

SYSTEMATIC REVIEW AND META-ANALYSIS

Drugs for treating severe hypertension in pregnancy: a network meta-analysis and trial sequential analysis of randomized clinical trials

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AIMS

Several antihypertensive drugs are used in the treatment of severe hypertension in pregnancy. The present study is a network meta-analysis comparing the efficacy and safety of these drugs.

METHODS

Electronic databases were searched for randomized clinical trials comparing drugs used in the treatment of severe hypertension in pregnancy. The number of women achieving the target blood pressure (BP) was the primary outcome. Doses required and time taken for achieving the target BP, failure rate, and incidences of maternal tachycardia, palpitation, hypotension, headache, and neonatal death and stillbirth were the secondary outcomes. Mixed treatment comparison pooled estimates were generated using a random-effects model. Odds ratios for the categorical and mean difference for the numerical outcomes were the effect estimates.

RESULTS

Fifty-one studies were included in the systematic review and 46 in the meta-analysis. No significant differences in the number of patients achieving target BP was observed between any of the drugs. Diazoxide [−15 (−20.6, −9.4)], nicardipine [−11.8 (−22.3, −1.2)], nifedipine/celastrol [−19.3 (−27.4, −11.1)], nifedipine/vitamin D [−17.1 (−25.7, −9.7)], nifedipine/resveratrol [−13.9 (−22.6, −5.2)] and glyceryl trinitrate [−33.8 (−36.7, −31)] were observed to achieve the target BP (in minutes) more rapidly than hydralazine. Nifedipine required fewer doses than hydralazine for achieving the target BP. Glyceryl trinitrate and labetalol were associated with fewer incidences of tachycardia and palpitation respectively than hydralazine. Trial sequential analysis concluded adequate evidence for hydralazine and nifedipine compared with labetalol. Moderate quality of evidence was observed for direct comparison estimate between labetalol and hydralazine but was either low or very low for other comparisons.

CONCLUSION

The present evidence suggests similar efficacy between nifedipine, hydralazine and labetalol in the treatment of severe hypertension in pregnancy. Subtle differences may exist in their safety profile. The evidence is inadequate for other drugs.

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- There is no consensus on the relative efficacy and safety of anti-hypertensive drugs used in the treatment of severe hypertension in pregnancy.
- Currently, head-to-head clinical trials comparing several such drugs are lacking.
- Several methodological flaws are noted with the existing systematic reviews of this topic.

WHAT THIS STUDY ADDS

- A similar efficacy was observed between hydralazine and nifedipine compared to labetalol.
- Adequacy of evidence for the above findings has been confirmed by trial sequential analysis.
- No significant differences exist in the safety profile of these drugs.

Introduction

Hypertension in pregnancy is defined as systolic blood pressure (SBP) above 140 mmHg and/or diastolic blood pressure (DBP) above 90 mmHg; severe hypertension as SBP \geq 160 mmHg with or without DBP \geq 110 mmHg [1]. Hypertension in pregnancy can be categorized as: chronic hypertension (before 20 weeks of gestation), gestational hypertension (later than 20 weeks) or pre-eclampsia (associated with organ damage) [2]. A prevalence of 3.6–9.1% has been reported for hypertension in pregnancy and 1.4–4% for pre-eclampsia [3]. Hypertensive women with pre-eclampsia have an increased risk of renal failure, hepatic failure, stroke and perinatal mortality [4]. Hypertensive crisis occurs in 1–2% of pregnant women [5].

Target blood pressure (BP) is recommended to be less than 140–150 mmHg for systolic and less than 90–100 mmHg for diastolic blood pressures in pregnant women with hypertension [6]. A trial of oral anti-hypertensives can be attempted for managing severe hypertension in pregnancy before initiating parenteral therapy [7]. Labetalol, nifedipine and hydralazine are the commonly used drugs for treating severe hypertension in pregnancy [8]. Despite being used for several decades, there is no consensus on the relative efficacy and safety of drugs used in treating severe hypertension in pregnancy, and a recent Cochrane review was inconclusive [9]. This is mainly due to the lack of head-to-head clinical trials comparing these drugs. A network meta-analysis offers advantage in comparing the interventions in the absence of head-to-head comparisons through a common comparator [10]. Hence, we carried out the present network meta-analysis to compare the drugs used for treating severe hypertension in pregnancy.

Methods

Search strategy

This review's protocol has been registered in PROSPERO (CRD42017076188). PubMed and Cochrane CENTRAL were searched with an appropriate search strategy (see supplementary appendix). We did not place any restrictions on the publication language or year. Additionally, we hand searched the cross-references of the included studies.

Eligibility criteria

We included only randomized clinical trials carried out in patients with severe hypertension that had compared more than one drug. No strict criterion was placed for severe hypertension in the present review but we have carried out a sensitivity analysis by excluding trials with different blood pressure criteria in their study participants. We excluded trials comparing different formulations/doses/routes of the same drug and that had evaluated either intravenous magnesium sulphate/oral atenolol/oral alpha-methyl dopa as the standalone anti-hypertensive drugs. Number of patients achieving the target BP was the primary outcome. Doses required and time taken for achieving the target BP, failure rate, incidences of maternal tachycardia, palpitation, maternal hypotension, headache, stillbirth, number of neonates with appearance, pulse, grimace, activity, respiration (APGAR) score $<$ 7, neonatal death and number of patients with new hypertensive crisis were the secondary outcomes.

Study procedure

Two authors performed an independent literature search and extracted the following details: trial site, year, trial design, participants, interventions and outcomes. Any disagreements between the authors were resolved through discussion. The present meta-analysis complies with the preferred reporting items in systematic review and meta-analysis (PRISMA) guidelines [11]. The risk of bias of the included studies was assessed using the Cochrane risk of bias tool [12]. We assessed publication bias only for those comparisons with at least five studies, using funnel plots and Egger's regression test [13]. We used a random-effects model for generating direct and mixed treatment comparison estimates. Direct estimates for any two interventions were obtained by pooling the data from head-to-head clinical trials comparing the same interventions. Mixed treatment comparison pooled estimates for the interventions were obtained by pooling the data both from the head-to-head clinical trials comparing the interventions and with the indirect estimates between the interventions through a common comparator. Odds ratio [95% confidence interval] was the effect estimate for categorical and weighted mean difference [95% confidence interval] for numerical outcomes. Inconsistency between direct and indirect pooled effect estimates was assessed by I^2 statistics, wherein a value of $<$ 3 was considered as

minimal, 3–6 as modest and >6 as large [14]. Sub-group analyses were carried out for severe pre-eclampsia, with different initial blood pressure thresholds, and for different definitions for target blood pressures. Sensitivity analysis was carried out by excluding trials that did not report the initial blood pressure criteria from the overall analysis and those trials that had recruited post-partum women with severe hypertension. Trial sequential analysis (TSA, Copenhagen, DK) was conducted for comparisons with a minimum of five studies to assess the cumulative evidence according to the information size achieved to date [15]. A relative risk reduction of 10% was considered as the clinically meaningful difference in the primary outcome. MetaXL was used for generating the pooled estimates [16]. Grading of the evidence for key comparisons was carried out using the grades of recommendation, assessment, development and evaluation (GRADE) working group approach [12].

Results

Search results

A total of 320 articles were retrieved, of which 51 [17–67] were included in the systematic review and 46 in the meta-analysis. The PRISMA flow chart is depicted in Figure 1. Table S1 represents the key characteristics of the included studies. Overall assessment of risk of bias revealed low risk for reporting and attrition bias with some of studies associated with either unclear or high risk in other domains (Figure S1). The following interventions were included in the systematic review: direct-acting vasodilators (hydralazine, dihydralazine, diazoxide, glyceryl trinitrate), sympatholytics (labetalol, ketanserin and urapidil), calcium channel blockers (nicardipine, nifedipine and isradipine), prostaglandins/prostaglandin analogues [prostaglandin A1 (PG_{A1}) and epoprostenol], centrally acting antihypertensive drug (clonidine), angiotensin converting

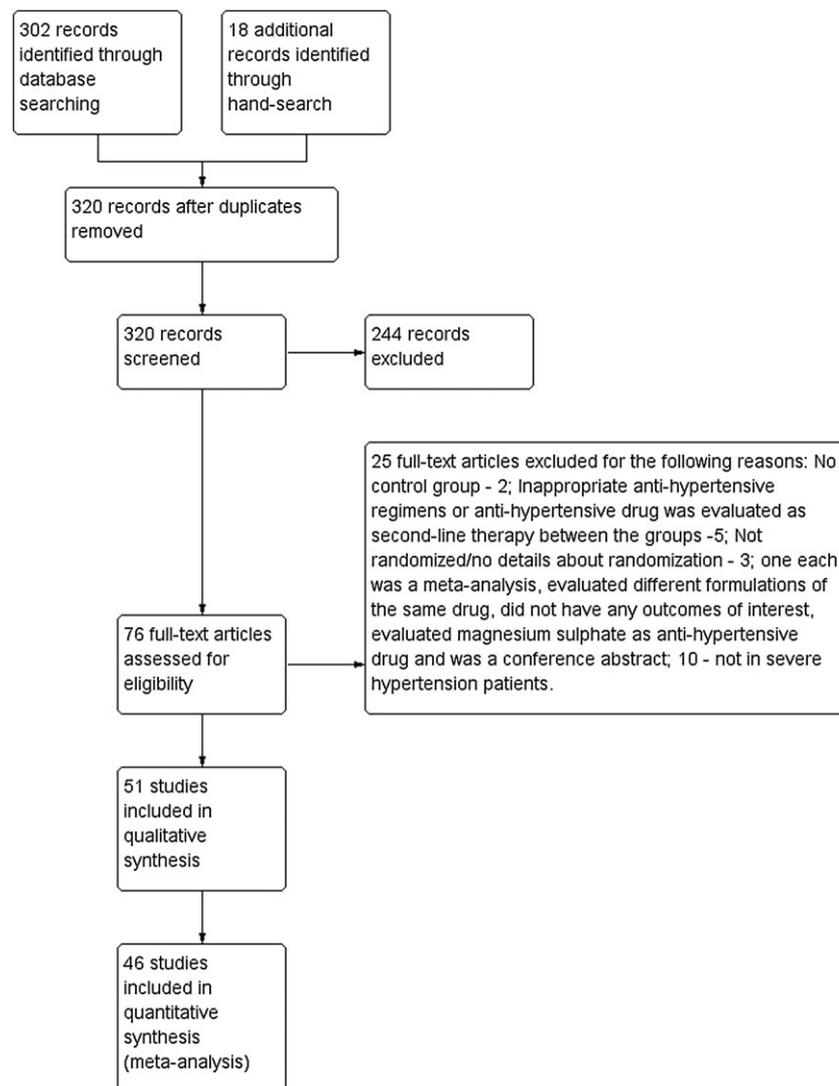


Figure 1

PRISMA flow diagram. Fifty-one studies were included in this systematic review and 46 in this meta-analysis

enzyme inhibitor (captopril) and drug combinations (nifedipine/celastrol, nifedipine/resveratrol and nifedipine/vitamin D). All the above drugs except clonidine and captopril were also evaluated in the meta-analysis.

Overall analysis of the pooled estimates for the primary outcome

Thirty-two studies with 3236 participants were included for the analysis of primary outcome. The network plot of the interventions assessed for the primary outcome is shown in Figure 2. No significant differences were observed in the proportion of patients achieving target blood pressure between the drugs. Surprisingly, nifedipine was observed with a better estimate compared to diazoxide (Table 1). However, for this comparison, there were no head-to-head clinical trials and the mixed treatment pooled estimate was based on the indirect comparison. Mild inconsistencies were observed between the direct and mixed treatment comparison estimates (\bar{H} ranged between 1 and 1.47).

Sub-group analyses for the primary outcome

Route of administration. Most of the drugs were administered intravenously (IV) either as bolus or infusion except for nifedipine. Details of the individual routes of the drugs used in the trials are given in Table S1. Twenty-eight studies (2799 participants) were included for the sub-group analysis compared to hydralazine IV bolus (Figure S2). Labetalol IV infusion [17.8 (3.9, 81)] and diazoxide IV bolus [2.8 (1.4, 5.8)] were observed with significantly increased proportion of patients achieving target BP. The direct comparison analysis revealed a better response with labetalol IV infusion

compared to diazoxide IV bolus [6.3 (1.7, 24)]. No inconsistency was observed between the direct and mixed treatment comparison pooled estimates ($\bar{H} = 1$).

Severe pre-eclampsia. We carried out a sub-group analysis of studies that had enrolled patients with severe pre-eclampsia. We have also included those studies where more than two-thirds of the patients were diagnosed with severe pre-eclampsia. Twenty-seven studies (2801 participants) were included and no significant differences were observed in the mixed treatment comparison pooled estimates between the drugs (Figure S3). However, the direct comparison pooled estimate for labetalol was significantly better than diazoxide [6.3 (1.7, 24)]. Mild inconsistency was observed between the direct and mixed treatment comparison estimates ($\bar{H} = 1.48$).

Initial blood pressure threshold. Studies varied in their definition of severe hypertension (Table S1). Due to paucity of studies, the sub-group analyses for this entity was restricted to only three categories (Table S2). No significant differences were observed with labetalol, nifedipine or glyceryl trinitrate with hydralazine, and labetalol, isradipine and ketanserin with dihydralazine. No inconsistency was observed between the direct and mixed treatment comparison pooled estimates ($\bar{H} = 1$).

Target blood pressure. The studies also varied in the definitions of target blood pressure in their study participants (Table S1). Due to paucity of studies in most of the categories, sub-group analyses were carried out for only two categories (Table S3). In the subset of studies with target blood pressure <160/100 mmHg, nifedipine was observed to outperform hydralazine [48.9 (5.6, 428.6)]. No inconsistency was

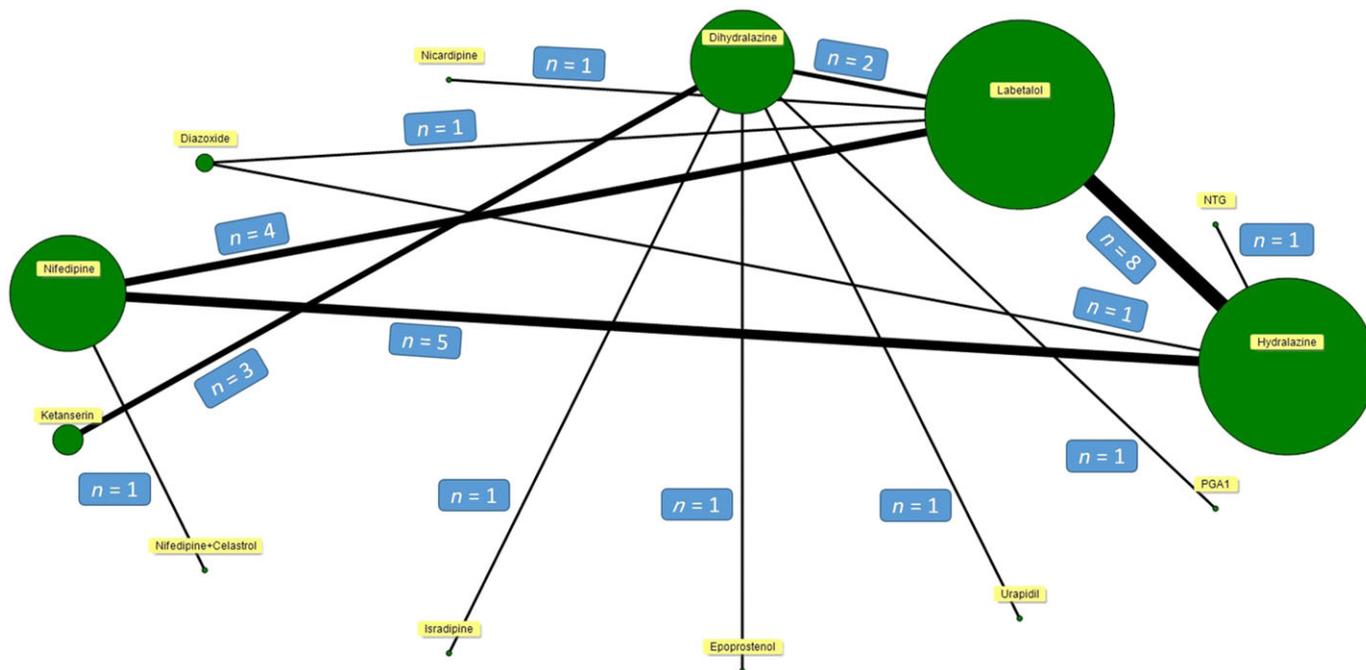


Figure 2

Network plot for primary outcome. The majority of the studies compared hydralazine with labetalol followed by nifedipine and labetalol

Table 1

Direct and mixed treatment comparison pooled estimates for primary outcome

Drugs	PGAT		GTN		Labetalol		Dihydralazine		Nifedipine		Diazoxide		Ketanserin		N/C		Nicardipine		Isradipine		Epoprostenol		Urapidil		Hydralazine		
	D	M	D	M	D	M	D	M	D	M	D	M	D	M	D	M	D	M	D	M	D	M	D	M	D	M	
PGAT	-	0.8	-	0.9	1	1	-	0.7	-	5.5	-	1.6	-	1.6	-	0.7	-	0.6	-	0.2	-	0.2	-	1	-	1.2	-
	[0, 270]	[0, 270]	[0, 270]	[0, 259]	[0.1, 55.3]	[0.1, 55.3]	[0, 215]	[0, 215]	[0, 1851]	[0, 1851]	[0, 106]	[0, 106]	[0, 106]	[0, 106]	[0, 106]	[0, 407]	[0, 407]	[0.1, 206]	[0.1, 206]	[0.2, 21.4]	[0.2, 21.4]	[0, 32.1]	[0, 287]	[0, 287]	[0, 359]	[0, 359]	
GTN	-	1.1	-	1.3	1.3	1.3	-	0.4	-	0.5	-	2.1	-	2.1	-	0.4	-	0.8	-	0.3	-	0.3	-	1.3	-	1.5	-
	[0.3, 4.9]	[0.3, 4.9]	[0.3, 4.9]	[0.3, 4.9]	[0.1, 3.3]	[0.1, 3.3]	[0.1, 3.3]	[0.1, 3.3]	[0.1, 2.4]	[0.1, 2.4]	[0, 169]	[0, 169]	[0, 169]	[0, 169]	[0, 169]	[13.1]	[13.1]	[0.1, 5.2]	[0.1, 5.2]	[0.3, 34.8]	[0.3, 34.8]	[0, 52.8]	[1.3, 449]	[1.3, 449]	[0.4, 5.6]	[0.4, 5.6]	
Labetalol	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	0.7	-	0.2	-	0.2	-	1.2	-	2.3	-
	[0.6, 3.5]	[0.6, 3.5]	[0.6, 3.5]	[0.6, 3.5]	[0.6, 3.5]	[0.6, 3.5]	[0.6, 3.5]	[0.6, 3.5]	[0.6, 3.5]	[0.6, 3.5]	[1.7, 24]	[1.7, 24]	[1.7, 24]	[1.7, 24]	[1.7, 24]	[1.7, 24]	[1.7, 24]	[0.3, 2.2]	[0.3, 2.2]	[0.2, 24.6]	[0.2, 24.6]	[0, 38]	[1.2, 330]	[1.2, 330]	[0.3, 2.8]	[0.3, 2.8]	
Dihydralazine	-	0.7	-	0.7	0.7	0.7	-	0.7	-	5.5	-	1.6	-	1.6	-	0.7	-	0.6	-	0.2	-	0.2	-	1	-	1.2	-
	[0, 41.7]	[0, 41.7]	[0, 41.7]	[0, 41.7]	[0, 41.7]	[0, 41.7]	[0, 41.7]	[0, 41.7]	[0, 41.7]	[0.1, 373]	[0.1, 373]	[0.1, 373]	[0.1, 373]	[0.1, 373]	[0.1, 373]	[0.1, 373]	[0.1, 373]	[0.2, 40.6]	[0.2, 40.6]	[0.2, 2.1]	[0.2, 2.1]	[0, 4.6]	[1, 54.2]	[1, 54.2]	[0.1, 54.2]	[0.1, 54.2]	
Nifedipine	-	3.6	-	3.6	3.6	3.6	-	3.6	-	3.6	-	2.3	-	2.3	-	1	-	0.9	-	0.3	-	0.3	-	1.4	-	2.1	-
	[0.6, 20.5]	[0.6, 20.5]	[0.6, 20.5]	[0.6, 20.5]	[0.6, 20.5]	[0.6, 20.5]	[0.6, 20.5]	[0.6, 20.5]	[0.6, 20.5]	[0.6, 20.5]	[0.1, 10]	[0.1, 10]	[0.1, 10]	[0.1, 10]	[0.1, 10]	[0.1, 10]	[0.1, 10]	[0.2, 3.5]	[0.2, 3.5]	[0.3, 32.3]	[0.3, 32.3]	[0, 49.8]	[1.4, 430]	[1.4, 430]	[0.9, 18.8]	[0.9, 18.8]	
Diazoxide	-	0.3	-	0.3	0.3	0.3	-	0.3	-	0.8	-	0.8	-	0.8	-	0.8	-	0.1	-	0.4	-	0.1	-	0.2	-	1.7	-
	[0, 22.7]	[0, 22.7]	[0, 22.7]	[0, 22.7]	[0, 22.7]	[0, 22.7]	[0, 22.7]	[0, 22.7]	[0, 22.7]	[0, 22.7]	[0, 22.7]	[0, 22.7]	[0, 22.7]	[0, 22.7]	[0, 22.7]	[0, 22.7]	[0, 22.7]	[0.6, 0.6]	[0.6, 0.6]	[0.4, 32.7]	[0.4, 32.7]	[0, 7.1]	[0.2, 61]	[0.2, 61]	[0.1, 30.3]	[0.1, 30.3]	
Ketanserin	-	0.4	-	0.4	0.4	0.4	-	0.4	-	0.4	-	0.4	-	0.4	-	0.4	-	0.4	-	0.1	-	0.1	-	0.6	-	0.7	-
	[0, 68.9]	[0, 68.9]	[0, 68.9]	[0, 68.9]	[0, 68.9]	[0, 68.9]	[0, 68.9]	[0, 68.9]	[0, 68.9]	[0, 68.9]	[0, 68.9]	[0, 68.9]	[0, 68.9]	[0, 68.9]	[0, 68.9]	[0, 68.9]	[0, 68.9]	[0.4, 29.2]	[0.4, 29.2]	[0.1, 1.7]	[0.1, 1.7]	[0, 3.5]	[0.6, 39.1]	[0.6, 39.1]	[0.7, 49.7]	[0.7, 49.7]	
N/C	-	0.9	-	0.9	0.9	0.9	-	0.9	-	0.9	-	0.3	-	0.3	-	0.3	-	0.9	-	0.3	-	0.3	-	1	-	3.7	-
	[0, 100.8]	[0, 100.8]	[0, 100.8]	[0, 100.8]	[0, 100.8]	[0, 100.8]	[0, 100.8]	[0, 100.8]	[0, 100.8]	[0, 100.8]	[0, 100.8]	[0, 100.8]	[0, 100.8]	[0, 100.8]	[0, 100.8]	[0, 100.8]	[0, 100.8]	[19.9, 19.9]	[19.9, 19.9]	[0.3, 69]	[0.3, 69]	[0, 100.8]	[1, 815]	[1, 815]	[0.1, 93]	[0.1, 93]	
Nicardipine	-	0.3	-	0.3	0.3	0.3	-	0.3	-	0.3	-	0.3	-	0.3	-	0.3	-	0.8	-	0.3	-	0.3	-	1.6	-	1.8	-
	[0, 57.6]	[0, 57.6]	[0, 57.6]	[0, 57.6]	[0, 57.6]	[0, 57.6]	[0, 57.6]	[0, 57.6]	[0, 57.6]	[0, 57.6]	[0, 57.6]	[0, 57.6]	[0, 57.6]	[0, 57.6]	[0, 57.6]	[0, 57.6]	[0, 57.6]	[0.3, 37.6]	[0.3, 37.6]	[0.3, 37.6]	[0.3, 37.6]	[0, 57.6]	[1.6, 495]	[1.6, 495]	[0.5, 6.7]	[0.5, 6.7]	
Isradipine	-	1	-	1	1	1	-	1	-	1	-	1	-	1	-	1	-	1	-	1	-	1	-	4.8	-	5.6	-
	[0, 46.5]	[0, 46.5]	[0, 46.5]	[0, 46.5]	[0, 46.5]	[0, 46.5]	[0, 46.5]	[0, 46.5]	[0, 46.5]	[0, 46.5]	[0, 46.5]	[0, 46.5]	[0, 46.5]	[0, 46.5]	[0, 46.5]	[0, 46.5]	[0, 46.5]	[1, 46.5]	[1, 46.5]	[1, 46.5]	[1, 46.5]	[0, 46.5]	[4.8, 474]	[4.8, 474]	[0.1, 600]	[0.1, 600]	
Epoprostenol	-	4.8	-	4.8	4.8	4.8	-	4.8	-	4.8	-	4.8	-	4.8	-	4.8	-	4.8	-	4.8	-	4.8	-	4.8	-	5.7	-
	[0, 940]	[0, 940]	[0, 940]	[0, 940]	[0, 940]	[0, 940]	[0, 940]	[0, 940]	[0, 940]	[0, 940]	[0, 940]	[0, 940]	[0, 940]	[0, 940]	[0, 940]	[0, 940]	[0, 940]	[4.8, 746]	[4.8, 746]	[4.8, 746]	[4.8, 746]	[0, 940]	[4.8, 746]	[4.8, 746]	[0, 940]	[0, 940]	
Urapidil	-	1.2	-	1.2	1.2	1.2	-	1.2	-	1.2	-	1.2	-	1.2	-	1.2	-	1.2	-	1.2	-	1.2	-	1.2	-	1.2	-
	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[1.2, 354]	[1.2, 354]	[1.2, 354]	[1.2, 354]	[0, 354]	[1.2, 354]	[1.2, 354]	[0, 354]	[0, 354]	
Hydralazine	-	1.2	-	1.2	1.2	1.2	-	1.2	-	1.2	-	1.2	-	1.2	-	1.2	-	1.2	-	1.2	-	1.2	-	1.2	-	1.2	-
	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[0, 354]	[1.2, 354]	[1.2, 354]	[1.2, 354]	[1.2, 354]	[0, 354]	[1.2, 354]	[1.2, 354]	[0, 354]	[0, 354]	

D, Direct pooled estimates; GTN, glyceryl trinitrate; M, Mixed treatment comparison estimates; N/C, nifedipine/celastrol; PGA1, prostaglandin A1. *P < 0.05 (statistically significant).

observed between the direct and mixed treatment comparison pooled estimates ($\bar{H} = 1$).

Sensitivity analysis and publication bias for the primary outcome

Four studies did not report the initial blood pressure criterion for recruiting their study participants, of which data from one was included in the analysis of primary outcome. Removal of data from this study did not significantly change the overall analysis (Figure S4).

Three studies recruited post-natal women of which data from two were included for the analysis of primary outcome. No significant changes were observed in the pooled estimates of the drugs after removing the data from the above studies (Figure S5).

No publication bias was detected for the following comparisons: hydralazine with labetalol ($P = 0.84$), nifedipine with hydralazine ($P = 0.69$) and nifedipine and labetalol ($P = 0.3$) for the primary outcome (Figure S6).

Trial sequential analysis for primary outcome

Trial sequential analysis was carried out between hydralazine and labetalol; nifedipine and hydralazine; and nifedipine with labetalol for the primary outcome. The pooled estimates were similar for hydralazine and nifedipine compared to labetalol and the evidence is sufficient for concluding the same (Figures S7 and S8). However, the evidence is inconclusive for nifedipine compared to hydralazine (Figure S9).

Pooled estimates for secondary outcomes

A summary of pooled estimates for all the secondary outcomes is listed in Table 2. Compared to hydralazine, glyceryl trinitrate, nicardipine, diazoxide, nifedipine/celastrol, nifedipine/vitamin D and nifedipine/resveratrol were associated with significantly shorter time to achieve the target blood pressure. Fewer doses were required for nifedipine compared to hydralazine for achieving the target blood pressure, whereas nicardipine and isradipine required significantly more. Glyceryl trinitrate and labetalol were associated with lesser incidences of tachycardia and palpitation respectively than hydralazine.

Grading the evidence

Grading of the quality of evidence was carried out for key comparisons. For the primary outcome, moderate quality was observed for the direct comparison pooled estimates between labetalol and hydralazine. Grading of the quality of evidence for other comparisons revealed either low or very low quality (Table 3).

Discussion

The present network meta-analysis was carried out to compare the efficacy and safety of drugs for treating severe hypertension in pregnancy. We have included 51 studies in this systematic review and 46 in the meta-analysis. No significant differences in the number of patients achieving target BP was noted between the drugs. Glyceryl trinitrate, nicardipine, diazoxide, nifedipine/celastrol, nifedipine/vitamin D and nifedipine/resveratrol were observed to require a significantly shorter time

to achieve the target BP than hydralazine. Nifedipine requires fewer doses than hydralazine to achieve the target BP. Glyceryl trinitrate and labetalol were associated with fewer incidences of tachycardia and palpitation respectively than hydralazine. Sub-group analyses revealed that labetalol IV infusion and diazoxide IV bolus could outperform hydralazine IV bolus. Similarly, labetalol IV infusion may perform better than diazoxide IV bolus, including in patients with severe pre-eclampsia. Trial sequential analysis concluded the presence of adequate evidence for hydralazine and nifedipine compared to labetalol. Moderate quality of evidence was observed for nifedipine and hydralazine but was either low or very low for others.

Network meta-analysis can estimate the relative effect even in the absence of head-to-head clinical trials through a common comparator; for example, if there are three interventions, namely A, B and C, and we assume that head-to-head clinical trials compared either A with B or B with C. With the aid of network meta-analysis modelling, through the common comparator (B), we can compute the relative effect estimate between A and C [10]. In the present network meta-analysis, we observed a similar efficacy profile between the several anti-hypertensive drugs used in pregnancy despite the absence of head-to-head comparisons for many drugs. The only other robust quantitative synthesis was from Duley *et al.* [9], where the authors included 35 studies but the results were inconclusive. Further, the authors of the study did not take into account the route of administration of the anti-hypertensive drugs, various initial and target blood pressure values and pre-eclampsia status; we have addressed all the above issues in the present study. Additionally, they did not validate their results by adjusting the pooled estimates to type 1 error for which we have carried out the trial sequential analysis. Trial sequential analysis can be considered as an interim analysis that accounts for the statistical diversity relating the accumulated evidence to the total sample size required [68]. We had observed that the evidence is sufficient to conclude a similar efficacy (in terms of number of patients achieving the target BP) between hydralazine and nifedipine compared to labetalol. Future investigators should be aware that conducting clinical trials with a similar comparison is futile. Also, we have noted that some of the investigators in recent times have started combining drugs such as vitamin D and resveratrol along with conventional antihypertensive drugs (nifedipine). Though few such trials were included in the present meta-analysis, no advantages have been observed with such drug combinations.

Our results are in line with the recommendations from Royal College of Obstetricians and Gynaecologists and American College of Obstetrics and Gynaecology where labetalol, nifedipine and hydralazine are listed as first-line drugs [69, 70]. Interestingly, the World Health Organization (WHO) has listed only intravenous hydralazine in its latest essential drugs list (EDL) for treating severe hypertension in pregnancy [71]. Although cost-effectiveness data for hydralazine and nifedipine is not available, because nifedipine can be administered orally, available as the generic preparation with a similar efficacy and safety profile confirmed in the present review and in previous reviews [72], the WHO may consider including nifedipine in the EDL for primary health care. Moreover, we observed that

Table 2

Mixed treatment comparison pooled estimates for secondary outcomes in comparison with hydralazine

Outcomes (Total number of studies; Total number of patients)											
Drugs	Maternal hypotension ^a (18; 2737)	Time for achieving target BP (16; 2702)	Failure rate ^a (17; 1803)	Number of doses required to achieve target BP ^b (16; 1575)	Stillbirth ^a (12; 1055)	Neonatal death ^a (12; 800)	Maternal tachycardia ^a (17; 2884)	Headache ^a (29; 3828)	Palpitation ^a (8; 782)	Number of patients with new HT crisis (4; 313)	Number of neonates with APGAR <7 (13; 2647)
Labetalol	0.23 [0, 1.2]	-1 [-22.2, 23]	0.6 [0.2, 1.6]	-0.1 [-0.3, 0.2]	0.9 [0.4, 2.3]	0.8 [0.2, 3.6]	0.4 [0.1, 1.5]	0.7 [0.3, 1.9]	0.4 [0.2, 0.9]	0.4 [0.1, 1.9]	1.4 [0.8, 2.4]
Nifedipine	0.7 [0.1, 4]	-3.5 [-26.5, 19.7]	0.7 [0.3, 1.5]	-0.4 [-0.7, -0.1]	1.4 [0.4, 5.1]	0.4 [0.1, 2.5]	0.6 [0.1, 2.1]	0.8 [0.3, 2.3]	1.5 [0.4, 5.9]	0.5 [0.3, 1.1]	1.1 [0.6, 2]
Glyceryl trinitrate	0.9 [0.5, 1.7]	-33.8 [-36.7, -31]*	0.7 [0.2, 2.4]	-	0.7 [0.1, 4]	-	0.5 [0.2, 0.9]*	0.4 [0.1, 3.9]	1.3 [0.1, 18.2]	-	0.6 [1.1, 2.5]
PGA1	-	-	-	-	-	-	-	-	-	-	-
Dihydralazine	2.3 [0.1, 48]	-	1.9 [0.1, 27.5]	-0.2 [-1.3, 1]	0.1 [0, 4.4]	0.2 [0, 10.1]	6.4 [0.5, 91.6]	3.1 [0.4, 3.4]	-	-	-
Nicardipine	-	-11.8 [-22.3, -1.2]*	0.6 [0.2, 2.3]	0.9 [0.5, 1.3]*	-	-	-	0.6 [0.2, 2.3]	3.5 [0.2, 82]	-	-
Diazoxide	0.8 [0.1, 12.6]	-15 [-20.6, -9.4]*	0.5 [0.1, 2.8]	-	2.4 [0.1, 7.1]	3.8 [0.1, 126.2]	1 [0.3, 3.4]	0.3 [0.1, 3.3]	-	-	0.9 [0.2, 4]
Ketanserin	0.3 [0.1, 8.3]	-	20.5 [0.8, 496.6]	-0.1 [-1.2, 1.1]	0.6 [0.1, 4.9]	1 [0.1, 165.6]	0.3 [0, 8.3]	0.3 [0.1, 8.3]	-	-	-
Nifedipine/Celastrol	0.6 [0.1, 15.4]	-19.3 [-27.4, -11.1]*	-	-	-	-	0.4 [0.1, 4.2]	1 [0.1, 8.2]	-	-	1.1 [0.4, 2.7]
Isradipine	-	-	-	1.7 [0.3, 2.1]*	0.1 [0, 4.6]	0.5 [0, 99]	-	-	-	-	-
Epoprostenol	-	-	-	-	-	0.2 [0, 27.8]	-	0.2 [0, 31.8]	-	-	-
Urapidil	1.1 [0, 181]	-	-	-	-	0.1 [0, 12.2]	-	-	-	-	-
Nifedipine/Vitamin D	0.3 [0.1, 5.8]	-17.7 [-25.7, -9.7]*	-	-	-	-	0.4 [0.1, 3.5]	1.5 [0.3, 8.1]	-	-	0.9 [0.4, 2.3]
Nifedipine/Resveratrol	0.2 [0.1, 7.4]	-13.9 [-22.6, -5.2]*	-	-0.3 [-1.3, 0.8]	-	-	0.7 [0.1, 10.6]	1.5 [0.2, 10.7]	-	-	0.8 [0.3, 2.2]

*P < 0.05 (statistically significant).

^aPooled estimates expressed in odds ratio [95% confidence interval].

^bPooled estimates expressed in mean difference [95% confidence interval].

BP, blood pressure; MTC, mixed treatment pooled estimates; PGA1, Prostaglandin A1.

Table 3

Grading the quality of evidence for key comparisons

Comparisons	Illustrative comparative risks (95% confidence intervals)		Effect estimate and quality of evidence for direct comparisons	Effect estimate and quality of evidence for mixed treatment comparisons
	Assumed risk ^a	Corresponding risk ^b		
Number of patients achieving target BP with labetalol compared to hydralazine	881 per 1000	914 per 1000 (833 to 956)	1.4 [0.7, 2.8] ⊕⊕⊕⊕ Moderate ^c	2.3 [0.3, 15.8] ⊕⊕⊕⊕ Low ^{c,e}
Number of patients achieving target BP with nifedipine compared to hydralazine	881 per 1000	964 per 1000 (833 to 992)	3.7 [0.7, 18.8] ⊕⊕⊕⊕ Low ^{c,e}	2.1 [0.9, 5.2] ⊕⊕⊕⊕ Low ^{c,e}
Number of doses required to achieve target BP with nifedipine compared to hydralazine	NA	NA	-0.1 [-1.1, 1] ⊕⊕⊕⊕ Very low ^{c,d,e}	-0.4 [-0.7, -0.1] ⊕⊕⊕⊕ Very low ^{c,d,e}
Time for achieving target BP with glyceryl trinitrate compared to hydralazine	NA	NA	-33.8 [-36.7, -31] ND	-33.8 [-36.7, -31] ND
Time for achieving target BP with nifedipine compared to hydralazine	NA	NA	-1.3 [-3.9, 1.3] ND	-11.8 [-22.3, -1.2] ND
Time for achieving target BP with diazoxide compared to hydralazine	NA	NA	-15 [-20.6, -9.4] ND	-15 [-20.6, -9.4] ND
Time for achieving target BP with nifedipine/celastrol compared to hydralazine	NA	NA	-21 [-24, -17.8] ND	-19.3 [-27.4, -11.1] ND
Time for achieving target BP with nifedipine/vitamin D compared to hydralazine	NA	NA	-19.3 [-22.2, -16.6] ND	-17.7 [-25.7, -9.7] ND
Time for achieving target BP with nifedipine/resveratrol compared to hydralazine	NA	NA	-15.5 [-19.8, -11.1] ND	-13.9 [-22.6, -5.2] ND

^aAssumed risk was the median control group risk across the studies for the categorical variables.

^bComputed only for the categorical outcomes based on assumed risk.

^cDowngraded one level for including studies with high risk of bias.

^dDowngraded one level as publication bias could not be ruled out.

^eDowngraded one level for serious limitations in the precision of the estimates.

Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; **Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; **Very low quality:** We are very uncertain about the estimate.

BP, blood pressure; NA, not assessed as the risk assessment was performed only for the categorical variable; ND, not determined due to very serious limitations in the precision of the estimates, publication bias could not be assessed and high risk of bias and the estimate was derived from only one study.

nifedipine performs better than hydralazine when the target BP is less than 160/110 mmHg.

We have observed that labetalol IV infusion performs better than hydralazine IV bolus. However, there were only two studies (with 51 patients) where labetalol was administered as IV infusion. Reports indicate the risk of severe hypotension with labetalol IV infusion [73]. Hence, considering the very low quality of evidence for this comparison and the potential risk involved, we do not recommend labetalol IV infusion. Further studies should explore the therapeutic utility of labetalol IV infusion for treating either severe or refractory hypertension in pregnancy.

We did not observe any significant differences in terms of either maternal or fetal safety profile between the evaluated drugs. In addition, maternal mortality is reported rarely in the included studies. We have excluded studies that have assessed the role of oral alpramolofex/atenolol, as their role for treating severe hypertension in contemporary

practice is not favoured due to weak anti-hypertensive effects [74]. Similarly, guidelines from the multidisciplinary working group of the National Partnership for Maternal Safety has advised not using magnesium sulphate for the sole anti-hypertensive purpose, and so we excluded it in this review. [75]

This is the first network meta-analysis in this field. The estimates generated from the present model will be useful to practitioners as it may take several years to conduct head-to-head clinical trials comparing several drugs for treating severe hypertension in pregnancy. Additionally, we have also confirmed the presence of adequate evidence at least for key comparisons. Various sub-group analyses based on route of administration, comorbidity with severe pre-eclampsia, pre-treatment and target blood pressure values were carried out. However, the following are the limitations of the study: the differences in the pre-treatment blood pressure values varied widely between the studies;

differences in the therapeutic response between primigravida and multigravida could not be explored as the authors rarely reported this variable in their studies; definition of failure rate differed across the studies; effects on uterine artery/umbilical artery/placental blood flow could not be assessed; effects on fetus such as fetal distress/congenital anomalies/small for gestational age was not assessed; and no strict definition of pre-eclampsia was assumed in this review.

In conclusion, the present network meta-analysis suggests similar efficacy between nifedipine, hydralazine and labetalol in the treatment of severe hypertension in pregnancy. The above drugs may also be useful in treating hypertension in severe pre-eclampsia. Moderate quality of evidence was observed for direct comparison pooled estimate between labetalol and hydralazine but was either low or very low for other comparisons. Negligible differences were observed in the individual safety profile. The cumulative evidence is inadequate for any meaningful conclusion for other drugs.

Competing Interests

There are no competing interests to declare.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

<http://onlinelibrary.wiley.com/doi/10.1111/bcp.13649/supinfo>

- Figure S1** Summary of risk of bias of the included studies
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- Figure S3** Forest plot of the pooled estimates of mixed treatment comparisons in severe pre-eclampsia
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