Nifedipine versus ritodrine for suppression of preterm labor: a meta-analysis
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Authors' objectives
To assess the effectiveness of nifedipine and ritodrine in the suppression of pre-term labour.

Searching
MEDLINE was searched from January 1966 to November 1998, and EMBASE from January 1980 to November 1998, using the following keywords: 'nifedipine', 'ritodrine' and 'randomised'. Cross-references of selected studies were checked. A formal assessment of publication bias was not possible due to small sample sizes.

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

Specific interventions included in the review
Direct comparisons of ritodrine and nifedipine were eligible. Ritodrine doses (where stated) ranged from an infusion of 50 microg/minute to 1 mg/minute with increments every 10 to 20 minutes until a maximum dose (ranging from 300 to 350 microg/minute were reported) was reached, contractions ceased, or no limit was specified.

Nifedipine doses (where stated) ranged from 10 to 30 mg sublingual, followed by varying regimes with maximum doses ranging from 80 to 160 mg. None of the studies that included women with ruptured membranes reported on the use of antibiotics. The use of corticosteroids was explicitly mentioned in some studies. Other cointerventions included: intravenous morphine, intravenous magnesium sulphate, terbutaline following ritodrine infusion, and indomethacin.

Participants included in the review
Pregnant women in pre-term labour were eligible, with pre-term defined as labour before 37 weeks of gestation. Both single and twin pregnancies were included. Some studies were limited to women with intact membranes, whilst others also included women with ruptured membranes or provided no details of the intactness of membranes. Gestational age ranged from 20 to 36 weeks.

Outcomes assessed in the review
The inclusion criteria were not defined in terms of outcome. Outcomes assessed included: delay in delivery for at least 48 hours; capacity to postpone delivery to at least 36 weeks gestation; perinatal mortality; respiratory distress syndrome (RDS); admission to neonatal intensive care unit (NICU); and maternal side-effects.

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

Assessment of study quality
Validity was assessed using method of randomisation, blinding, power analysis, and use of intention to treat analysis (ITT). The authors do not state how the papers were assessed for validity, or how many of the reviewers performed the validity assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. For each study, inclusion and exclusion criteria, validity criteria, the use of additional drugs (including betamethasone) and outcome data were documented. Additional information presented in tables included the following:
author, year of publication, pregnancy details, gestational age, and intervention details.

**Methods of synthesis**
How were the studies combined?
If homogeneity could not be rejected, a pooled odds ratio (OR) and 95% confidence interval (CI) was calculated for each of the outcomes using the Mantel-Haenszel method (see Other Publications of Related Interest). Risk difference and 95% CI were also calculated.

How were differences between studies investigated?
Statistical heterogeneity was assessed for each of the outcomes using the Breslow-Day test with p values less than 0.05 considered to indicate statistical significance (see Other Publications of Related Interest).

**Results of the review**
Ten RCTs were included (680 women).

Different methods of allocation were used including sealed envelopes (5 RCTs), computer-generated lists (2 RCTs) and unspecified (3 RCTs). Six studies used an ITT analysis. None of the studies were blinded.

Nifedipine versus ritodrine.

1. Delivery within 48 hours (7 RCTs).
   Homogeneity could not be rejected (p=0.22). Nifedipine reduced the risk of delivery within 48 hours, although not significantly (OR 0.85, 95% CI: 0.69, 1.0). Risk difference was -2.7% (95% CI: -12, 6).

2. Postponement of delivery to at least 36 weeks gestation (7 RCTs). Homogeneity could not be rejected (p=0.86). Nifedipine significantly reduced the risk of delivery before 36 weeks (OR 0.72, 95% CI: 0.55, 0.91). Risk difference was -11% (95% CI: -20, -1.5). There appears to be a misprint for the lower 95% CI (could be - rather than B as printed).

3. Perinatal mortality (6 RCTs).
   Homogeneity could not be rejected (p=0.19). There was no significant difference between nifedipine and ritodrine (OR 1.2, 95% CI: 0.69, 2.1). Risk difference was 0.7% (95% CI: -2.8, 4.3).

4. RDS (3 RCTs).
   Homogeneity could not be rejected (p=0.09). Nifedipine significantly reduced the risk of RDS (OR 0.72, 95% CI: 0.54, 0.96). Risk difference was -10% (95% CI: -20, -0.2).

5. Admission to NICU (2 RCTs).
   Homogeneity could not be rejected (p=0.42). Nifedipine significantly reduced the risk of admission (OR 0.60, 95% CI: 0.42, 0.86).

   Meta-analysis was not possible due to inconsistencies in definitions of side-effects between studies. The percentage of patients experiencing side-effects whilst on nifedipine was 16% (23 out of 147), compared with 45% (73 out of 132) of women using ritodrine. There appears to be a misprint for the latter: based on the patient numbers provided, the proportion of patients experiencing side-effects whilst on ritodrine should be 55%.

**Authors' conclusions**
Compared to ritodrine, nifedipine significantly reduced the risk of delivery before 36 weeks, and also within 48 hours, although not significantly. Since studies on long-term outcome are lacking, the choice between nifedipine and ritodrine can only be based on obstetrical and short-term neonatal outcomes. From that perspective, nifedipine should be the drug of choice for the suppression of pre-term labour.

CRD commentary
The aims were stated, and inclusion criteria were defined in terms of study design, participants and intervention. Two relevant databases were searched and keywords used were given. It was not reported whether any language restrictions were applied and no attempt was made to locate unpublished material, raising the possibility of publication bias. Methods used to select studies were not described. Validity was assessed using defined criteria and results of this assessment were presented, but methods used to assess validity were not described. Relevant information on the primary studies was presented in tabular format but no details were given about methods used to extract data. Statistical heterogeneity was assessed prior to meta-analysis, and homogeneity was demonstrated using forest plots (though some studies had very wide CI for ORs, particularly for perinatal mortality and RDS which may have concealed heterogeneity).

The evidence supports the authors' conclusions.

Implications of the review for practice and research
Practice: The authors state that from the perspective of obstetrical and short-term neonatal outcomes, nifedipine should be the drug of choice for the suppression of pre-term labour.

Research: The authors mention the lack of studies that examined long-term outcomes. They also state that placebo-controlled trials of nifedipine are probably not required.

Bibliographic details

PubMedID
10535341

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Female; Humans; Infant Mortality; Infant, Newborn; Nifedipine /adverse effects /therapeutic use; Obstetric Labor, Premature /complications /prevention & control; Odds Ratio; Pregnancy; Randomized Controlled Trials as Topic; Respiratory Distress Syndrome, Newborn /complications /epidemiology; Risk Assessment; Ritodrine /adverse effects /therapeutic use; Tocolytic Agents /adverse effects /therapeutic use; Treatment Outcome

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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.