Use of isoxsuprine hydrochloride as a tocolytic agent in the treatment of preterm labour: a systematic review of previous literature

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CRD summary
This review concluded that there was preliminary evidence in favour of the effectiveness of isoxsuprine in prolonging pregnancy in women at risk of abortion or premature delivery. This was based on the synthesis of small, old studies of unclear quality. Given multiple concerns over the evidence base and the review methods, the authors’ conclusion cannot be regarded as reliable.

Authors' objectives
To assess the evidence for the use of isoxsuprine in women at risk of premature labour.

Searching
MEDLINE (from 1963) and EMBASE (from 1985) were searched without language restriction up to August 2009. The Cochrane Central Register of Controlled Trials (CENTRAL, reported as Issue 3, 2004) was also searched. Search terms were reported.

Study selection
Studies that reported on the use of isoxsuprine in women at risk of pre-term labour were eligible for inclusion. Outcomes assessed were abortion (delivery at less than 26 weeks gestation), premature delivery (delivery at between 26 and 38 weeks gestation) and term delivery (delivery at over 38 weeks gestation).

Included studies assessed the use of isoxsuprine as either acute (intravenous administration) or maintenance (oral or intramuscular administration) therapy or as a combination of the two. In the small number of controlled studies, a placebo comparator was used. The age of women in the included studies ranged from 16 to 42 years. Five studies included only women at risk of abortion. All the included studies were published between 1961 and 1981.

The authors did not state how the studies were selected for the review.

Assessment of study quality
Two reviewers independently assessed the studies for validity. It appeared that this was done according to guidelines in the Cochrane Handbook.

Data extraction
Outcome data were extracted and classified as positive or negative. Outcomes considered positive were those reported as "positive", "good" "term delivery", "pregnancy ongoing", "patient discharged", "at home", "at least eighth month" and delay of delivery by more than one week. Outcomes considered negative were those reported as "negative", "abortion", "premature delivery", "baby died" or a delay of delivery by up to one week. Durations of delays in delivery were also extracted.

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis
Fisher's exact test was used to compare data from the groups in the double-blind controlled studies and to compare positive versus negative outcomes across studies. One controlled study was excluded from analysis because the sample size was considered to be too small. Data on delay of pregnancy was analyzed by the Kruskal-Wallis test.

Results of the review
Twenty-five studies (n=2,107 women) were included in the review. Three were controlled studies; two of the controlled
studies were described as double blind. Eleven studies provided individual patient data (IPD) on 479 patients. Sample size ranged from 12 to 338.

The two double-blind studies found an overall positive effect of isoxsuprine in 92% of patients compared with 44.5% for placebo control (p<0.001). For women at risk of premature delivery, the figures were 94.7% for isoxsuprine compared with 41.2% for placebo (p<0.001). For those at risk of abortion, 92.5% of those treated with isoxsuprine showed a positive outcome, while 46.4% of those in the placebo groups did so (P<0.001).

The 11 studies providing IPD showed a beneficial effect of isoxsuprine in prolonging pregnancy in 54.5% of women at risk of abortion and in 82.3% of those at risk of premature delivery.

Analysis of all studies showed a beneficial effect of isoxsuprine in prolonging pregnancy in 77.3% cases at risk of abortion and 89% at risk of premature delivery.

Only four studies (n=209 women) reported the incidence of adverse events. Twenty-one percent of women (n=44) reported a total of 62 adverse events. These included tachycardia (13.9%), hypotension (5.7%), nausea (5.3%) and constipation (2.4%).

Authors' conclusions
There was preliminary evidence in favour of the effectiveness of isoxsuprine in prolonging pregnancy in women at risk of abortion or premature delivery.

CRD commentary
The review question was clear and was supported by some inclusion criteria. Three relevant databases were searched with no language restrictions, but no attempts to identify unpublished studies were reported; this may have increased the possibility of selection bias in the review. Methods designed to reduce reviewer bias and error were reported for the assessment of validity but not for the other stages of the review process.

The methods used to assess study quality were not clearly reported and there was very little information on the results of the assessment process. There was also limited information on the characteristics of the included studies, which were all published over 30 years ago and were mostly small in size. It did not appear that the methods used to combine outcomes were informative, nor did it appear that appropriate methodology was used for the statistical pooling of these outcome data. In particular, the failure to take account of the study as a factor in the analysis must be regarded as a serious flaw in the synthesis.

In view of all the issues outlined, the authors' conclusion cannot be regarded as reliable.

Implications of the review for practice and research
Practice: The authors stated that the review supports the therapeutic use of isoxsuprine for tocolysis.

Research: The authors stated that controlled clinical trials of tocolytic agents including isoxsuprine in combination with antenatal steroids would have value. They also stated that comparisons of isoxsuprine and other currently prescribed beta-mimetics should be evaluated.

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