Nifedipine in the management of preterm labor: a systematic review and metaanalysis
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CRD summary
The review concluded that nifedipine appeared to be a more effective tocolytic agent than beta_2-adrenergic-receptor agonists and better tolerated compared with beta_2-adrenergic-receptor agonists and magnesium sulfate in women with preterm labor. The review was generally well conducted, but the authors’ conclusions regarding magnesium sulphate may be too strong given the small number of trials included in the analyses.

Authors' objectives
To determine the efficacy and safety of nifedipine as a tocolytic agent in women with preterm labour.

Searching
MEDLINE, EMBASE, LILACS, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL, five registers of ongoing trials and Google Scholar were searched to 31 December 2010. There were no language restrictions. Search terms were reported. Proceedings from the Society for Maternal-Fetal Medicine and international meetings on preterm birth and tocolysis, published systematic reviews, reviews and textbooks were searched. Reference lists of identified studies were searched.

Study selection
Randomised controlled trials of nifedipine versus other tocolytic agents, placebo or no treatment for tocolysis in women with preterm labour were eligible for inclusion. Both acute and maintenance tocolysis were included. Trials were excluded if they only studied different doses of nifedipine or other calcium channel blockers and where nifedipine was given in addition to another tocolytic drug or after failure of a tocolytic drug.

The included acute tocolysis trials studied nifedipine versus beta_2-adrenergic-receptor agonists, magnesium sulphate, atosiban or nitric oxide. Trials for maintenance tocolysis studied nifedipine versus no treatment or placebo. Drug doses and administration routes varied across studies. Primary outcomes were delivery within 48 hours and seven days of treatment for acute tocolysis, delivery before 34 and 37 weeks gestation for maintenance tocolysis, perinatal death, neonatal intensive care unit stay, neurodevelopmental disability at two years of age and severe maternal adverse drug reactions. Various secondary outcomes were listed in the review. Gestational age at inclusion ranged from 20 to 36 weeks. Most trials reported administration of antenatal corticosteroids. Trials were mainly conducted in Asia, Europe and USA.

Two authors independently performed study selection. Disagreements were resolved by discussion.

Assessment of study quality
Trial quality was assessed using a modified Jadad scale of blinding, randomisation, allocation concealment and dropouts and withdrawals to give a score out of 8. Trials that scored 6 or more were considered high quality.

Two authors independently performed quality assessment. Disagreements were resolved by discussion.

Data extraction
Two reviewers independently used a standardised form to extract data on maternal and foetal outcomes. These data were used to calculate risk ratios (RR) or weighted mean differences (WMD), and 95% confidence intervals (CI). Intention-to-treat (ITT) data were used where available. Disagreements between reviewers were resolved by discussion. Trial authors were contacted.

Methods of synthesis
A fixed-effects meta-analysis was undertaken to obtain pooled risk ratios and weighted mean differences, together with 95% CIs. Statistical heterogeneity was assessed with $I^2$. A random-effects meta-analysis was used where $I^2$ was greater
than 50%. The number needed to treat (NNT) was calculated. Sensitivity analysis was undertaken based on trial quality. Publication bias was assessed using funnel plots and Egger’s test. Various stratified analyses based on clinical criteria were reported.

Results of the review
Twenty-six trials were included in the review (n=2,179 women): 23 trials of acute tocolysis and three trials of maintenance tocolysis. The quality of the included cohorts was variable: 13 trials scored 6 or more (high quality), five trials scored 4 or 5 and eight trials scored less than 3.

Acute tocolysis: For the primary outcomes, compared with beta₂-adrenergic-receptor agonists, nifedipine was associated with a statistically significant reduction in the risk of delivery within seven days of treatment (RR 0.82, 95% CI 0.70 to 0.97, NNT=12, I²=0%; 10 trials) and admission to neonatal intensive care unit (RR 0.77, 95% CI 0.62 to 0.93, NNT=12, I²=0%; nine trials). There was no difference in perinatal mortality, mental retardation at two years and risk of delivery within 48 hours of treatment. Secondary outcome results were presented in the review.

For the primary outcomes, compared with magnesium sulphate, nifedipine was associated with a significant reduction in severe maternal adverse events (RR 0.46, 95% CI 0.23 to 0.93; one trial) and admission to neonatal intensive care unit (RR 0.72, 95% CI 0.53 to 0.97; one trial). There was no significant difference in risk of delivery within 48 hours of treatment. Secondary outcome results were presented in the review.

Evidence for nifedipine versus atosiban (one trial) and for nitric oxide donors (one trial) did not show any statistically significant benefits on primary outcomes.

Maintenance tocolysis: Compared with placebo/no treatment, nifedipine did not have any statistically significant benefits on primary outcomes.

There was no evidence of publication bias in any of the analyses. Sensitivity analysis on the basis of quality did not alter the results substantially.

Authors’ conclusions
In women with preterm labour, nifedipine appeared to be a more effective tocolytic agent than beta₂-adrenergic-receptor agonists and a better tolerated tocolytic agent compared with beta₂-adrenergic-receptor agonists and magnesium sulphate.

CRD commentary
Inclusion criteria for the review were clearly defined. Several relevant data sources were searched without language restrictions. Publication bias was assessed and was not detected. Attempts were made to reduce reviewer error and bias throughout the review process. Quality assessment based on standard criteria indicated the variable quality of the included data, which the authors acknowledged. A fixed-effects meta-analysis was undertaken and statistical heterogeneity was assessed, which was appropriate.

This review was generally well conducted, but the authors’ conclusions regarding magnesium sulphate may be too strong given the small number of trials (in some cases only one) included in the analyses.

Implications of the review for practice and research
Practice: The authors stated that there was insufficient evidence to justify routine use of nifedipine as a long-term maintenance tocolytic agent after an episode of preterm labour had subsided.

Research: The authors stated that further adequately powered studies were needed to assess the optimal dose of nifedipine and its efficacy and safety in women with multiple gestations, preterm pre-labour rupture of membranes and very low gestational ages. Further studies were needed to assess its effectiveness as maintenance therapy after preterm labour has been arrested and the cost-effectiveness of this intervention. Long-term consequences of exposure of infants to this calcium channel blocker needed to be determined.
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