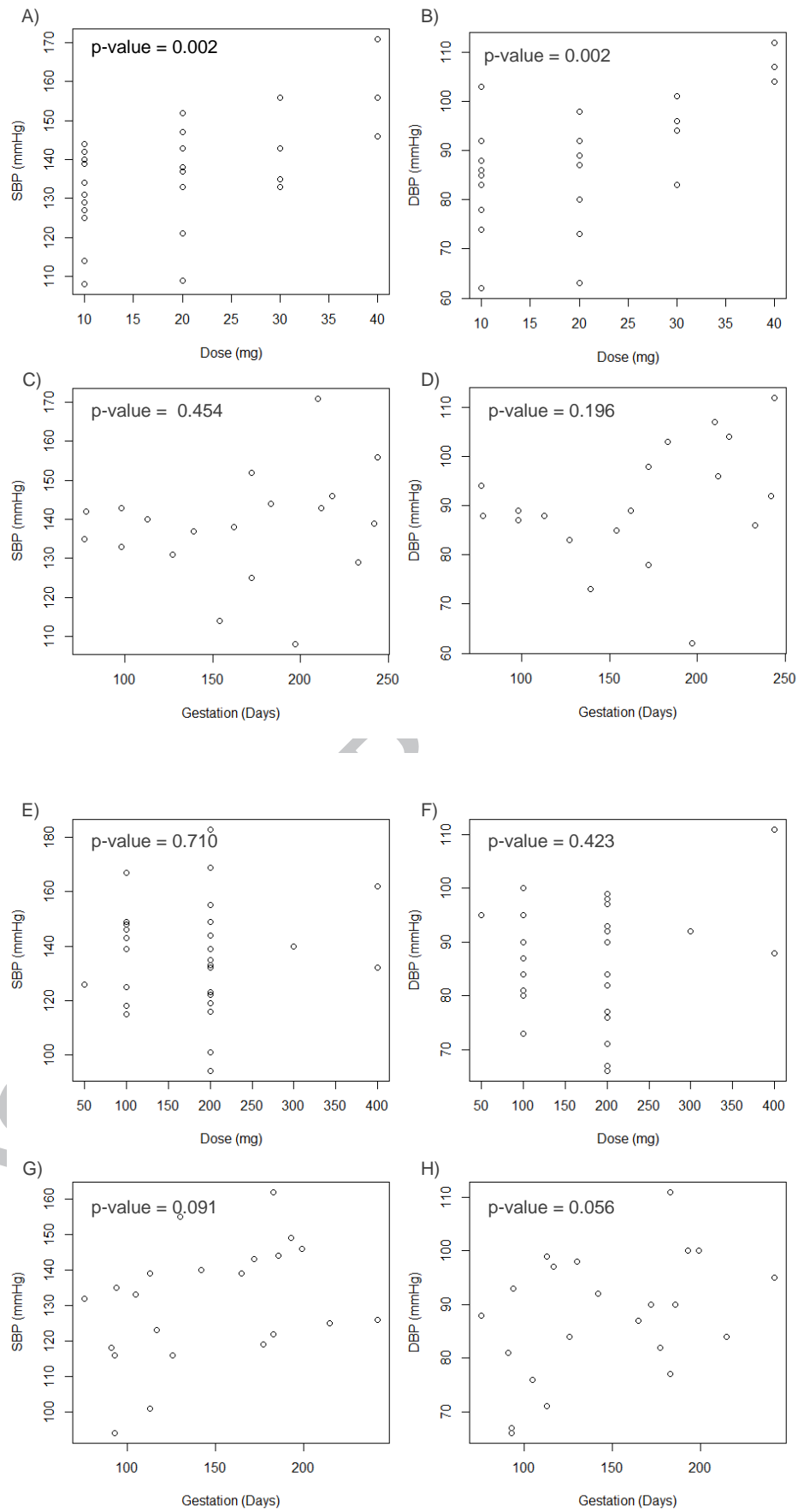


Figure 1. Panels A and B show a significant trend between the dose of nifedipine and pre-dose SBP and DBP values ($p=0.002$ for both). The plots in panels C and D demonstrate that there was no correlation for nifedipine between gestation at monitoring and the pre-dose SBP and DBP values ($p=0.454$ and $p=0.196$ respectively). Panels E and F show no trend between the dose of labetalol and pre-dose SBP and DBP values ($p=0.710$ and $p=0.423$ respectively). The plots in panels G and H show a lack of correlation for labetalol between gestation and pre-dose SBP and DBP values ($p=0.091$ and $p=0.056$ respectively).

Time Series Data

Figure 2 shows the binned time series data.

SBP and DBP

Blood pressure readings post-dose were grouped into quartiles that correspond to the following time frames: 0-2.5, 2.5-4, 4-6.4 and 6.4 - 12.5 hours for labetalol and 0-3, 3-5.7, 5.7-8.5 and 8.5-16.4 hours for nifedipine. For labetalol there appeared to be a BP lowering effect within 2.5 hours of drug ingestion on both the SBP and DBP; this effect was short lasting. A similar trend was not seen for nifedipine.

HR

Data was binned into the same quartiles as for SBP and DBP. No strong trend similar to that seen for BP after labetalol or nifedipine treatment was observed, however there did appear to be opposite effects; a reduction in HR with labetalol and a rise with nifedipine.

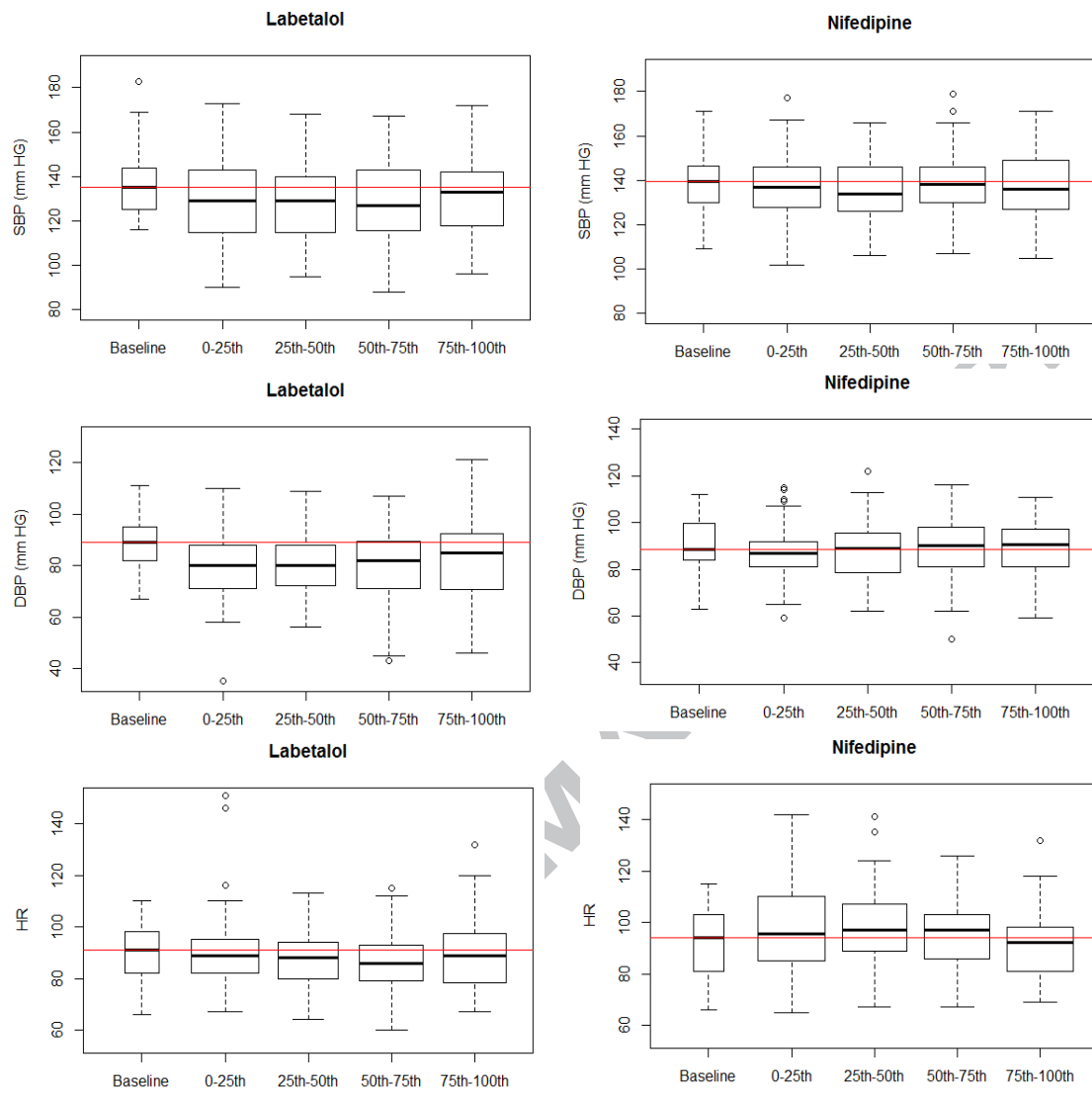


Figure 2. Boxplots of the binned time-series data for pre-dose baseline values and subsequent time quartiles for SBP, DBP and HR. The box shows the inter-quartile range with the solid horizontal line within the box the median.

Time Series Data Analysis

The trends, described above, were further assessed using the indirect response model. The raw data and model mean fit are shown in figure 3. These data show a modest difference between the drug effects on both the SBP and DBP time-series ($p=0.014$). For HR we found that the dynamics were different qualitatively between the two drugs; a stimulatory effect was found for nifedipine and an inhibitory one for labetalol.

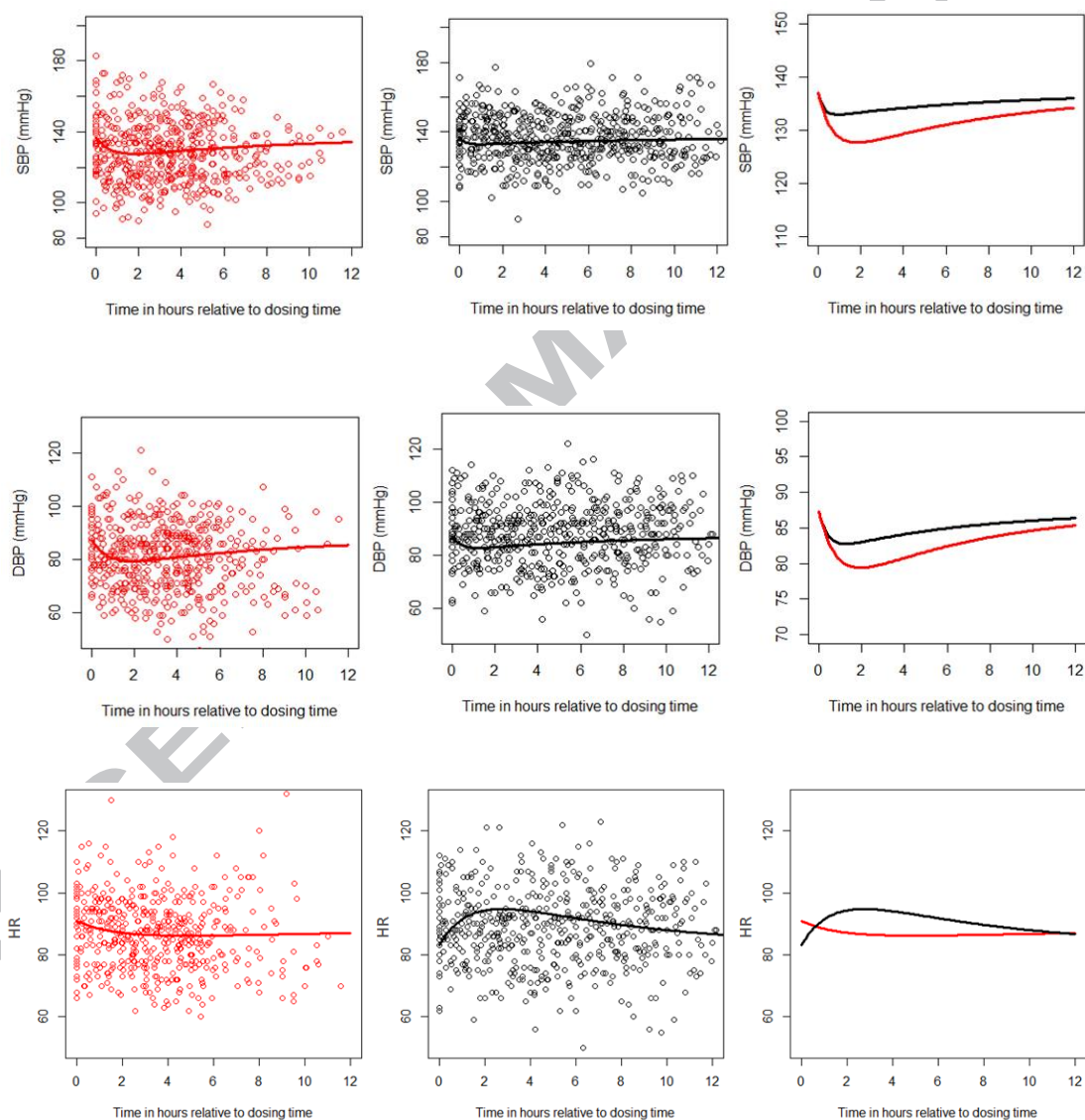


Figure 3. SBP, DBP and HR values for labetalol (red open circles) and nifedipine (black open circles) after a single dose together with the mean simulation (solid lines).

Having established that a treatment effect existed on the SBP, DBP and HR time-series data, we next evaluated whether this effect was modulated by the gestation at which the monitoring was performed. Table 2 shows that there was an effect of gestation on the treatment effect on SBP ($p < 0.001$); the drug effect decreased with advancing gestation. An effect of gestation on treatment effect on DBP was not observed. For HR we found a modest effect of gestation for patients treated with labetalol ($p = 0.046$) but no effect on patients treated with nifedipine (Table 3).

	SBP: p-value	DBP: p-value
Inhibitory		
No inter-visit correlation (1)		
Inter-visit correlation (2)	1 v 2 $p < 0.001$	1 v 2 $p < 0.001$
Type of Drug (3)	2 v 3 $p = 0.014$	2 v 3 $p = 0.014$
Drug/Gestation interaction (4)	3 v 4 $p < 0.001$	3 v 4 $p = 1$

Table 2. Going from model (1)-(4) involves increasing the complexity of the model by including an additional parameter to account for that extra information e.g. model (4) accounts for inter-visit correlation, type of drug and a drug/gestation time interaction.

	HR:Labetalol: -2LL	HR:Nifedipine: -2LL
Inhibitory		Condition failed
No inter-visit correlation (1)		
Stimulatory	Condition failed	
No inter-visit correlation (2)		
Inhibitory		Not applicable
Inter-visit correlation (3)	1 v 3 $p = 0.008$	
Stimulatory	Not applicable	
Inter-visit correlation (4)		2 v 4 $p < 0.001$
Gestation (5)	3 v 5 $p = 0.046$	4 v 5 $p = 0.317$

Table 3. The $-2 \times \log$ -likelihood (-2LL) values for the model iterations, given in parentheses, for HR. Models (1) and (2) assess whether the inhibitor or stimulatory model best describes the data. Models (3) and (4) assess what effect inter-visit correlations has on model fit. Final model (5) assesses what effect gestation time has after accounting for inter-visit correlations.

The models taken forward to assess time in target for SBP and DBP were model iteration number 3 in Table 2. Although for SBP we found that gestation did effect the treatment, the confidence intervals of the interaction term included zero. This suggests the effect is highly uncertain and so a model without that interaction was taken forward.

Time In Target

To assess the clinical value of both drugs, time in target was determined. For SBP we found that 80% of women spent the whole 8 hours within the target range (SBP<140mmHg) for both labetalol and nifedipine. For DBP, of the women on nifedipine 79% spent the whole 8 hours in target: 13% spent a proportion of time above target (DBP>99mmHg) and 8% were below target (DBP<80mmHg). In the labetalol group only 40% were in target during the 8 hours. Although no woman on labetalol had a DBP>99mmHg, 60% of the women spent a varying proportion of the 8-hour window below the target range.

Discussion

This study has found a clinically significant difference in the BP lowering effects of labetalol and nifedipine MR. By using an indirect response model we were able to statistically compare the different effect of each drug on the BP as well as determining if there was any effect according to the individual or gestation. This is a relatively novel technique within the speciality partly attributed to the lack of pharmacodynamics research during pregnancy. Although this was an exploratory study and the results should be interpreted with caution, our findings suggest that nifedipine MR provides more stable day-time BP control, with less variation in BP over the dosing interval when compared to labetalol. In particular, significantly more women taking labetalol spent a larger proportion of time below the diastolic target compared to those taking nifedipine.

Labetalol is a combined α_1 and non-selective β adrenoreceptor antagonist with the ratio of α to β receptor potency about 1:3 for oral administration [11]. In our study labetalol had a relatively quick onset of action with a BP lowering effect seen by 2.5 hours post dose, the maximum effect being around 2.5 hours for DBP and 4 hours for SBP. These findings correlate with an earlier study by Saotome et al. [11]. The BP lowering effect was short lasting and the BP had returned to baseline by 6.4 hours. These results suggest that the dosing interval of labetalol during pregnancy should be 6-hourly to achieve a consistent reduction in BP over time. Labetalol is known to produce a reduction in HR which is relative to the dose [12]. The simultaneous lowering in the pulse rate was seen in our study and demonstrates the more potent effects at the β -receptor.

Nifedipine is a dihydropyridine derivative calcium channel blocker (CCB) that inhibits the influx of calcium through channels in smooth muscle resulting in vasodilation. It is known to produce a reflex tachycardia secondary to activation of the sympathetic nervous system [13]. An acute BP lowering effect of nifedipine MR was not seen for either SBP or DBP. This result was expected due to the longer duration of action and the fact that the women had

usually taken a dose of nifedipine in the 12 hours prior to commencement of the monitoring which would still be exerting some effect. An increase in heart rate was noted in women who took nifedipine.

A small double-blind randomized control trial comparing the acute effects of oral nifedipine and intravenous labetalol in a cohort of women with pre-eclampsia also found opposing effects on HR [14]. In this study both drugs had a significant BP lowering effect by 60 minutes post dose. We did not see this acute effect in our nifedipine group; this may be explained by the high SBP (SBP>170mmHg) inclusion criteria in the previous study [14].

In the non-pregnant population beta-blockers have been found to increase BP variation [15], which has been linked to an increase in vascular events such as stroke and myocardial infarction independent of mean BP [16]. It has been suggested that the improved cardiovascular protection of CCBs compared to beta-blockers may be due to a reduction in the average BP in combination with a reduction in BP variability [17].

Within the pregnant population, a small study by Maggioni et al. found DBP variation to be associated with FGR [18] which might contribute to the previously reported link between FGR and beta-blockers [19]. More recently secondary analysis of the BP variability in the CHIPS cohort found that increased variability (between clinic visits) resulted in more adverse maternal outcomes, but interestingly lower variability was associated with more adverse perinatal outcomes such as FGR and pre-term delivery [20].

Blood pressure variability is not routinely considered in antenatal care but should be a focus of future work. Antihypertensive treatment targets should ideally include a reduction in BP variability as this, in combination with a reduction in mean BP, appears to be cardioprotective [21]. The finding that treatment with nifedipine resulted in reduced BP variability (compared to those on labetalol) in high-risk pregnant women concurs with previous effects reported in non-pregnant individuals. This study was not powered to determine whether a reduction in BP variability was associated with a

difference in maternal or fetal outcomes; future work however, using the effect sizes determined by this study, could aim to address this important research question in women with CHT.

Magee et.al found improved maternal outcomes with tighter BP control attributed to fewer episodes of severe hypertension [6]. We found no significant difference between labetalol and nifedipine on the SBP, however, a larger proportion of women in our study who were taking labetalol spent more time with their DBP<80mmHg compared to those on nifedipine MR. Due to earlier studies [5] concern with regards to running DBP too low may exist amongst obstetricians, therefore with its quicker onset of action labetalol may be better suited in the emergency setting when more rapid lowering of BP is desired.

Pregnancy is known to affect the pharmacokinetics and pharmacodynamics of both drugs, but the available data is limited and the optimal dosing regime remains uncertain. Our data would suggest that a twice-daily dosing regime of labetalol would not be sufficient to maintain BP within target over a 24-hour period and further studies on optimal dosing frequency should be undertaken.

This study has several limitations. The study was small and exploratory and included a clinically representative mixed cohort of women from different ethnic backgrounds, with different causes and severity of hypertension. Our study also relied on women accurately reporting time of drug ingestion. Lastly, the antihypertensive treatment in our cohort was not randomised. In the non-pregnant population, treatment of hypertension is tailored according to ethnicity as this has been shown to impact on the efficacy [22]. Black patients when compared to white patients respond less well to beta-blocker monotherapy [23]. Knowledge of this may have resulted in preferential prescribing of nifedipine to black women in our study; however, the number of black women in each group was comparable. Furthermore, ethnicity is an important confounder that we were unable to adjust for due to the limited numbers. A feasibility study has recently been completed that supports a

larger RCT to compare the efficacy of different antihypertensive medications in the different ethnic groups [24].

Conclusion

There are significant and important differences between the BP lowering effects of nifedipine and labetalol in pregnant women with CHT. Women taking nifedipine have a more stable daytime BP profile whereas those on labetalol spent a larger proportion of time with their DBP below 80mmHg. To date ABPM is not routinely used in the obstetric setting and clinicians frequently make management decisions based on single office BP measurements. Our study therefore has clinical implications; in addition to confirming the utility of ABPM, application of knowledge of the likely duration of BP lowering effects and the interpretation of BP readings accounting for drug ingestion time would substantially improve the dosing of antihypertensives in women with CHT in pregnancy. However, although the evaluation of BP lowering effects of these drugs is important, it is the overall effect on pregnancy outcome that is of paramount importance and currently this remains uncertain. A large RCT is required to investigate this further.

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Disclosure of interests

I certify that none of the authors have any relevant financial and/or non-financial relationships to disclose.

Contribution to authorship

I certify that each co-author listed participated sufficiently in the work to take responsibility for the content, and that all those who qualify are listed.

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ACCEPTED MANUSCRIPT

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Abstract**Aim**

To compare the blood pressure (BP) lowering effects of labetalol and nifedipine modified release (MR) in hypertensive pregnant women. We also investigated the effect on the heart rate (HR) and determined the proportion of time spent in target.

Methods

This was an exploratory study. Women with chronic hypertension taking either labetalol or nifedipine were offered 24-hour ambulatory blood pressure monitoring (ABPM). Sleep, wake and drug ingestion times were self-reported. An indirect response model was used to analyse the systolic BP (SBP), diastolic BP (DBP) and HR time-series; the effect of gestation and type of drug was evaluated.

Results

Forty-eight women were recruited: 24 in each group. There was no difference in clinical characteristics. In women taking nifedipine there was a positive association between the dose of nifedipine and pre-dose BP $p=0.002$, this was not present in the labetalol group.

There was a difference between the drug effects on both the SBP and DBP time-series ($p=0.014$). In comparison to labetalol, there was less variation in day time BP in those women prescribed nifedipine. Women on labetalol spent a larger proportion of time with their DBP below target ($<80\text{mmHg}$). The HR dynamics were qualitatively different, a stimulatory effect was found with nifedipine compared to an inhibitory effect with labetalol.

Conclusion

There are significant and important differences between the BP lowering effects of nifedipine and labetalol. A large randomised control trial is required to investigate the relationship between BP variability and time in target on pregnancy outcomes.

Keywords

Chronic hypertension.

Labetalol.

Nifedipine MR.

Antihypertensives.

Blood pressure control

Ambulatory blood pressure monitoring

Highlights

- The blood pressure lowering effects are different between labetalol and modified release nifedipine
- Labetalol has a quick onset of action that is short lasting
- Nifedipine results in a more stable blood pressure profile
- Ambulatory blood pressure monitoring can be successfully utilised in pregnancy and aids clinical decisions

ACCEPTED MANUSCRIPT

Table 1. Patient demographics and delivery outcome presented as either mean \pm sd, N (%) or median (IQR)

Figure 1. Panels A and B show a significant trend between the dose of nifedipine and pre-dose SBP and DBP values ($p=0.002$ for both). The plots in panels C and D demonstrate that there was no correlation for nifedipine between gestation at monitoring and the pre-dose SBP and DBP values ($p=0.454$ and $p=0.196$ respectively). Panels E and F show no trend between the dose of labetalol and pre-dose SBP and DBP values ($p=0.710$ and $p=0.423$ respectively). The plots in panels G and H show a lack of correlation for labetalol between gestation and pre-dose SBP and DBP values ($p=0.091$ and $p=0.056$ respectively).

Figure 2. Boxplots of the binned time-series data for pre-dose baseline values and subsequent time quartiles for SBP, DBP and HR. The box shows the inter-quartile range with the solid horizontal line within the box the median.

Figure 3. SBP, DBP and HR values for labetalol (red open circles) and nifedipine (black open circles) after a single dose together with the mean simulation (solid lines).

Table 2. Going from model (1)-(4) involves increasing the complexity of the model by including an additional parameter to account for that extra information e.g. model (4) accounts for inter-visit correlation, type of drug and a drug/gestation time interaction.

Table 3. The $-2 \times \log$ -likelihood ($-2LL$) values for the model iterations, given in parentheses, for HR. Models (1) and (2) assess whether the inhibitor or stimulatory model best describes the data. Models (3) and (4) assess what effect inter-visit correlations has on model fit. Final model (5) assesses what effect gestation time has after accounting for inter-visit correlations.