Hydralazine for treatment of severe hypertension in pregnancy: meta-analysis
Magee L A, Cham C, Waterman E J, Ohlsson A, von Dadelszen P

CRD summary
This review compared the effects of hydralazine with other antihypertensives for the treatment of severe hypertension in pregnancy. The authors concluded that the findings are not robust enough to guide clinical practice, though they do not support the use of hydralazine. The conclusions follow from the evidence presented, although there were some weaknesses in the conduct of the review.

Authors’ objectives
To evaluate the effects of hydralazine in comparison with other antihypertensives for the treatment of severe hypertension in pregnancy.

Searching
MEDLINE was searched for articles published in any language from 1966 to September 2002; the search terms were reported. The journal Hypertension in Pregnancy was handsearched, as were conference proceedings, textbooks and bibliographies. Abstracts were included.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Trials comparing hydralazine with another short-acting antihypertensive (generally via parenteral administration) were eligible for inclusion. The included studies used the following comparators: nifedipine, labetalol, ketanserin, urapidil, epoprostenol and isradipine.

Participants included in the review
Pregnant women with moderate to severe hypertension, regardless of type, were eligible for inclusion. The mean diastolic blood pressure at enrolment was used to define the severity of hypertension: mild (90 to 99 mmHg), moderate (100 to 109 mmHg), or severe (110 mmHg or greater). In the majority of the included studies the women had severe hypertension. Over half of the trials included women with different types of hypertension (pre-existing hypertension and gestational hypertension with or without proteinuria). In the other included studies women were classified as having pre-eclampsia (pregnancy-induced hypertension with proteinuria) or pregnancy-induced hypertension (when women with and without proteinuria were enrolled).

Outcomes assessed in the review
Clinical outcomes relating to maternal, perinatal or paediatric benefit or risk were assessed. There were 12 maternal outcomes including persistent severe hypertension and hypotension; 11 maternal side-effects including any side-effect, headache, and nausea or vomiting; and 13 perinatal outcomes including death, stillbirth and Apgar score. Adverse effects on foetal heart rate were also assessed. The definition of persistent severe hypertension varied between the studies.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The studies were assessed for methods of randomisation and blinded assessment of the outcome. The authors did not state how the papers were assessed for validity, or how many reviewers performed the validity assessment.
Data extraction
Two reviewers independently extracted the data, with any disagreements resolved by discussion. In relation to maternal haemodynamic outcomes and stillbirth, data from studies of single drugs (monotherapy) alone were used. Neonatal outcomes were assessed if the antihypertensive could be expected to be in the maternal-foetal bloodstream at delivery. The relative risk (RR), with 95% confidence interval (CI), and the risk difference were calculated for each trial. Where necessary, authors were contacted for missing information or clarification.

Methods of synthesis
How were the studies combined?
The studies were combined in a fixed-effect meta-analysis comparing hydralazine with all other antihypertensives. The primary summary statistic was the RR; the risk difference was used as a secondary measure.

How were differences between studies investigated?
The studies were stratified according to the comparator used and each of the groups was then pooled in a meta-analysis. In addition to the stratified analysis, a chi-squared test was used to investigate statistical heterogeneity between the studies (a P-value of less than 0.10 was considered statistically significant).

Results of the review
Twenty-one RCTs (n=893) were included.

Half of the studies described adequate randomisation methods and in four the outcome assessment was blinded. The majority of the trials were small: a median of 37 women were enrolled (range: 6 to 200).

Maternal outcomes.
There was no difference in the impact on persistent severe hypertension between hydralazine and all other antihypertensives combined (RR 1.08, 95% CI: 0.78, 1.49; 14 trials). Statistically significant heterogeneity was found. When a subgroup analysis was performed, there was a higher rate of persistent severe hypertension with hydralazine than with nifedipine or isradipine and a trend towards a lower rate of persistent severe hypertension with hydralazine than with labetalol. Again, there was statistically significant heterogeneity.

Hydralazine was associated with higher rates of maternal hypotension than the other antihypertensives (RR 3.29, 95% CI: 1.50, 7.23; 13 trials). There was statistically significant heterogeneity. There was also a statistically significant higher risk of Caesarean section, placental abruption and oliguria with hydralazine than with the other antihypertensives.

Maternal side-effects.
When compared with all the other antihypertensives, there were more maternal side-effects of any kind with hydralazine (RR 1.50, 95% CI: 1.16, 1.94; 12 trials). There was statistically significant heterogeneity. When a subgroup analysis was performed, there were more headaches, palpitations and maternal tachycardia with hydralazine than with labetalol or ketanserin.

Foetal heart rate.
There were more adverse effects on foetal heart rate with hydralazine than with the other antihypertensives (RR 2.04, 95% CI: 1.32, 3.16; 12 trials). There was statistically significant heterogeneity.

Perinatal outcomes.
There were more low Apgar scores at one minute with hydralazine than with the other antihypertensives (RR 2.70, 95% CI: 1.27, 5.88; 3 trials). There was a trend towards an increase in stillbirths with hydralazine. When a subgroup analysis was performed, hydralazine was associated with less bradycardia than labetalol.
The authors noted that all outcomes for which the RR was increased without statistically significant heterogeneity showed heterogeneity when the analysis was repeated using the risk difference.

**Authors’ conclusions**
The results were not robust enough to guide clinical practice, but they should generate uncertainty about the use of hydralazine as first-line treatment for severe hypertension in pregnancy.

**CRD commentary**
The review addressed a clear research question using defined inclusion criteria. Although there were no language restrictions, the sources of literature searched were fairly limited and, therefore, studies might have been missed. The data extraction was carried out in duplicate, which helps minimise error and bias, though it was unclear whether similar strategies were used for the study selection and quality assessment processes. The quality assessment only addressed two aspects of quality; important criteria such as concealment of allocation and loss to follow-up were not assessed. Adequate details of the individual studies were provided. Appropriate measures of effect were calculated and the authors assessed statistical heterogeneity. The conclusions appear to follow from the evidence presented.

**Implications of the review for practice and research**
Practice: The authors stated that the results are not robust enough to guide clinical practice, but they should generate uncertainty about the use of hydralazine as first-line treatment for severe hypertension in pregnancy.

Research: The authors stated that adequately powered clinical trials are required to provide definitive data, with the most promising comparison being between nifedipine and labetalol or possibly ketanserin. The outcomes assessed should include Caesarean section for foetal distress.

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