Papers

Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis

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Abstract

Objective To review outcomes in randomised controlled trials comparing hydralazine against other antihypertensives for severe hypertension in pregnancy.

Study design Meta-analysis of randomised controlled trials (published between 1966 and September 2002) of short acting antihypertensives for severe hypertension in pregnancy. Independent data abstraction by two reviewers. Data were entered into RevMan software for analysis (fixed effects model, relative risk and 95% confidence interval); in a secondary analysis, risk difference was also calculated.

Results Of 21 trials (893 women), eight compared hydralazine with nifedipine and five with labetalol. Hydralazine was associated with a trend towards less persistent severe hypertension than labetalol (relative risk 0.29 (95% confidence interval 0.08 to 1.04); two trials), but more severe hypertension than nifedipine or isradipine (1.41 (0.95 to 2.09); four trials); there was significant heterogeneity in outcome between trials and differences in methodological quality. Hydralazine was associated with more maternal hypotension (3.29 (1.50 to 7.23); 13 trials); more caesarean sections (1.30 (1.08 to 1.59); 14 trials); more placental abruption (4.17 (1.19 to 14.28); five trials); more maternal oliguria (4.00 (1.22 to 12.50); three trials); more adverse effects on fetal heart rate (2.04 (1.32 to 3.16); 12 trials); and more low Apgar scores at one minute (2.70 (1.27 to 5.88); three trials). For all but Apgar scores, analysis by risk difference showed heterogeneity between trials. Hydralazine was associated with more maternal side effects (1.50 (1.16 to 1.94); 12 trials) and with less neonatal bradycardia than labetalol (risk difference –0.24 (–0.42 to –0.06); three trials).

Conclusions The results are not robust enough to guide clinical practice, but they do not support use of hydralazine as first line for treatment of severe hypertension in pregnancy. Adequately powered clinical trials are needed, with a comparison of labetalol and nifedipine showing the most promise.

Introduction

In both the United States and the United Kingdom, reports into maternal mortality have consistently shown the excess maternal mortality associated with the hypertensive disorders of pregnancy, particularly the severe hypertension of pre-eclampsia.[1–6] In the most recent triennium in the UK series (1997-9),[6] maternal mortality from hypertensive disease was most commonly attributed to intracerebral haemorrhage. There is general consensus that maternal risk is decreased by antihypertensive treatment that acutely lowers very high blood pressure.[1 7 8] Recognition of this specific risk has meant that the control of acutely raised blood pressure has become central for women with severe hypertension, particularly that of pre-eclampsia.[6]

Three short acting antihypertensive agents—hydralazine, labetalol, and short acting (sublingual or orally administered) nifedipine—are commonly used to control acute, very high blood pressure in women with severe hypertension in pregnancy, who may require emergency caesarean section and often receive magnesium sulphate.[1] All three agents have their proponents and detractors.

For many years, hydralazine has been the recommended antihypertensive of first choice for severe hypertension in pregnancy.[1 7 8] Its side effects (such as headache, nausea, and vomiting) are common and mimic symptoms of deteriorating pre-eclampsia. Although a precipitous hypotensive overshoot may occur with any antihypertensive agent used to treat the severe hypertension of pre-eclampsia,[9–13] a meta-analysis of clinical trials showed that maternal hypotension may be more common with parenteral hydralazine, which was also associated with an excess of caesarean sections, placental abruptions, and low Apgar scores (<7) at five minutes.[14]

Short acting nifedipine has the clinical advantage of being able to be given as required by midwives or nurses in the absence of a doctor. However, uncertainty exists about how safe short acting calcium channel blockers are for the mother.[15] When used for treating hypertension in patients with coronary artery disease or diabetes, these agents have been associated with excess cardiovascular morbidity and mortality.[16 17] Two case reports of transient neuromuscular weakness in patients taking nifedipine and magnesium sulphate have caused concern about concomitant use of these agents.[18 19] The withdrawal of short acting nifedipine from some markets has been lamented by many experts in the field of pregnancy hypertension.[20]

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Labetalol has been used extensively in pregnancy and has a favourable side effect profile. However, specific concern has been raised about the risk of neonatal bradycardia with parenteral labetalol.[21]

This meta-analysis of randomised controlled trials for treatment of moderate to severe hypertension in pregnancy aimed to compare the effects of short acting antihypertensive agents (in comparison to parenteral hydralazine) on perinatal, maternal, and neonatal outcomes, particularly maternal hypotension.

Methods

We updated our previous literature review (1966-97)[14] by searching Medline (1997-September 2002), the journal *Hypertension in Pregnancy* (hand-searched), conference proceedings, bibliographies (including those of relevant publications in the Cochrane Database of Systematic Reviews), and textbooks. We looked for articles addressing the treatment of severe hypertension in pregnancy with short acting antihypertensive agents, comparing them with parenteral hydralazine.

For the Medline search we used (and exploded) {"antihypertensive agent", "bed rest", "plasma volume", "plasma substitute" or "hospitalization"} AND {"pregnancy", "pregnancy complications", "maternal mortality", "perinatology", "neonatology", "infant, newborn, diseases", "infant mortality", or "infant"}.

Criteria for inclusion were moderate to severe hypertension in pregnancy (regardless of type), randomised controlled trial, hydralazine compared with another short acting antihypertensive (generally via parenteral administration), and relevant clinical outcomes addressing maternal, perinatal, or paediatric benefit or risk. Articles in any language were included. Abstracts without accompanying articles were included if they met the above criteria. We contacted authors for missing information or clarification, when necessary. Data were abstracted independently by two reviewers (LAM and CC, PvD, or EJW), and discrepancies were resolved by discussion.

The severity of hypertension was defined according to mean diastolic blood pressure at enrolment: mild (90-99 mm Hg), moderate (100-109 mm Hg), or severe ($\geq$110 mm Hg). The type of hypertension was defined according to national high blood pressure education programme (NHBPEP) standards.[7]

Some trials enrolled mixed populations of women with either pre-existing hypertension or gestational hypertension with or without proteinuria; we used the term "mixed" hypertension in such instances. Otherwise, we used pre-eclampsia when all trial participants had pregnancy induced hypertension with proteinuria at enrolment, and pregnancy induced hypertension when women both with and without proteinuria were enrolled.

Data from trials of single drugs were accepted for maternal haemodynamic outcomes and stillbirth, and for neonatal outcomes if the antihypertensive could be expected to be in the maternal-fetal bloodstream at delivery and could affect the health of the neonate. In the case of duplicate publications, the most recent and complete data were included in the analysis.

Outcome definitions that were not standardised were documented at data abstraction and considered as potential sources of variation in outcome between studies. Maternal outcomes were persistent severe hypertension, need for additional antihypertensive therapy, maternal hypotension, caesarean section, placental abruption, maternal mortality or morbidity (eclampsia, intracerebral haemorrhage, HELLP (haemolysis, raised liver enzymes, low platelets) syndrome, pulmonary oedema, oliguria, and disseminated intravascular coagulation), and maternal side effects (overall and those thought to indicate deteriorating maternal pre-eclampsia: headache, visual symptoms, epigastric pain, and nausea or vomiting). Perinatal outcomes were adverse effects on fetal heart rate, stillbirth, Apgar scores at one minute and five minutes, neonatal death, neonatal bradycardia, tachycardia, hypotension, hypothermia, hypoglycaemia, admission to neonatal intensive care unit, respiratory

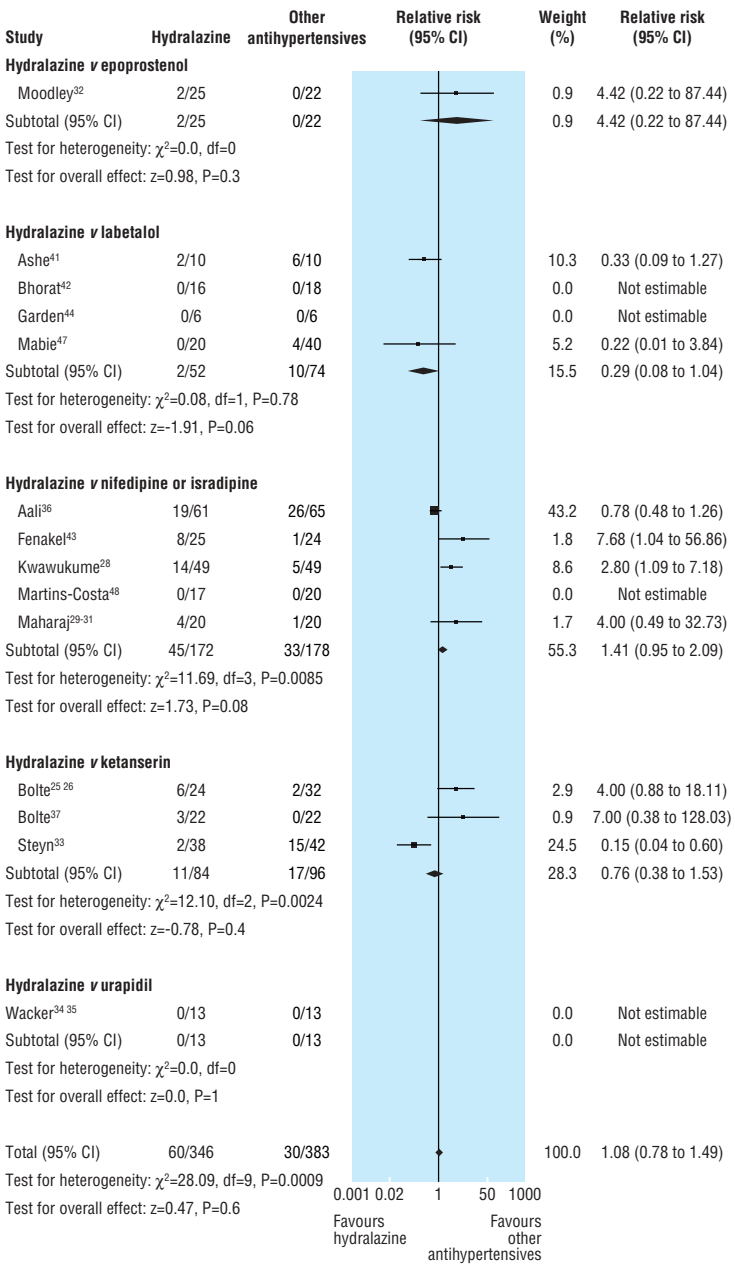

Fig 1 Persistent severe maternal hypertension in trials that compared hydralazine with other antihypertensives

Table 1 Randomised controlled trials for management of severe hypertension in pregnancy

Trial	No of women	Type of hypertension*	Severity of hypertension	Antihypertensive compared with hydralazine	Route (hydralazine /other antihypertensive)†	Method of randomisation	Blinding to outcome
Aali and Nejad[36]	126	Pre-eclampsia	Severe	Nifedipine	Intravenous bolus/ sublingual	Not known	Partial (for blood pressure only)
Ashe et al[41]	20	Mixed	Severe	Labetalol	Intravenous infusion	Not known	Not known
Bhorat et al[42]	34	Pregnancy induced hypertension	Severe	Labetalol	Intravenous bolus/infusion	Not known	No
Bolte et al[25 26]	44	Mixed	Severe	Ketanserin	Intravenous infusion/intravenous bolus→infusion	Adequate	No
Bolte et al[37]	66	Not stated	Severe	Ketanserin	"Intravenous"	Not known	Not known
Duggan et al[39]	9	Mixed	Severe	Nifedipine	Intravenous+oral placebo/ oral+intravenous placebo	Not known	Yes
Fenakel et al[43]	49	Pregnancy induced hypertension	Severe	Nifedipine	Intravenous bolus/sublingual‡	Inadequate	No
Garden et al[44]	6	Mixed	Severe	Labetalol	Intravenous infusion	Not known	Not known
Harper and Murnaghan[27]	30	Mixed	Moderate	Labetalol	Intravenous bolus	Adequate	No
Howarth et al[45]	33	Mixed	Moderate to severe	Urapidil	Intravenous bolus	Adequate	No
Jegasothy and Paranthaman[46]	200	Mixed	Severe	Nifedipine	Intravenous/ sublingual‡	Inadequate	No
Kwawukume and Ghosh[28]	98	Pre-eclampsia	Severe	Nifedipine	Intravenous/ sublingual‡	Inadequate	No
Mabie et al[47]	60	Mixed	Severe	Labetalol	Intravenous bolus	Adequate	No
Maharaj et al[29-31]	40	Pregnancy induced hypertension	Severe	Isradepine	Intravenous bolus/infusion	Adequate	Not known
Martins-Costa et al[48]	37	Pregnancy induced hypertension	Severe	Nifedipine	Intravenous/oral	Adequate	Yes
Moodley and Gouws[32]	47	Mixed	Severe	Epoprostenol	Intravenous infusion	Adequate	Not known
Rodriguez[40]	27	Pre-eclampsia	Severe	Nifedipine	Intravenous,/ intramuscular or sublingual	Adequate	No
Rossouw et al[49]	20	Mixed	Moderate to severe	Ketanserin	Intravenous bolus	Not known	Yes
Seabe et al[50]	33	Pregnancy induced hypertension	Severe	Nifedipine	Intravenous bolus/oral	Adequate	No
Steyn and Odendaal[33]	80	Mixed	Mod	Ketanserin	Intravenous bolus	Adequate	Yes
Wacker et al[34 35]	26	Pre-eclampsia	Mod	Urapidil	Intravenous bolus	Adequate	No

*Mixed=pre-existing or gestational hypertension (with or without proteinuria); pregnancy induced hypertension=with or without proteinuria.
†When route of drug administration was the same for both groups, only one route is stated.
‡Switched to oral therapy when hypertension had been controlled with short acting agents.

distress syndrome, intraventricular haemorrhage, and necrotising enterocolitis.

We used Cochrane review manager software (Revman version 4.0.1; Oxford, UK) for quantitative analyses. We determined heterogeneity between trials by examining the forest plot (of relative risk for each trial, and with the χ^2 statistic, using $P<0.10$) to reflect statistically significant heterogeneity.[22] A P value <0.10 was considered significant given that χ^2 is known not to be sensitive to heterogeneity between trials.[22 23] When heterogeneity between trials was found, we examined differences in study design (for example, method of randomisation), characteristics of participants (for example, type of pregnancy hypertension), intervention (for example, drug and dosage), and outcome definitions (for example, the diastolic blood pressure at which additional antihypertensive therapy was prescribed). The summary statistic was relative risk (and 95% confidence interval), a relative effect measure appropriate for use when summarising evidence.[22] In addition, we calculated risk difference, as recommended by the neonatal review group of the Cochrane Collaboration.[24] Risk difference is a measure of absolute effect and is sensitive to between trial differences in absolute event rates. In the calculation of risk difference, all trials (even those without reported events in either arm of the trial) contribute to the summary statistic. Data were entered by subgroup according to the type of antihypertensive that was compared with hydralazine. The fixed effects model was used, on the assumption that any between trial differences in outcome were due to random variation, so trials were weighted on the basis of precision. For outcomes with significant differences between groups, the median event rate and its range were also presented.

Results

We identified 11 new trials in 16 publications (from 1991 to 2002) that met the inclusion criteria.[25–40] Therefore, this study includes 21 trials (1085 women), including the 10 trials[41–50] in the previous meta-

Table 2 Maternal and perinatal outcomes in trials comparing hydralazine with other antihypertensives for severe hypertension of pregnancy

Outcome	No of trials	No of women	Relative risk (95% CI)	Heterogeneity χ^2	df	P value	Risk difference (95% CI)	Heterogeneity χ^2	df	P value
Maternal outcomes										
Persistent severe hypertension	14	729	1.08 (0.78 to 1.49)	28.09	9	0.0009*	0.01 (–0.04 to 0.06)	44.36	13	<0.0001*
Additional drugs for blood pressure	10	564	1.32 (0.83 to 2.13)	14.06	6	0.029*	0.03 (–0.02,0.08)	22.92	9	0.006*
Maternal hypotension	13	687	3.29 (1.50 to 7.23)*	3.22	6	0.78	0.04 (0.01 to 0.08)*	40.66	12	0.0001*
Eclampsia	8	311	0.75 (0.20 to 2.86)	1.40	3	0.70	–0.01 (–0.05 to 0.04)	2.03	7	0.96
HELLP syndrome	2	142	2.33 (0.83 to 6.67)	3.70	1	0.05*	0.08 (0.00 to 0.17))	18.87	1	<0.0001*
Placental abruption	5	203	4.17 (1.19 to 14.28)*	1.29	4	0.86	0.08 (0.01 to 0.15)*	7.9	4	0.095*
Caesarean section	14	650	1.30 (1.08 to 1.59)*	12.19	11	0.35	0.08 (0.02 to 0.13)*	25.67	13	0.02*
Intracerebral haemorrhage	1	44	3.03 (0.13 to 100)	0	0	NA	0.05 (–0.08 to 0.17)	0	0	NA
Pulmonary oedema	3	161	4.00 (0.65 to 25.00)	1.09	1	0.30	0.05 (–0.01 to 0.12)	7.05	2	0.03*
Oliguria	3	105	4.00 (1.22 to 12.50)*	0.10	2	0.95	0.17 (0.05 to 0.29)*	7.44	2	0.02*
Disseminated intravascular coagulation	1	44	0.33 (0.01 to 7.69)	0	0	NA	–0.05 (–0.17 to 0.08)	0	0	NA
Maternal death	9	471	3.33 (0.52 to 20.00)	0	2	1.00	0.01 (–0.02 to 0.04)	2.11	8	0.98
Maternal side effects										
Any	12	494	1.50 (1.16 to 1.94)*	27.51	11	0.004*	0.12 (0.05 to 0.19)*	51.38	11	<0.0001*
Headache	11	528	1.61 (1.06 to 2.38)*	14.34	10	0.16	0.07 (0.01 to 0.13)*	29.15	10	0.001*
Visual symptoms	1	44	9.09 (0.51 to 100)	0	0	NA	0.18 (0.00 to 0.36)	0	0	NA
Nausea or vomiting	6	210	2.22 (0.94 to 5.26)	4.17	4	0.38	0.08 (0.00 to 0.16)	12.61	5	0.03*
Epigastric pain	1	44	0.67 (0.12 to 3.57)	0	0	NA	–0.05 (–0.23 to 0.14)	0	0	NA
Flushing	3	119	0.31 (0.12 to 0.79)*	8.08	2	0.02*	–0.20 (–0.32 to –0.08)*	30.42	2	<0.0001*
Palpitations	5	132	3.57 (1.72 to 7.69)*	3.11	4	0.54	0.28 (0.15 to 0.41)*	15.06	4	0.005*
Tachycardia >110 beats/min	5	305	5.56 (2.38 to 12.5)*	4.42	4	0.35	0.18 (0.11 to 0.25)*	11.96	4	0.02*
Dizziness	5	153	1.82 (0.53 to 6.25)	3.35	3	0.34	0.04 (–0.04 to 0.12)	5.72	4	0.22
Bronchospasm	1	12	0.33 (0.17 to 6.67)	0	0	NA	–0.17 (–0.59 to 0.25)	0	0	NA
Drugs changed because of side effects	7	328	2.44 (0.38 to 14.28)	0.03	1	0.86	0.01 (–0.02 to 0.05)	1.65	6	0.95
Effects on fetus										
Adverse effects on fetal heart rate	12	601	2.04 (1.32 to 3.16)*	13.60	8	0.09	0.07 (0.03 to 0.12)*	45.97	12	<0.0001*
Perinatal outcomes										
Perinatal death	17	744	1.43 (0.77 to 2.63)	4.21	12	0.98	0.02 (–0.02 to 0.05)	7.25	16	0.97
Stillbirth	17	744	2.00 (0.85 to 4.76)	0.66	5	0.99	0.02 (–0.01 to 0.05)	4.61	16	1.00
Neonatal death	17	729	1.00 (0.43 to 2.38)	3.74	8	0.88	0.00 (–0.03 to 0.03)	5.47	16	0.99
1-minute Apgar <7	3	52	2.70 (1.27 to 5.88)*	4.03	2	0.13	0.36 (0.13 to 0.59)*	4.48	2	0.11
5-minute Apgar <7	6	271	1.23 (0.69 to 2.22)	3.74	5	0.59	0.03 (–0.05 to 0.11)	5.85	5	0.32
Admission to neonatal intensive care unit	1	98	1.18 (0.59 to 2.38)	0	0	NA	0.04 (–0.13 to 0.21)	0	0	NA
Neonatal bradycardia	3	50	0.16 (0.02 to 1.11)	0.01	1	0.91	–0.24 (–0.42 to –0.06)*	15.43	2	0.0004*
Neonatal hypotension	1	19	5.88 (0.28 to 100)	0	0	NA	0.17 (–0.20 to 0.53)	0	0	NA
Neonatal hypothermia	1	25	Not estimable				0.00 (–0.16 to 0.16)	0	0	NA
Neonatal hypoglycaemia	3	64	0.88 (0.14 to 5.26)	0.84	(1)	0.36	–0.01 (–0.13 to 0.10)	0.94	2	0.63
Respiratory distress syndrome	6	250	1.56 (0.78 to 3.13)	2.68	(5)	0.75	0.05 (–0.03 to 0.12)	3.72	5	0.59
Intraventricular haemorrhage	2	72	4.17 (0.47 to 33.33)	0.11	(1)	0.74	0.07 (–0.05 to 0.18)	0.75	1	0.39
Necrotising enterocolitis	1	53	2.86 (0.12 to 100)	0	(0)	NA	0.04 (–0.06 to 0.14)	0	0	NA

NA=not applicable; HELLP=haemolysis to elevated liver enzymes to low platelets
*Significant at the P<0.05 level, and discussed in the text.

analysis.[14] Table 1 shows selected characteristics of included trials. About half (12/21 trials) enrolled mixed populations of women with pregnancy hypertension; hypertension was usually severe (16/21 trials). In two trials, single doses were given,[27 39] and in three trials patients were switched to oral antihypertensives when blood pressure had been stabilised.[28 43 46] Most commonly, hydralazine was compared with standard doses of other antihypertensives: nifedipine (eight trials); labetalol (five trials); ketanserin (four trials); urapidil (two trials); epoprostenol (one trial); or isradipine (one trial with three publications).

Most trials were small, with a median of 37 women enrolled (range 6-200). Half (11/21) described adequate methods of randomisation, but seven publications did not describe the method at all. Assessment of outcome was blinded in four trials, and for some outcomes in one other trial. The quality of the methods had no discernible impact on outcome.

Table 2 presents the maternal and perinatal outcomes in trials that compared hydralazine with other antihypertensives. If the results of the trial that compared hydralazine and epoprostenol are excluded,[32] the results of outcomes to which this trial

contributed (persistent severe hypertension, caesarean section, maternal side effects, perinatal mortality, and respiratory distress syndrome) are not changed.

Maternal outcomes

Persistent severe hypertension was variably defined as diastolic blood pressure ≥90 mm Hg,[33] ≥95 mm Hg,[29–31] ≥100 mm Hg,[41 42 44 47–49] or ≥110 mm Hg[25 26 28 43]; mean arterial blood pressure ≥120 mm Hg[45]; and failure to achieve a drop in systolic/diastolic blood pressure of 30/15 mm Hg.[32] Hydralazine did not differ from other antihypertensives in impact on persistent severe hypertension or on use of additional antihypertensives (table 2). However, the results differed by more than could be expected by chance alone, with the heterogeneity explained largely by the type of the other antihypertensive. Hydralazine was associated with a trend towards lower rates of persistent severe hypertension (median event rate 0% (range 0-20%) *v* labetalol (5% (0-60%)); relative risk 0.29 (0.08 to 1.04); two trials; $\chi^2=0.08$, df=1, P=0.78; risk difference −0.11 (−0.21 to −0.02); four trials; $\chi^2=6.91$, df=3, P=0.08; fig 1) and was not associated with use of additional antihypertensives (5% (0-10)% for hydralazine *v* 5% (0-10)% for labetalol; relative risk 1.00 (0.07 to 13.87); one trial; $\chi^2=0$, df=0; risk difference 0 (−0.12 to 0.12); two trials; $\chi^2=0$, df=1, P=1.00). Hydralazine was associated with a trend towards more persistent severe hypertension (29% (0-32%) compared with nifedipine or isradipine (5% (0-40%); relative risk 1.41 (0.95 to 2.09); four trials; $\chi^2=11.69$, df=3, P=0.009; risk difference 0.08 (−0.01 to 0.16); five trials; $\chi^2=12.36$, df=4, P=0.02; fig 1) and with use of additional antihypertensives (13% (0-32%) for hydralazine *v* (5% (0-24%)) nifedipine only; relative risk 2.13 (1.20 to 3.85); four trials; $\chi^2=5.24$, df=3, P=0.15; risk difference 0.08 (0.02 to 0.14); five trials; $\chi^2=12.32$, df=4, P=0.02), but there was still significant heterogeneity between trials within this subgroup. In the three trials with nifedipine or isradipine in which hydralazine was associated with more severe hypertension, the methods of allocation concealment were either clearly inadequate[28 43] or unstated,[29–31] but other characteristics of the trials did not differ.

In comparison with ketanserin, hydralazine was not associated with a consistent effect on maternal blood pressure (fig 1); this effect was partially explained by the doses of hydralazine used. A low dose hydralazine infusion (1 mg/h intravenously, increased by 1 mg/h every hour to a maximum of 10 mg/h) was associated with a trend towards more persistent severe hypertension than ketanserin (5 mg intravenous bolus, then 4 mg/h intravenously).[25 26] Higher dose bolus hydralazine (5 mg intravenously every 20 min) was associated with less persistent severe hypertension than ketanserin (10 mg intravenously every 20 min).[33]

Hydralazine was associated with more maternal hypotension than other antihypertensives (0% (0-67%) *v* 0% (0-17%); table 2, fig 2). Calculations of risk difference showed significant heterogeneity between trials, which was largely absent when subgroups of other antihypertensive agents were examined: hydralazine *v* labetalol (risk difference 0.10 (0 to 0.20); four trials; $\chi^2=6.46$, df=3, P=0.09); hydralazine *v* nifedipine or isradipine (0.01 (−0.01 to 0.04); six trials; $\chi^2=6.58$, df=5, P=0.25); hydralazine *v* urapidil (0.16 (−0.11 to 0.42); one trial); and hydralazine *v* ketanserin (0.18 (−0.04 to 0.39); two trials; $\chi^2=0.51$, df=1, P=0.47). In the hydralazine *v* labetalol subgroup in which there was still heterogeneity, the incidence of maternal hypotension with hydralazine ranged from 0% (in 10 patients) to 67% (in 4 of 6 patients); the rate of 67% occurred in the very small trial by Garden et al,[44] in which hydralazine was given in higher dosage (initially 10 mg/h, by intravenous infusion) than in other trials.

Several maternal outcomes occurred more often with hydralazine than with other antihypertensives: caesarean section (67% (8-100%) *v* 59% (5-100%) for other antihypertensives); placental abruption (18% (3-20%) *v* 0% (0-2%)); and maternal oliguria (17% (4-41%) *v* 0% (0-9%)) (table 2); however, the risk difference analysis showed heterogeneity between trials. Groups did not differ in other measures of maternal morbidity—eclampsia, intracerebral haemorrhage, HELLP syndrome, pulmonary oedema, disseminated intravascular coagulation, or mortality. However, the two trials that reported HELLP syndrome as an outcome differed by more than could be expected by

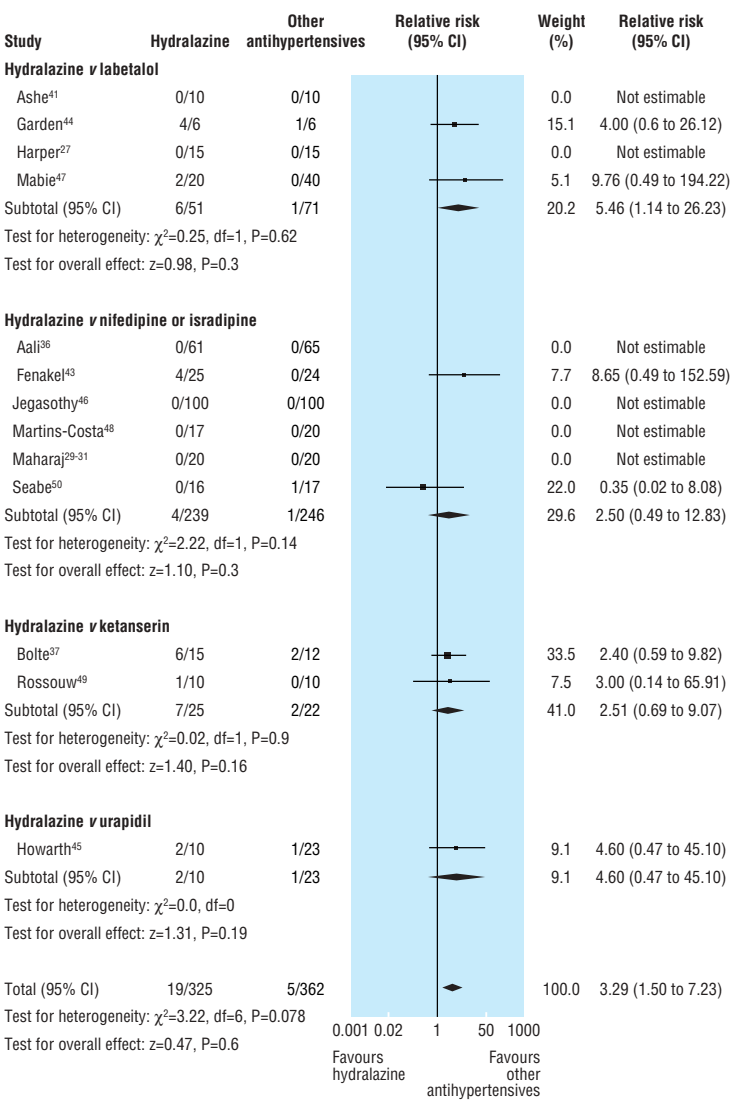

Fig 2 Maternal hypotension in trials that compared hydralazine with other antihypertensives

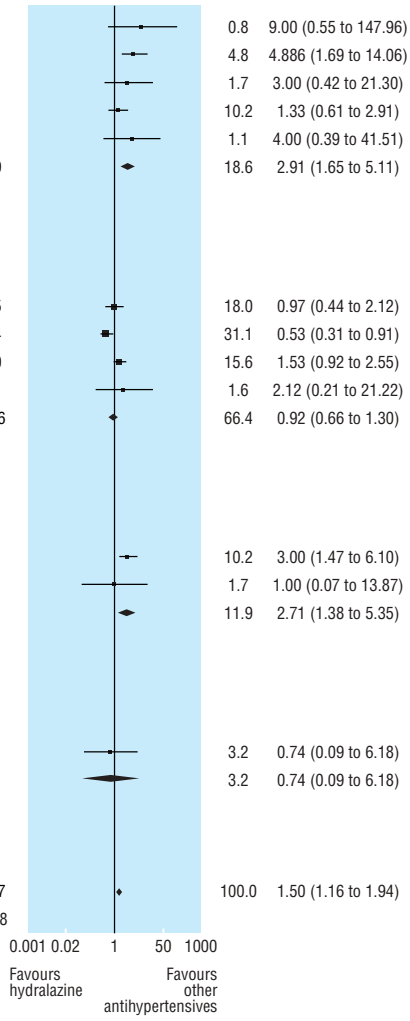

Fig 3 Any maternal side effect reported in trials that compared hydralazine with other antihypertensives

chance alone[25 26 28]: comparing hydralazine with nifedipine, Kwawukume and Ghosh reported no raised liver enzymes,[28] but in a comparison of hydralazine and ketanserin Bolte et al reported a significantly higher incidence (45% *v* 9%) of HELLP syndrome (using Sibai's definition in the hydralazine group[51]).[25 26]

In summary, hydralazine was associated with more persistent severe hypertension than nifedipine or isradipine, and more of the following outcomes when compared with all antihypertensives: maternal hypotension, placental abruption, caesarean section, and maternal oliguria. However, absolute event rates ranged widely within trials, and outcomes showed significant heterogeneity when risk difference was used as the summary statistic.

Maternal side effects

Hydralazine was associated with more maternal side effects (of any sort) and headache than other antihypertensives (40% (10-82%) *v* 17% (0-75%) and 29% (0-67%) *v* 0% (0-20%), respectively; table 2). For any maternal side effects, the significant heterogeneity between trials was confined to the nifedipine subgroup (fig 3). In particular, the trial by Fenakel et al found that hydralazine was associated with fewer side effects than nifedipine.[43] The dose of hydralazine was higher than in the other three trials, and the dose of nifedipine was the same. However, the duration of treatment was longer than in other trials (days to weeks, rather than hours to days) because women were changed to oral antihypertensive therapy.

Hydralazine was associated with more palpitations than other antihypertensives (18% (11-81%) *v* 0% (0-17%); table 2). Three of the five trials compared hydralazine with labetalol, and within this subgroup the effect was significant (relative risk 5.26 (2.00 to 14.28); three trials; $\chi^2=0.29$, df=2, P=0.87; risk difference 0.48 (0.30 to 0.67); three trials; $\chi^2=4.79$, df=2, P=0.09).

Hydralazine was also associated with more maternal tachycardia than other antihypertensives (24% (10-67%) *v* 0% (0-6%); table 2). Three of the five trials were comparisons of hydralazine against nifedipine, and within this subgroup the results were significant (relative risk 5.56 (2.17 to 14.29); three trials; $\chi^2=4.10$, df=2, P=0.13; risk difference 0.18 (0.11 to 0.25); three trials; $\chi^2=11.96$, df=4, P=0.02).

Hydralazine was associated with less flushing than nifedipine (0-12.5% *v* 0-58%; only comparisons with nifedipine reported flushing); however, there was heterogeneity between trials. More flushing was reported in the trial by Fenakel et al, which treated women for longer than other trials.[43] Groups did not differ in visual symptoms, nausea or vomiting, epigastric pain, dizziness, or bronchospasm (table 2).

Despite the high prevalence of side effects (in 85 of 227 patients given hydralazine and 61 of 257 patients given other antihypertensives), few women changed drugs because they experienced side effects (3 of 161 changing from hydralazine, 1 of 167 changing from other antihypertensives); the proportion did not differ between groups.

In summary, hydralazine was associated with more maternal side effects than labetalol or ketanserin, and more headache, palpitations, and maternal tachycardia than other antihypertensives. Whether hydralazine was associated with more side effects than nifedipine was unclear. For all outcomes, absolute event rates ranged widely within trials and significant heterogeneity was seen when risk difference was used as the summary statistic.

Adverse effects on fetal heart rate

Adverse effects on fetal heart rate were defined as "acute fetal distress"[39 43 45 49]; need for caesarean section due to fetal distress[28] or a decelerative fetal heart rate pattern[33]; "deterioration in the cardiotocographic tracings"[48]; abnormal fetal heart rate patterns in the six hours after treatment[34 35]; "abnormal" fetal heart rate in labour[47]; fetal heart rate decelerations[29–31]; late decelerations during continuous fetal heart rate monitoring[41]; or "CTG abnormalities."[36] Hydralazine was associated with more adverse effects on fetal heart rate than other antihypertensives (11% (0-56%) *v* 0% (0-50%)), with the significant heterogeneity isolated to the hydralazine *v* labetalol subgroup (fig 4). The doses of hydralazine and labetalol were lower in the trial of Ashe et al (hydralazine 3.7 mg/h given intravenously *v* labetalol 20 mg/h given intravenously with increases every 30

min)[41] and higher in the trial of Mabie et al (hydralazine 5 mg given intravenously every 10 min *v* labetalol 20 mg given intravenously, then 30 mg given intravenously every 10 min)[47]; otherwise, the differences remained unexplained, although both trials were small and the 95% confidence intervals overlapped substantially.

Perinatal outcomes

Hydralazine was associated with more low Apgar scores at one minute than other antihypertensives (67% (38-83%) *v* 15% (14-67%); table 2), but the incidence of low Apgar scores at five minutes did not differ between groups. Hydralazine was associated with less neonatal bradycardia than labetalol (0% (0-0%) *v* 21% (0-100%)), but the results differed more than could be expected by chance alone, as we reported earlier.[14] Few trials reported other perinatal outcomes, and these outcomes (perinatal mortality; admission to neonatal intensive care unit; neonatal hypotension, hypothermia or hypoglycaemia; or complications of prematurity: respiratory distress syndrome, intraventricular haemorrhage or necrotising enterocolitis) did not differ between groups. However, figure 5 shows a statistical trend towards more stillbirths with hydralazine than with other antihypertensives (0% (0% to 31%) *v* 0% (0% to 22%)).

In summary, hydralazine was associated with more low Apgar scores at one minute and a trend towards an increase in stillbirth compared with other antihypertensives. Hydralazine was associated with less neonatal bradycardia than labetalol.

Discussion

This meta-analysis of randomised controlled trials for the treatment of severe hypertension in pregnancy shows that hydralazine was associated with some poorer maternal and perinatal outcomes than other antihypertensives, particularly labetalol and nifedipine. Hydralazine was found to be a less effective antihypertensive than nifedipine or isradipine, and did not clearly differ from labetalol. In comparison with all other antihypertensives, hydralazine was associated with more of several adverse outcomes: maternal hypotension, placental abruption, adverse effects on fetal heart rate, caesarean section, maternal oliguria, stillbirth (statistical trend only), and low Apgar score at one minute. Hydralazine was associated with less neonatal bradycardia than labetalol, but no trials since our previous meta-analysis reported this outcome.

Hydralazine was more poorly tolerated than other antihypertensives. More maternal side effects were seen than with labetalol or ketanserin. More headaches (raising the issue of imminent eclampsia), palpitations, and maternal tachycardia were seen than with other antihypertensives, with the exception of nifedipine; in trials that showed these side effects, outcomes differed more than could be expected by chance alone, possibly because of differences in design of the trials.

Use of summary statistics

How the consistency of the results differed according to the summary statistic used is worth comment. We used relative risk as the primary summary statistic for this meta-analysis and used risk difference in a secondary analysis. All outcomes for which relative risk was significantly increased, without heterogeneity, showed significant heterogeneity in the analysis that used risk difference, with the exception of low Apgar scores at one minute. Risk difference is sensitive to heterogeneity between trials, and the results of the risk difference analyses highlight the great variability in event rate between trials, which was due, at least in part, to the small sample sizes. The variability in event rates precludes us from extrapolating the results to a specific patient population.

Alternatives to hydralazine

These results are biologically plausible. Rapid or excessive falls in maternal blood pressure may decrease placental perfusion (reflected by abnormal fetal heart rate patterns) and lead to placental abruption, caesarean section, and low Apgar scores at one minute (with recovery by five minutes with resuscitation). The

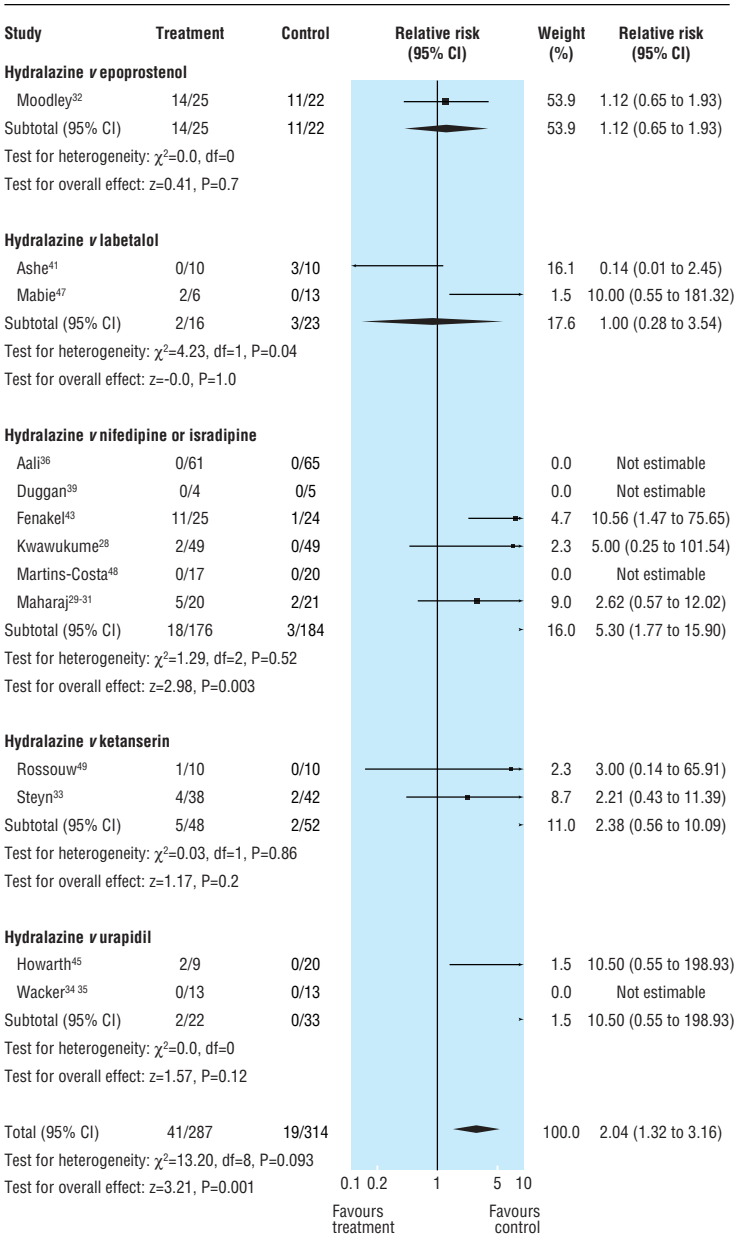

Fig 4 Adverse effects on fetal heart rate (FHR) in trials that compared hydralazine with other antihypertensives

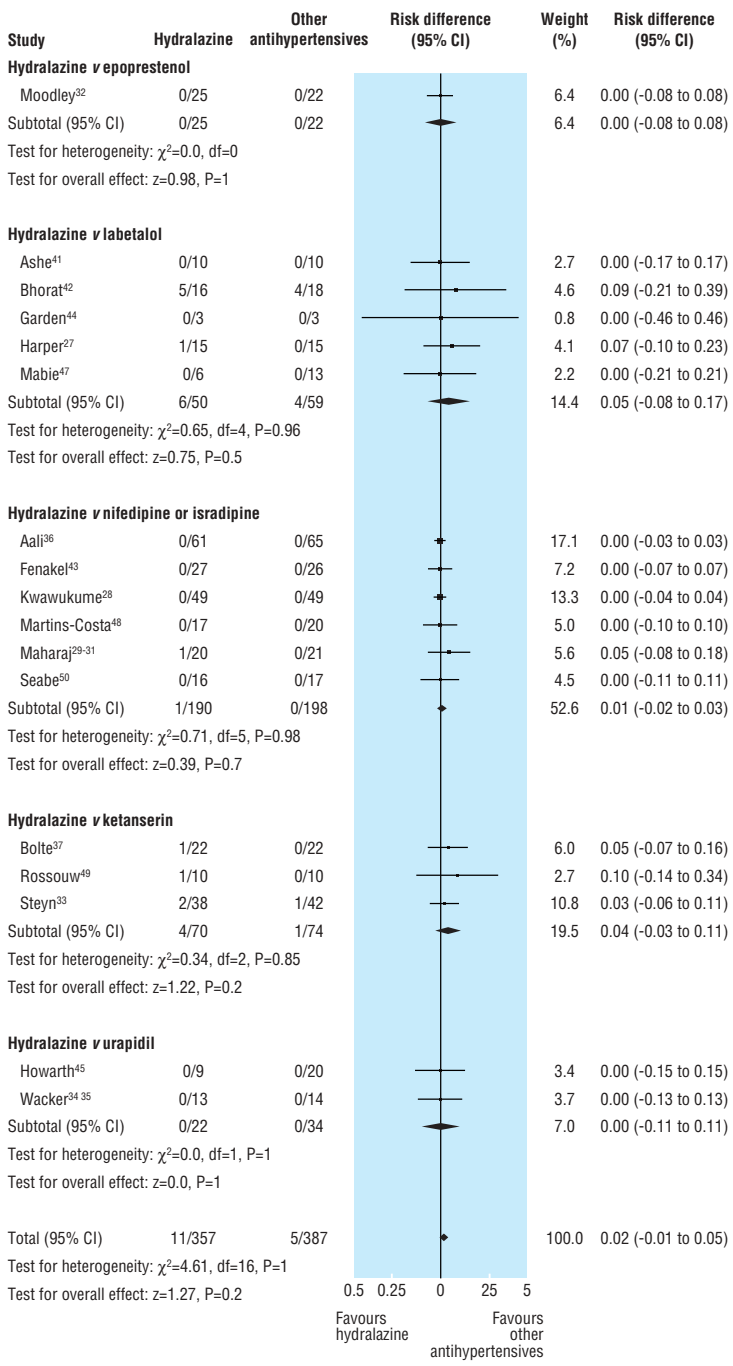

Fig 5 Stillbirth in trials that compared hydralazine with other antihypertensives

unpredictability of the timing and magnitude of the blood pressure lowering effect of hydralazine may make its use in pregnancy problematic. The results of this meta-analysis do not support recent recommendations favouring initial use of hydralazine over other antihypertensives (including ketanserin).[7]

Nifedipine seems to be a reasonable alternative to hydralazine. In two case reports, profound muscle weakness and respiratory arrest were associated with concomitant use of nifedipine and magnesium sulphate.[18 19] However, no neuromuscular blockade was described in any of the trials comparing hydralazine with nifedipine or isradipine, even though magnesium sulphate was given to all[43] or some[28] women, and no such blockade was reported in the Magpie trial, in which 29% of women allocated to receive magnesium sulphate also received nifedipine.[52] Any risk of neuromuscular blockade is thus likely to be low, and the effect is reversible with calcium gluconate.

Parenteral labetalol also seems to be a reasonable alternative to hydralazine. Although it may be less effective in preventing recurrent severe hypertension, labetalol controlled severe hypertension in 87% of women and was similar to other antihypertensive agents in the need to prescribe further antihypertensives. No new trials were available to update the previously observed association between parenteral labetalol and (usually transient) neonatal bradycardia[14]; neonatologists should continue to be made aware when intravenous labetalol has been used during labour and delivery.

Ketanserin, an agent investigated most widely in the Netherlands and South Africa, compared favourably with hydralazine.

Of course, there are other limitations to this review that have not been discussed. Meta-analysis is based on a retrospective and observational study design, which relies on published data. However, trials provide the least biased form of information about therapeutic interventions and outcome, and the results of this meta-analysis are biologically plausible.

The most recent Cochrane review found no good evidence that one short acting antihypertensive is better than another, with the exception of ketanserin, which is associated with more persistent hypertension.[53] The Cochrane inclusion and exclusion criteria differed somewhat from those in this study, but the most important difference seems to be in the reviews' methods. In the absence of significant between-trial heterogeneity in outcome, we pooled the results from all trials comparing hydralazine and other antihypertensives, whereas the Cochrane review had five subgroups of trials comparing hydralazine and other antihypertensives, with different outcomes reported in each group. In our review, pooling had the advantage of not being based on the assumption that different antihypertensives would cause differences in maternal or perinatal outcome, and where differences between trials existed, pooling informed the reader about how differences in design of the studies and in the intervention may have influenced the results. Pooling resulted in greater statistical power where significant heterogeneity between trials did not exist, and allowed overall conclusions to be drawn from the data.

Conclusions

The results of this review should generate uncertainty about the agent of first choice for treating severe hypertension in pregnancy. Definitive data from adequately powered clinical trials are needed, with the most promising comparison being that of nifedipine with labetalol (or perhaps ketanserin if it is available locally). Such trials should include caesarean section for fetal distress as an outcome. One trial has compared nifedipine with labetalol, but only 50 women were enrolled and caesarean section was not reported.[54] The results of this review support the use of antihypertensive agents other than hydralazine for the

What is already known on this topic

Hydralazine has been the recommended treatment for severe hypertension in pregnancy, but its side effects mimic symptoms of deteriorating pre-eclampsia

What this study adds

The results of this meta-analysis do not support the use of hydralazine as first line treatment for severe hypertension in pregnancy

Adequately powered clinical trials, starting with a comparison of labetalol and nifedipine, are needed

acute management of severe hypertension in pregnancy.

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