Calcium channel blockers for inhibiting preterm labour (Review)

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TABLE OF CONTENTS

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ABSTRACT

Background
Preterm birth is a major contributor to perinatal mortality and morbidity and affects approximately six to seven per cent of births in developed countries. Tocolytics are drugs used to suppress uterine contractions. The most widely tested tocolytics are betamimetics. Although they have been shown to delay delivery, betamimetics have not been shown to improve perinatal outcome, and they have a high frequency of unpleasant and even fatal maternal side effects. There is growing interest in calcium channel blockers as a potentially effective and well tolerated form of tocolysis.

Objectives
To assess the effects on maternal, fetal and neonatal outcomes of calcium channel blockers, administered as a tocolytic agent, to women in preterm labour.

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group's specialised register of controlled trials (June 2002), the Cochrane Controlled Trials Register (The Cochrane Library, Issue 2, 2002), MEDLINE (1965 to June 2002), EMBASE (1988 to June 2002), and Current Contents (1997 to June 2002). We also contacted recognised experts and cross referenced relevant material.

Selection criteria
All published and unpublished randomised trials in which calcium channel blockers were used for tocolysis for women in labour between 20 and 36 weeks' gestation.

Data collection and analysis
Standard methods of the Cochrane Collaboration and the Cochrane Pregnancy and Childbirth Group were used. Evaluation of methodological quality and trial data extraction were undertaken independently by three authors. Additional information was sought to enable assessment of methodology and conduct of intention-to-treat analyses. Meta-analysis was conducted assessing the effects of calcium channel blockers compared with any other tocolytic agent. Results are presented using relative risk for categorical data and weighted mean difference for continuous data.

Main results
Twelve randomised controlled trials involving 1029 women were included. When compared with any other tocolytic agent (mainly betamimetics), calcium channel blockers reduced the number of women giving birth within seven days of receiving treatment (relative risk (RR) 0.76; 95% confidence interval (CI) 0.60 to 0.97) and prior to 34 weeks' gestation (RR 0.83; 95% CI 0.69 to 0.99). Calcium channel blockers also reduced the requirement for women to have treatment ceased for adverse drug reaction (RR 0.14; 95% CI 0.05 to 0.36), the frequency of neonatal respiratory distress syndrome (RR 0.63; 95% CI 0.46 to 0.88), necrotising enterocolitis (RR 0.21; 95% CI 0.05 to 0.96), intraventricular haemorrhage (RR 0.59 95% CI 0.36 to 0.98) and neonatal jaundice (RR 0.73; 95% CI 0.57 to 0.93).

Authors' conclusions
When tocolysis is indicated for women in preterm labour, calcium channel blockers are preferable to other tocolytic agents compared, mainly betamimetics. Further research should address the effects of different dosage regimens and formulations of calcium channel blockers on maternal and neonatal outcomes.

PLAIN LANGUAGE SUMMARY

Calcium channel blockers have fewer adverse effects for women in preterm labour than betamimetic drugs, and appear at least as good at postponing preterm birth

Even short-term postponement of preterm birth (before 37 weeks) can help improve outcomes for babies, as the mother can take steroid drugs which help develop the baby's lungs in a short time. The most common drugs to try and stop preterm labour are betamimetics. Calcium channel blocker drugs are another option (usually nifedipine). They are commonly used for high blood pressure, but might also relax uterine contractions. The review found that calcium channel blockers seem to be at least as good as betamimetics, and maybe better, for postponing preterm labour. Calcium channel blockers have far fewer adverse effects on the mother.

BACKGROUND

Preterm birth, defined as birth occurring between 20 and 36 weeks of gestation is a major contributor to perinatal mortality and morbidity, and affects approximately six to seven per cent of births in developed countries (Lumley 1993). The birth of a preterm infant who requires intensive care for its survival is a crisis, not only for the infant, but also for the parents (McCain 1993).

Of all perinatal deaths, approximately 75 per cent occur in infants born preterm, although many of these infants are already either dead or lethally malformed at the onset of preterm labour (Keirse 1989). No progress has been made over the last two decades in reducing the incidence of preterm birth in high income countries but some benefits have been identified from prolongation of pregnancy by enabling corticosteroids to be administered to hasten fetal lung maturation (Crowley 1998) and to effect transfer to a centre with neonatal intensive care facilities (Powell 1995). A range of drugs (tocolytics) has been used to inhibit preterm labour in order to allow time for such co-interventions to occur. The tocolytics which have been most widely tested are the betamimetics (ritodrine, salbutamol and terbutaline), and they have been shown to be effective in delaying delivery by up to seven days and longer, although no impact has yet been shown on perinatal mortality (King 1988; Gyetvai 1999). Betamimetics have a high frequency of unpleasant, sometimes severe maternal side effects including tachycardia, hypotension, tremulousness and a range of biochemical disturbances. Furthermore, betamimetic treatment has been reported to have been associated with at least 25 maternal deaths mainly from pulmonary oedema (Papatsonis 2001). There is a need, therefore, for an effective tocolytic agent with less side effects than the betamimetics.

Calcium channel blockers or calcium antagonists are non-specific smooth muscle relaxants, predominantly used for the treatment of hypertension in adults. They exert their tocolytic effect by preventing the influx of extracellular calcium ions into the myometrial cell. They are entirely non-specific for uterine as distinct from other smooth muscle cells, but have been demonstrated in vitro to have potent relaxant effect on human myometrium (Saade 1994). The most widely used and studied calcium channel blocker is nifedipine which (like nicardipine) belongs to the dihydropiridine group. Nifedipine was first reported in 1980 in an observational study to be an effective tocolytic agent with minimal side effects (Ulmsten 1980) but it has not replaced the betamimetics as the most commonly used tocolytic agent in clinical practice. Concerns arose from animal studies (Harake 1987) that nifedipine may have adverse effects on the fetal and placental circulation, and although there have been subsequent studies which failed to confirm this (Meyer 1990), it is necessary to review the evidence for the safety and efficacy of this treatment.

OBJECTIVES

1. To assess the effects on maternal, fetal and neonatal outcomes of calcium channel blockers administered as a tocolytic agent to women in preterm labour when compared with either placebo or no intervention.

2. To assess the effects on maternal, fetal and neonatal outcomes of calcium channel blockers administered as a tocolytic agent to women in preterm labour when compared with any other tocolytic agent.

CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

Types of studies

All published and unpublished randomised trials in which calcium channel blockers were used for tocolysis in the management of preterm labour.

Types of participants

Women assessed as being in preterm labour (between 20 and 36 weeks) and considered suitable candidates for tocolysis.

Types of intervention

Calcium channel blockers administered as a tocolytic by any route.

Types of outcome measures

Maternal outcomes:
pregnancy prolongation (interval between randomisation and delivery);
delivery prior to 37 completed weeks;
delivery prior to 34 completed weeks;
delivery within seven days of treatment;
delivery within 48 hours of treatment;
maternal adverse drug reaction;
cessation of treatment for maternal adverse drug reaction;
maternal sepsis;
antepartum haemorrhage;
postpartum haemorrhage;
maternal admission to intensive care unit;
maternal death;
maternal length of hospital stay;
maternal satisfaction with treatment.

Fetal outcomes:
fetal death;
fetal death excluding congenital abnormality;
oligohydramnios.

Neonatal outcomes:
gestation at birth;
neonatal death;
neonatal death excluding congenital abnormality;
perinatal mortality;
perinatal mortality excluding congenital abnormality;
birthweight;
birthweight < 10th centile for gestational age;
Apgar score of < 7 at five minutes;
neonatal sepsis;
neonatal jaundice;
respiratory distress syndrome;
duration of mechanical ventilation;
intraventricular haemorrhage;
intraventricular haemorrhage (grade three or four);
bronchopulmonary dysplasia;
necrotising enterocolitis;
admission to neonatal intensive care unit;
neonatal length of hospital stay;
retinopathy of prematurity;
long term disability.

A priori sub-group analyses:
any dihydropiridine calcium channel blocker compared with any betamimetic agent;
tocolysis commenced prior to 28 weeks gestation;
tocolysis commenced prior to 32 weeks gestation;
tocolysis commenced after membrane rupture;
tocolysis for women with multiple gestation.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

This review has drawn on the search strategy developed for the Pregnancy and Childbirth Group as a whole. The full list of journals and conference proceedings as well as the search strategies for the electronic databases, which are searched by the Group on behalf of its reviewers, are described in detail in the 'Search strategies for the identification of studies section' within the editorial information about the Cochrane Pregnancy and Childbirth Group. Briefly, the Group searches on a regular basis MEDLINE, the Cochrane Controlled Trials Register and reviews the Contents tables of a further 38 relevant journals received via ZETOC, an electronic current awareness service.

Relevant trials, which are identified through the Group's search strategy, are entered into the Group's Specialised Register of Controlled Trials. Please see Review Group's details for more detailed information. Date of last search: June 2002.

In addition, the reviewers conducted a systematic literature search which included electronic databases: the Cochrane Controlled Trials Register (The Cochrane Library, Issue 2, 2002), MEDLINE (1965 to June 2002), EMBASE (1988 to June 2002), Current Contents (1997 to June 2002), using search terms: tocolysis, nifedipine, calcium channel blocker, ritodrine, terbutaline, and salbutamol. A manual search of the references of all retrieved articles was also performed. We also sought unpublished trials and abstracts submitted to major international congresses and contacted expert informants.

METHODS OF THE REVIEW

The standard methods of the Cochrane Collaboration were used for the consideration of trials for inclusion. Evaluation of methodological quality, and trial data extraction were undertaken independently by the authors (J King, V Flenady, D Papatsonis)

as described in Clarke 2001. Differences in interpretation were resolved by discussion.

Methods used for assessing data quality

Four major sources of potential bias and methods of avoidance of these biases were considered when assessing trial quality: (1) selection bias - blinding of randomisation; (2) performance bias - blinding of intervention; (3) attrition bias - complete follow-up; (4) detection bias - blinding of outcome assessment. The quality assessment was based on the systematic assessment for the opportunity for each of these biases to arise. Thus, the reviewers judged for each trial whether each criterion was met. A rating of A-Yes, B-Unclear, or C-No was allocated to each criterion. The quality assessment rating included in the Table of Included Studies refers to the blinding of randomisation only where a rating of A-Adequate, B-Unclear, C-Inadequate or D-Not used was given for each trial. An a priori decision was made to exclude trials when outcome data were unavailable for more than 20 per cent of participants.

Data collection and analysis

Additional information was sought from investigators of ten included studies (Read 1986; Ferguson 1990; Janky 1990; Bracero 1991; Kupferminc 1993; Papatsonis 1997; Garcia-Velasco 1998; Koks 1998; Larmon 1999; Weerakul 2002) and data were provided and included for seven of these studies (Ferguson 1990; Janky 1990; Kupferminc 1993; Papatsonis 1997; Garcia-Velasco 1998; Koks 1998; Larmon 1999; Weerakul 2002). Three trials included women with a multiple pregnancy (Janky 1990; Kupferminc 1993; Koks 1998). In the analysis of these trials, outcomes for all babies are presented.

Analysis was conducted to assess the effects of calcium channel blockers when compared with any other tocolytic. The prespecified comparison of calcium channel blockers and no treatment or placebo was not able to be conducted as no trials which addressed this question were identified. One subgroup analysis was performed comparing tocolysis with the dihydropiridine class of calcium channel blockers (nifedipine and nicardipine) with betamimetics, as this was thought to be an important clinically relevant comparison. The other prespecified subgroup analyses were not able to be undertaken due to insufficient data. Also due to insufficient data, a planned sensitivity analysis by trial quality was not conducted. Analyses were conducted using a fixed effects model or a random effects model in the presence of statistically significant heterogeneity. Statistical heterogeneity between trials was assessed using the chi squared test for heterogeneity. Results are presented using relative risk for categorical data and weighted mean difference for variables measured on a continuous scale and include 95% confidence intervals. Results are also expressed using numbers needed to treat (NNT) where appropriate.

DESCRIPTION OF STUDIES

Thirty-two studies were identified as potentially eligible for inclusion in this review. Eight trials were excluded and a further twelve studies are unable to be included until additional information is provided by the authors. Therefore, this review includes twelve randomised trials testing the effects of calcium channel blockers for tocolysis in preterm labour.

Excluded studies

As this review evaluated tocolytic therapy for women in preterm labour, two trials evaluating maintenance therapy of women following successful tocolysis were excluded (Carr 1993; El-Sayed 1998). Another trial (Meyer 1990) was excluded because it enrolled women only after subcutaneous terbutaline failed to stop regular uterine contractions. This may have introduced a systematic bias favouring nifedipine since only women who did not respond to the beta-adrenergic agonist were admitted to the trial. Furthermore, the treatment groups were unbalanced (24 versus 34). Another trial (Kose 1995), which was translated from Turkish, was excluded because the treatment groups were unbalanced: 52 women received nifedipine and only 21 ritodrine. The reason for this imbalance and also the method of randomisation was not able to be determined. Two trials were excluded as the intervention tested was the addition of a calcium channel blocker for women receiving tocolysis with a betamimetic agent (Rodriguez-Esc 1981; Piovano 1985).Two trials were excluded on the basis of quasi-random allocation to treatment (Dunstan-Boone 1990; Smith 1993).

Included studies

A total of 1029 women participated in the 12 included trials comparing calcium channel blockers with other tocolytic agents for preterm labour (Read 1986; Ferguson 1990; Janky 1990; Bracero 1991; Glock 1993; Kupferminc 1993; Jannet 1997; Papatsonis 1997; Garcia-Velasco 1998; Koks 1998; Larmon 1999; Weerakul 2002). In one trial (Koks 1998) only the subset of trial participants who did not receive prior betamimetic therapy (57 of 102 subjects) was included.

Participants

The participants included in these trials were reasonably homogeneous. The minimum gestational age at inclusion ranged from 20 to 26 weeks, and the maximum from 33.5 to 36 weeks. The mean gestational age at entry, when described, was between 28 and 32 weeks' gestation. Preterm labour was reasonably consistently defined across the trials, most excluding those women with a cervical dilatation of greater than 4cm. Four trials included women admitted for preterm labour with preterm premature rupture of membranes (Ferguson 1990; Janky 1990; Papatsonis 1997; Koks 1998) and three trials included twin pregnancies (Janky 1990; Kupferminc 1993; Koks 1998). All the trials excluded those women who had contra-indications to either calcium channel blockers or to betamimetics. The standard contra-indications for tocolysis were

reported as exclusion criteria in the majority of included trials, i.e., fetal distress, chorioamnionitis, severe preeclampsia/eclampsia, and abruptio placentae.

Tocolysis

Ten trials compared oral nifedipine with other tocolytic agents (Read 1986; Ferguson 1990; Janky 1990; Bracero 1991; Glock 1993; Kupferminc 1993; Papatsonis 1997; Garcia-Velasco 1998; Koks 1998; Weerakul 2002). Eight of these trials used ritodrine as the other tocolytic. Initial tocolytic therapy with nifedipine was administered orally or sublingually, as either capsules or tablets (whole, or crushed and dissolved in water). Dosage varied from 30 mg/day to 160 mg/day until uterine contractions stopped. The largest trial (Papatsonis 1997) used a higher dose of nifedipine than most of the included trials (up to 40mg in the first hour). All ten trials continued oral nifedipine after the initial treatment but three trials (Ferguson 1990; Bracero 1991; Garcia-Velasco 1998) did not report the total duration of treatment. Ritodrine was usually started at 50 µg/minute except for Janky 1990; Papatsonis 1997; Koks 1998. Janky 1990 and Koks 1998 started at a loading dose of 150 to 200 µg/minute and the rate was increased up to 300 or 350 µg/minute until uterine contractions stopped. Papatsonis 1997 started ritodrine at a loading dose of 383 µg/minute and gradually decreased to a minimum of 100 µg/minute. Two trials used nicardipine as the calcium channel blocker, one trial compared intravenous nicardipine with salbutamol (Jannet 1997) and the other oral nicardipine with magnesium sulphate (MgSO4) (Larmon 1999).

Most trials used oral maintenance in both treatment groups until 34 to 37 weeks gestation.

Outcomes

There was some inconsistency across the trials with respect to the way in which maternal outcomes were reported. Although the clinically important outcome of delay in delivery for greater than or equal to 48 hours was reported in nine trials, only four trials reported delay for greater than or equal to seven days. Discontinuation of treatment because of adverse side effects was reported in eleven of the 13 trials. With the exception of neonatal mortality, neonatal outcomes were less consistently reported, and definitions were often lacking (eg criteria for diagnosing respiratory distress syndrome, sepsis or for admission to neonatal intensive care unit (NICU)).

The neonatal outcomes of the trial of Papatsonis 1997 were reported more comprehensively in a subsequent publication, with precise definitions. This second report used a more stringent definition for admission to the NICU than the one used in the initial report. Because the other trials used a more general definition (usually not defined, but presumably any admission to NICU) in order to maintain consistency, we have chosen to use the data from the primary publication for Papatsonis 1997. Some degree of assessment bias is possible for the neonatal morbidity indices in all of the trials because neonatal assessment was undertaken by clinicians not blinded to maternal treatment allocation. None of the trials described any intention to undertake longer term neonatal assessment, which is an important deficiency in this evidence.

Please see Table of Characteristics of Included Studies for further details.

METHODOLOGICAL QUALITY

The included trials were considered to be of reasonable quality. Ten of the included trials reported concealed random allocation to treatment and therefore received an A quality rating. In two trials the precise method of random allocation to treatment was not described (Kupferminc 1993; Jannet 1997). For all of the included trials, blinding of the intervention was not performed. Blinded assessment of outcomes was not reported in any of the included studies. In this review, an attempt was made to conduct an intention-to-treat analysis for all outcomes. Although some trials had post-randomisation exclusions, the rate of exclusions was generally low and not considered by the authors of this review to be a threat to its validity. In one trial (Glock 1993) 20% of randomised women were excluded from the analysis because they failed to meet the inclusion criteria.

Further information on methods and outcomes has been sought from trial investigators and will be included in future updates when available. Please see Table of Characteristics of Included Studies for further details.

RESULTS

This review includes data from 12 trials with a total of 1029 women.

Maternal outcomes

When compared with any other tocolytic agent, the use of calcium channel blockers resulted in a statistically significant decrease in the number of women giving birth within seven days of initiation of treatment (relative risk (RR) 0.76; 95% confidence interval (CI) 0.60 to 0.97) and prior to 34 weeks gestation (RR 0.83; 95%CI 0.69 to 0.99). The number needed to treat (NNT) for the outcome of birth within seven days is 11 (95% CI 6 to 100). This means that, on average, for every 11 women treated with calcium channel blockers instead of any other tocolytic drug, one less birth occurs within this time period. However, the confidence intervals indicate that as few as six or as many 100 women would need to be treated with a calcium channel blocker to achieve this result. Maternal adverse drug reaction was reduced (RR 0.32; 95% CI 0.24 to 0.41) and cessation of treatment for maternal drug reaction was markedly reduced (RR 0.14; 95% CI 0.05 to 0.44). The NNT for maternal adverse drug reaction was three (95% CI 3 to 4) and for drug reaction requiring cessation of treatment was 14 (95% CI 10 to 25). A trend toward superior tocolytic benefit was apparent

in the outcomes of birth prior to 37 weeks gestation (RR 0.95; 95% CI 0.83 to 1.09), within 48 hours of initiation of treatment (RR 0.80; 95%CI 0.61 to 1.05) and for pregnancy prolongation (interval from treatment to delivery), (weighted mean difference (WMD) 3.83 days; 95% CI -3.04 to 10.70). For the outcome of pregnancy prolongation, a random effects model was used in the meta-analysis due to statistical heterogeneity.

Neonatal outcomes
When compared with any other tocolytic agent, the use of calcium channel blockers resulted in a statistically significant increase in gestation at birth (WMD 0.70 weeks; 95% CI 0.19 to 1.20), and a reduction in neonatal respiratory distress syndrome (RDS) (RR 0.63; 95% CI 0.46 to 0.88), necrotising enterocolitis (RR 0.21; 95% CI 0.05 to 0.96) and intraventricular haemorrhage (RR 0.59; 95% CI 0.36 to 0.98). The risk reduction for the outcome of respiratory distress syndrome (RDS) gives a NNT of 14 (95% CI 8 to 50) and for intraventricular haemorrhage 13 (95% CI 7 to 100). Less neonatal jaundice was also shown for infants of women receiving calcium channel blockers (RR 0.73; 95% CI 0.57 to 0.93). No statistically significant differences were shown for the outcomes of birthweight, admissions to neonatal intensive care unit, Apgar score less than seven at five minutes, neonatal sepsis, or perinatal mortality.

Subgroup analysis: Any dihydropiridine calcium channel blocker compared with any betamimetic agent.

Nine of the 12 trials were included in the subgroup analysis of any dihydropiridine compared with any betamimetic agent. This analysis demonstrated similar effects as shown in the overall analysis on the prolongation of pregnancy indices. In addition to the statistically significant reduction in the number of women giving birth within seven days of initiation of treatment and prior to 34 weeks gestation, this subgroup analysis demonstrated a statistically significant reduction in birth within 48 hours (RR 0.72; 95% CI 0.53 to 0.97). This subgroup analysis also showed similar neonatal effects to that of the overall analysis (statistically significant reduction in RDS and jaundice). In addition, a statistically significant increase in mean birthweight was demonstrated (WMD 122.68g; 95% CI 3.50 to 241.86).

A sensitivity analysis was undertaken to test the effect of the decision made by the reviewers to include data for the outcome of admission to neonatal intensive care unit (NICU) from the primary publication for the Papatsonis 1997 trial. When data were used from the subsequent publication (which applied a more stringent admission definition), the trend toward a reduction in NICU admissions for infants of women treated with calcium channel blockers is strengthened, and becomes statistically significant (RR 0.78 95% CI 0.64 to 0.94) in the overall comparison; however, it does not reach statistical significance for the subgroup analysis of any dihydropiridine compared with any betamimetic agent.(RR 0.84; 95% CI 0.71 to 1.00) (data not shown).

A number of clinically important outcomes were unable to be adequately assessed due to insufficient data, including fetal growth restriction which might be increased in the circumstance of artificially prolonged pregnancy. The planned subgroup analyses to explore the effects at different gestational age thresholds and according to membrane status and multiple gestation were unable to be conducted due to unavailability of data.

DISCUSSION

Based on the data included in this review comparing the effects of calcium channel blockers (mainly nifedipine) with other tocolytic agents (mainly betamimetics), calcium channel blockers are shown to be a more effective tocolytic agent (less births within seven days of imitation of treatment and before 34 weeks gestation) with improvement in some clinically important neonatal outcomes (less respiratory distress syndrome, intraventricular haemorrhage, necrotising enterocolitis and jaundice) and a marked reduction in adverse maternal side effects.

An important clinical aspect to tocolysis, particularly if maternal transport to a tertiary centre is being planned, is speed of onset of action. Because in most of the trials of calcium channel blockers the medication was administered as an oral preparation, and in the trials of betamimetics the agents were administered intravenously, there is the possibility that betamimetics might have a more rapid onset of action enabling a more expeditious transfer with less risk of delivery prior to arrival at the referral centre. Two trials (Read 1986 and Janky 1990) assessed uterine quiescence at two hours as an index of successful tocolysis, and no statistically significant difference was seen between the two agents.

The largest trial (Papatsonis 1997), which had the most favourable outcomes, used a higher dosage regimen for nifedipine than that used in most of the other trials (up to 40mg in the first hour) and this might be the most appropriate one to use. The manufacturers' withdrawal of the capsule formulation for sublingual use of nifedipine has limited clinicians' options for a fast acting means of administering the drug, and alternative methods are being used such as dissolving tablets in water. The impact of this on tocolytic effectiveness is unable to be addressed in this review.

There is a substantial amount of evidence from controlled trials (a further 12 trials) comparing calcium channel blockers with betamimetic agents for which the data were not available in a format which allowed inclusion in this review. The reviewers regard this as an important deficiency, and are making determined efforts to obtain further information for inclusion in subsequent versions of this review. However, in reviewing the information currently available from these trials awaiting assessment, it does not appear that as a group, their results differ substantially or systematically from the trials included in this review. This supports the conclusion that calcium channel blockers should be preferred over be-

tamimetics for those women who are considered likely to benefit from tocolytic treatment.

AUTHORS' CONCLUSIONS

Implications for practice

Based on the results of this review, it would seem justified to conclude that when tocolysis is indicated for women in preterm labour, calcium channel blockers should be preferred to betamimetics. The formulation (capsules versus tablets) and dosage regimens differed somewhat amongst the included trials, and it was not possible to determine from the data in this review that one regimen is preferable to another.

Implications for research

The findings of this review suggest that it does not seem justifiable to ask women in preterm labour to participate in further trials comparing betamimetics with nifedipine or other calcium channel blockers. Although it would be informative to see the results of placebo controlled trials of calcium channel blockers, it is considered unlikely that these will be conducted given the unequivocal impact that this method of tocolysis has on short term postponement of delivery and the opportunity that this provides for effecting in-utero transfer and steroid administration. Further trials testing different dosage regimens (high versus low, particularly addressing speed of onset of uterine quiescence) and formulation (capsules versus tablets) utilising blinding of the intervention would add to our understanding about optimal usage of nifedipine as a tocolytic. Long term follow-up of the neurodevelopmental status of infants should be included as an important outcome variable in any further trials of tocolytic agents.

POTENTIAL CONFLICT OF INTEREST

B Carbonne, D Papatsonis, and G Dekker were co-authors in a non-Cochrane systematic review of nifedipine and beta-agonists (Tsatsaris 2001). D Papatsonis and G Dekker were co-authors of a randomised trial of nifedipine and ritodrine for preterm labour (Papatsonis 1997).

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- J P Kelly Research Foundation, Mater Hospital, South Brisbane, Queensland AUSTRALIA

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	**Bracero 1991**
Methods	Blinding of randomisation: Yes, sealed envelopes. Blinding of intervention: No. Blinded outcome assessment: No. Completeness of follow-up: 7 post randomisation exclusions.
Participants	49 women in preterm labour at 20-36 weeks. Exclusion criteria: ruptured membranes, multiple pregnancy.
Interventions	CCB Group: Nifedipine 30mgs po initially then 20mgs q6h for 24hrs then 20mgs q8h for 24hrs followed by maintenance 20mgs q8-12h prn. Other tocolytic group: Ritodrine, 100 µg/min increasing by 50µg/min q10min prn to a maximum of 350µg/min. Oral maintenance 10-20mg q4-6 h.
Outcomes	Delivery < 48 hrs; pregnancy prolongation; maternal adverse drug reaction and maternal adverse drug reaction requiring cessation of treatment; GA at birth; admission to NICU; RDS; neonatal jaundice, sepsis, NEC; fetal and neonatal death.
Notes	No additional data received. Sample size calculation: Not reported. Antenatal corticosteroids: Not reported. GBS protocol: Not reported.
Allocation concealment	A – Adequate

Study	**Ferguson 1990**
Methods	Blinding of randomisation: Yes, sealed envelopes.

Characteristics of included studies (*Continued*)

	Blinding of intervention: No. Blinded outcome assessment: No. Completeness of follow-up: No. 3 post randomisation exclusions.
Participants	66 women in preterm labour at 20-36 weeks gestation. Exclusion criteria: multiple pregnancy.
Interventions	CCB Group: Nifedipine 10mg capsule s/l repeated in 20 mins oral maintenance 20 mg q4-6h. Other tocolytic group: Ritodrine, 50 µg/min increasing by 50 µg 15-30 mins up to a maximum of 350µg/min. Oral maintenance 10-20 q4-6 h.
Outcomes	Delivery < 37 wks; delivery < 48 hrs; maternal adverse drug reaction and maternal adverse drug reaction requiring cessation of treatment; RDS; IVH all Grades; fetal deaths; neonatal deaths.
Notes	Additional data received. Sample size calculation: Not reported. Antenatal corticosteroids: Yes. GBS protocol: Vaginal cultures and intrapartum antibiotics for GBS positive.
Allocation concealment	A – Adequate

Study	**Garcia-Velasco 1998**
Methods	Blinding of randomisation: Yes, sealed envelopes. Blinding of intervention: No. Blinded outcome assessment: No. Completeness of follow-up: Yes.
Participants	52 women in preterm labour at 26-34 weeks. Exclusion criteria: women with ruptured membranes, multiple pregnancy.
Interventions	CCB Group: Nifedipine 10mgs s/l and 20mgs po then 10-20 q4-6 h prn. Other tocolytic group: IV Ritodrine, 50 µg/min increasing by 50 ug q20mins to max of 350µg/min maintained for 12 hrs. The oral maintenance 5mgs q3h. Indomethacin given in both groups for continued uterine activity after 12 h or treatment was not well tolerated.
Outcomes	Delivery < 48 hrs; delivery < 37 wks; pregnancy prolongation; maternal adverse drug reaction requiring cessation of treatment; birthweight; admission to NICU; RDS; maternal length of hospital stay.
Notes	Additional data received. Sample size calculation: Yes - based on change in maternal BP and pulse. Antenatal corticosteroids: Yes. GBS protocol: Not reported.

Characteristics of included studies (*Continued*)

Allocation concealment	A – Adequate

Study	**Glock 1993**
Methods	Blinding of randomisation: Yes, sealed envelopes. Blinding of intervention: No. Blinded outcome assessment: No. Completeness of follow-up: No. 20 post randomisation exclusions.
Participants	100 women in preterm labour less than 34 wks gestation. Exclusion crtiteria: Multiple pregnancy, ROM, tocolysis this pregnancy, maternal medical complications, congenital malformations, IUGR.
Interventions	CCB: Nifedipine 10mg s/l repeated prn every 20 mins to max of 40mg in first hr. Once contractions ceased 20mg q4h for 48 h, then maintenance 10mg q8h until 34 wks. Other tocolytic group: MgSO4 load 6gIV over 30 mins then 2g per hr IV up to 4g per hr as required for 24 h, then weaned at 0.5g every 4-6 hrs, then maintenance therapy of oral terbutaline 5mg q6h until 34 wks.
Outcomes	Delivery < 48 hrs; delivery < 37 wks; delivery < 34 wks; pregnancy prolongation index; maternal adverse drug reaction requiring cessation of treatment; birthweight; perinatal mortality.
Notes	Sample size calculation: No. Antenatal corticosteroids: Yes. GBS protocol: Vaginal culture and intrapartum antibiotics for GBS positive.
Allocation concealment	A – Adequate

Study	**Janky 1990**
Methods	Blinding of randomisation: Yes, sealed envelopes. Blinded intervention: No. Blinded outcome assessment: No. Completeness of follow-up: Yes.
Participants	62 women in preterm labour at 28-36 weeks gestation. Exclusion criteria: Chorioamnionitis and maternal medical conditions, cervix > 4cms, ROM after 34 weeks.
Interventions	CCB Group: Nifedipine 10mgs s/l then 20mgs q8h. Ceased after 7 days Other tocolytic group: IV Ritodrine, 200 to 300 µg/min until contractions ceased then 100µg/min for 24 hr then oral maintenance 20mgs 4-6 h for 6 days.
Outcomes	Pregnancy prolongation; maternal adverse drug reaction requiring cessation of treatment; birthweight; fetal death neonatal death.
Notes	Additional data received. Sample size calculation: Not reported. Antenatal corticosteroids: Not reported.

	GBS protocol: Not reported.
Allocation concealment	A – Adequate

Study	**Jannet 1997**
Methods	Blinding of randomisation: Unclear. Blinded intervention: No. Blinded outcome assessment: No. Completeness of follow-up: No.
Participants	90 women in preterm labour 25 to 35.5 wks. Exclusion criteria: multiple pregnancy ROM, maternal medical conditions, standard contraindications to tocolytics.
Interventions	CCB Group: IV Nicardipine 3mg/h for 2 hrs increasing prn up to a maximum of 6mg/hr until contractions cease then oral 20mgs q8h until 37 wks. Other tocolytic group: IV Salbutamol 150µg/hr, increasing after 2 h to 300µg/hr maintained for 48 hrs then oral maintenance 8mg q6h po and 2 rectal suppositories of salbutamol 2mgs daily until 37 weeks.
Outcomes	Delivery < 37 hrs; delivery < 34 wks; maternal adverse drug reaction; birthweight; GA at birth; admission to NICU.
Notes	4 post randomisation exclusions (2 in each group). Sample size calculation: No. Antenatal steroids: Not reported. GBS protocol: Not reported.
Allocation concealment	B – Unclear

Study	**Koks 1998**
Methods	Blinding of randomisation: Yes, sealed envelopes. Blinding of intervention: No. Blinded outcome assessment: No. Completeness of follow-up: No. 2 post randomisation exclusions.
Participants	102 women in preterm labour at 24-34 wks. Exclusion criteria: maternal medical conditions, chorioamnionitis.
Interventions	CCB Group: Nifedipine s/l 30mgs then po 20mgs q4-12 h reducing to 20mgs q8h to 34 wks 'prn'. Other tocolytic group: IV Ritodrine, 200µg/min up to max of 400µg/min then oral maintenance 80mgs q8h to 34 weeks.
Outcomes	Delivery < 34 wks; delivery < 48 hrs; delivery < 7 days; maternal adverse drug reaction requiring cessation of treatment; GA at birth; birthweight; Apgar score < 7 at 5 min; NICU admission; RDS; neonatal jaundice;

	fetal death; neonatal death.
Notes	Outcomes for a subset of trial participants (57) included in review. Additional data received. Sample size calculation: Not reported. Antenatal corticosteroids: Yes - wkly to 32 wks. GBS protocol: Vaginal culture and intrapartum antibiotics for GBS positive.
Allocation concealment	A – Adequate

Study	**Kupferminc 1993**
Methods	Blinding of randomisation: Unclear, "Computerised list" - Blinding of intervention: No. Blinded outcome assessment: No. Completeness of follow-up: Yes.
Participants	71 women in preterm labour at 26-34 weeks. Exclusion criteria: women with ruptured membranes.
Interventions	CCB Group: Nifedipine 30 mg po then 20mgs after 90 min if required then maintenance 20mgs q8h until 34-35 wks. Switch to Ritodrine if contractions continue after 150 mins. Other tocolytic group: IV Ritodrine 50µg/min increasing by 15 µg q15 to a maximum of 300ug/min for 12 hours, oral maintenance 10mgs q3h until 34-35 wks.
Outcomes	Delivery < 37 wks; delivery < 48 hrs; delivery <7 days; maternal adverse drug reaction requiring cessation of treatment; NICU admission; RDS; fetal death; neonatal death.
Notes	Additional data received. Sample size calculation: Yes - based on maternal cardiovascular changes. Antenatal corticosteroids: Yes. GBS protocol: Not reported.
Allocation concealment	B – Unclear

Study	**Larmon 1999**
Methods	Blinding of randomisation: Yes, sealed envelopes. Blinding of intervention: No. Blinded outcome assessment: No. Completeness of follow-up: Yes.
Participants	122 women in preterm labour between 22-34 wks. Exclusion criteria: multiple pregnancy, ROM, chorioamnionitis, medical conditions, standard contraindications to tocolytics.
Interventions	CCB Group: Nicardipine 40 mg po then 20mgs q2h prn up to 3 doses then oral maintenance 45mgs q12h until 37 wks. Other tocolytic group: IV MgSO4 loading dose of 6g then 2g/hr increasing up to a maximum of 4g/hr prn. Oral maintenance Mg lactate 4 tabs q12h until 37 wks.
Outcomes	Maternal adverse reaction; pregnancy prolongation;

Characteristics of included studies (*Continued*)

	NICU admission; GA at birth; birthweight; fetal death; neonatal death. Additional data received for: birth prior to 37 wks and 34 wks; birth within 48hrs and 7days of treatment; maternal adverse drug reaction requiring cessation of treatment; Apgar score <7 at 5 mins; RDS.
Notes	Sample size calculation: Yes - based on successful tocolysis at 6 hrs. Antenatal steroids: Yes, for women 24-34 weks gestation. GBS protocol: All women received ampicillin awaiting results of vaginal culture for GBS, 7 day course for those GBS positive. Addtional data and information were received from authors and included in the review.
Allocation concealment	A – Adequate

Study	**Papatsonis 1997**
Methods	Blinding of randomisation: Yes, sealed envelopes. Blinding of intervention: No. Blinded outcome assessment: No. Completeness of follow-up: Yes.
Participants	185 women in preterm labour at 20-34 wks. Exclusion criteria: multiple pregnancy, chorioamnionitis, maternal medical conditions.
Interventions	CCB Group: Nifedipine 10mgs s/l, repeated if necessary po 10mg q15mins up to 40mg in the first hour. Maintenance 60-160mgs/day up to 34 weeks. Other tocolytic group: Ritodrine commencing at 383µg/min increasing prn until cessation of contractions then decreasing depending on the time lag after which tocolysis is established (minimum 100 µg/min) and continued for 3 days. Maintenance 40mg po q8h up to 34 weeks in two of the three participating hospitals.
Outcomes	Delivery < 37 wks; delivery < 34 wks; delivery < 7 days; delivery < 48 hrs; gestational age; birthweight; maternal adverse drug reaction requiring cessation of treatment; fetal death; NICU admission; RDS; neonatal death; Apgar score < 7 at 5 mins; neonatal jaundice; NEC; IVH.
Notes	12 exclusions in published report - additional data received and included. Sample size calculation: Yes - based on delay in delivery < 7 days. Antenatal corticosteroids: Yes. GBS protocol: vaginal culture on admission and antibiotics for positive GBS.
Allocation concealment	A – Adequate

Study	**Read 1986**
Methods	Blinding of randomisation: Unclear. Blinding of intervention: No. Blinded outcome assessment: No. Completeness of follow-up: Yes.
Participants	40 women in preterm labour at 20-35 wks.

Characteristics of included studies (*Continued*)

	Exclusion criteria: multiple pregnancy, chorioamnionitis, maternal medical conditions, ROM.
Interventions	CCB Group: Nifedipine 30mgs po then 20mg q8h for 3 days. Ritodrine started after 2 hrs if contractions were undiminished. Other tocolytic group: Ritodrine 50 µg/min increasing by 50µg q 10 mins to a maximum of 300µg. Maintained for 12 h then oral maintenance for 48 h.
Outcomes	Delivery < 48 hrs; maternal adverse drug reaction; pregnancy prolongation; birthweight.
Notes	No additional outcomes data available. Sample size calculation: No. Antenatal corticosteroids: Not reported. GBS protocol: Not reported.
Allocation concealment	B – Unclear

Study	**Weerakul 2002**
Methods	Blinding of randomisation: Yes, sealed envelopes. Blinding of intervention: No. Blinded outcome assessment: No. Completeness of follow-up: One post randomisation exclusion.
Participants	90 women in preterm labour with a singleton pregnancy between 28-34 wks gestation. Exclusion criteria: multiple pregnancy, ruptured membranes, previous tocolytics, cervix >3cms dilated, chorioamnionitis, infection, fetal distress, fetal anomalies, medical or obstetric complications.
Interventions	CCB Group: Nifedipine 10mgs s/l capsule crushed repeated after 15 mins, then 20mg after 30 mins to a maximum in the first hr of 40mg. Maintenance of 60-120 mg daily for 3 days. Other tocolytic group: Terbutaline IV loading of 0.25mg, then infusion commencing at 5µg/min increasing by 5µg/min every 15 mins depending on contractions to a maximum of 15µg/min. Following uterine quiesence infusion maintained for 2 hrs then subcutaneous injection 0.25mg q4h for 24hrs.
Outcomes	Delivery after 48 hrs; delivery after 7 days; delivery after 37 weeks; pregnancy prolongation; GA at birth; birthweight; maternal adverse drug reaction. Additional data received on the following: Delivery within 48 hrs; Delivery within 7 days; Delivery within 37 weeks; Delivery within 34 weeks; Use of antenatal steroids; Maternal sepsis, maternal death, APH, PPH. Apgar score<7 at 5 mins; admission to NICU; neonatal mechanical ventilation, jaundice, sepsis, NEC, IVH, ROP; Perinatal death.
Notes	Additional information on methods and outcomes data were received. Sample size calculation: Yes - no details given. Antenatal corticosteroids: Yes - all women enrolled. GBS protocol: No. One post randomisation exclusion in the other tocolytic group (terbutaline) due to patient transfer to private hospital.

Allocation concealment A – Adequate

AB: antibiotics
APH: antepartum haemorrhage
BP: blood pressure
CCB: calcium channel blocker
GA: gestational age
GBS: group B Streptococcus
hrs: hours
IUGR: intrauterine growth restriction
IV: intravenous
IVH: intraventricular haemorrhage
MgSO4: magnesium sulphate
min: minute
NEC: neonatal necrotising enterocolitis
NICU: neonatal intensive care unit
po: orally
PPH: postpartum haemorrhage
prn: as necessary
q6h: every six hours
RDS: neonatal respiratory distress syndrome
ROM: rupture of membranes
s/l: sublingual
µg: micrograms
wks: weeks

Characteristics of excluded studies

Study	Reason for exclusion
Carr 1993	Trial of maintenance tocolytic therapy.
Dunstan-Boone 1990	Quasi-random allocation to treatment.
El-Sayed 1998	Trial of maintenance tocolytic therapy.
Kose 1995	Information was not available on: 1. reasons for imbalance in numbers in study groups: 52 women in nifedipine group and 21 in ritodrine group; and 2. method of randomisation.
Meyer 1990	Women were eligible for trial entry only after subcutaneous terbutaline failed to stop regular uterine contractions and the numbers in each group (34 versus 24) raise concerns about the randomisation process.
Piovano 1985	Trial tested the addition of a calcium channel blocker for women receiving tocolysis with a betamimetic agent.
Rodriguez-Esc 1981	Trial tested the addition of a calcium channel blocker for women receiving tocolysis with a betamimetic agent.
Smith 1993	Quasi-random allocation to treatment.

ANALYSES

Comparison 01. Any calcium channel blocker compared with any other tocolytic agent

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Birth prior to 37 weeks gestation	6	558	Relative Risk (Fixed) 95% CI	0.95 [0.83, 1.09]
02 Birth prior to 34 weeks gestation	6	619	Relative Risk (Fixed) 95% CI	0.83 [0.69, 0.99]
03 Birth within seven days of treatment	4	453	Relative Risk (Fixed) 95% CI	0.76 [0.60, 0.97]
04 Birth within 48 hours of treatment	9	761	Relative Risk (Fixed) 95% CI	0.80 [0.61, 1.05]
05 Pregnancy prolongation (days)	7	592	Weighted Mean Difference (Fixed) 95% CI	5.71 [1.95, 9.47]
06 Maternal adverse drug reaction	8	717	Relative Risk (Fixed) 95% CI	0.32 [0.24, 0.41]
07 Maternal drug reaction requiring cessation of treatment	10	833	Relative Risk (Fixed) 95% CI	0.14 [0.05, 0.36]
08 Duration of maternal hospital stay (days)	1	52	Weighted Mean Difference (Fixed) 95% CI	0.18 [-1.04, 1.40]
09 Gestation at birth (completed weeks)	6	587	Weighted Mean Difference (Fixed) 95% CI	0.70 [0.19, 1.20]
10 Birthweight (grams)	8	717	Weighted Mean Difference (Fixed) 95% CI	84.42 [-10.13, 178.97]
11 Apgar score < 7 at five minutes	4	478	Relative Risk (Fixed) 95% CI	0.77 [0.35, 1.71]
12 Admission to intensive care nursery	9	771	Relative Risk (Fixed) 95% CI	0.78 [0.64, 0.95]
13 Respiratory distress syndrome	9	763	Relative Risk (Fixed) 95% CI	0.63 [0.46, 0.88]
14 Neonatal jaundice	2	227	Relative Risk (Fixed) 95% CI	0.73 [0.57, 0.93]
15 Neonatal sepsis	4	378	Relative Risk (Fixed) 95% CI	0.73 [0.46, 1.16]
16 Necrotising enterocolitis	3	323	Relative Risk (Fixed) 95% CI	0.21 [0.05, 0.96]
17 Intraventricular haemorrhage	3	340	Relative Risk (Fixed) 95% CI	0.59 [0.36, 0.98]
18 Intraventricular haemorrhage grades three or four	3	340	Relative Risk (Fixed) 95% CI	0.50 [0.16, 1.55]
19 Retinopathy of prematurity	1	185	Relative Risk (Fixed) 95% CI	0.11 [0.01, 1.93]
20 Perinatal mortality	10	810	Relative Risk (Fixed) 95% CI	1.65 [0.74, 3.64]
21 Perinatal mortality excluding congenital abnormality	10	820	Relative Risk (Fixed) 95% CI	1.42 [0.61, 3.31]
22 Fetal death	10	820	Relative Risk (Fixed) 95% CI	3.00 [0.13, 71.07]
23 Fetal death excluding congenital abnormality	10	820	Relative Risk (Fixed) 95% CI	Not estimable
24 Neonatal death	11	883	Relative Risk (Fixed) 95% CI	1.58 [0.74, 3.39]
25 Neonatal death excluding congenital abnormality	10	820	Relative Risk (Fixed) 95% CI	1.42 [0.61, 3.31]

Comparison 02. Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Birth prior to 37 weeks gestation	4	389	Relative Risk (Fixed) 95% CI	0.89 [0.76, 1.05]
02 Birth prior to 34 weeks gestation	3	328	Relative Risk (Fixed) 95% CI	0.79 [0.65, 0.96]
03 Birth within seven days of treatment	2	242	Relative Risk (Fixed) 95% CI	0.76 [0.59, 0.99]
04 Birth within 48 hours of treatment	6	470	Relative Risk (Fixed) 95% CI	0.72 [0.53, 0.97]
05 Pregnancy prolongation (days)	5	381	Weighted Mean Difference (Fixed) 95% CI	8.24 [3.67, 12.81]
06 Maternal adverse drug reaction	5	426	Relative Risk (Fixed) 95% CI	0.40 [0.30, 0.55]
07 Maternal drug reaction requiring cessation of treatment	7	542	Relative Risk (Fixed) 95% CI	0.09 [0.02, 0.38]
08 Duration of maternal hospital stay (days)	1	52	Weighted Mean Difference (Fixed) 95% CI	0.18 [-1.04, 1.40]
09 Gestation at birth (completed weeks)	4	376	Weighted Mean Difference (Fixed) 95% CI	0.83 [0.21, 1.44]
10 Birthweight (grams)	5	426	Weighted Mean Difference (Fixed) 95% CI	122.68 [3.51, 241.86]
11 Apgar score < 7 at five minutes	2	267	Relative Risk (Fixed) 95% CI	0.57 [0.21, 1.52]
12 Admission to intensive care nursery	7	572	Relative Risk (Fixed) 95% CI	0.84 [0.71, 1.00]
13 Respiratory distress syndrome	7	552	Relative Risk (Fixed) 95% CI	0.64 [0.45, 0.91]
14 Neonatal jaundice	2	227	Relative Risk (Fixed) 95% CI	0.73 [0.57, 0.93]
15 Neonatal sepsis	3	289	Relative Risk (Fixed) 95% CI	0.75 [0.47, 1.19]
16 Necrotising enterocolitis	2	234	Relative Risk (Fixed) 95% CI	0.21 [0.04, 1.25]
17 Intraventricular haemorrhage	2	251	Relative Risk (Fixed) 95% CI	0.62 [0.37, 1.04]
18 Intraventricular haemorrhage grades three or four	2	251	Relative Risk (Fixed) 95% CI	0.63 [0.18, 2.16]
19 Retinopathy of prematurity	1	185	Relative Risk (Fixed) 95% CI	0.11 [0.01, 1.93]
20 Perinatal mortality	7	529	Relative Risk (Fixed) 95% CI	1.39 [0.60, 3.24]
21 Perinatal mortality excluding congenital abnormality	7	529	Relative Risk (Fixed) 95% CI	1.20 [0.49, 2.94]
22 Fetal death	7	529	Relative Risk (Fixed) 95% CI	3.00 [0.13, 71.07]
23 Fetal death excluding congenital abnormality	7	529	Relative Risk (Fixed) 95% CI	Not estimable
25 Neonatal death	8	592	Relative Risk (Fixed) 95% CI	1.40 [0.63, 3.12]
26 Neonatal death excluding congenital abnormality	7	529	Relative Risk (Fixed) 95% CI	1.20 [0.49, 2.94]

INDEX TERMS

Medical Subject Headings (MeSH)

Calcium Channel Blockers [*therapeutic use]; Obstetric Labor, Premature [*prevention & control]; Randomized Controlled Trials; Tocolytic Agents [*therapeutic use]

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Calcium channel blockers for inhibiting preterm labour
Authors	King JF, Flenady VJ, Papatsonis DNM, Dekker GA, Carbonne B
Contribution of author(s)	James King, Vicki Flenady and Dimitri Papatsonis undertook independent quality assessments, data extraction, resolved differences by discussion and assembled the review. All authors assisted with the interpretation and final editing.
Issue protocol first published	2000/3
Review first published	2002/2
Date of most recent amendment	17 November 2004
Date of most recent SUBSTANTIVE amendment	20 September 2002
What's New	This review updates the review 'Calcium channel blockers for inhibiting preterm labour ' which was first published in the Cochrane Library Issue 2, 2002. This update includes published and unpublished data from one additional trial (Weerakul 2002) and unpublished information from the author of one previously included trial (Larmon 1999). The review now contains twelve trials which enrolled 1029 women. The extra data included in this review result in a marginal decrease in the previously demonstrated effect on the outcome of birth within 48 hours of commencement of treatment (no longer statistically significant) but show a reduction (which reached statistical significance) in the outcome of birth prior to 34 weeks associated with the use of calcium channel blockers. These additional data strengthen the beneficial effect of calcium channel blockers on several neonatal outcomes. The conclusions of the earlier version of the review remain basically unchanged. Calcium channel blockers are a safer and more effective tocolytic agent than betamimetics for mothers and babies.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	01 October 2002
Date new studies found and included/excluded	30 June 2002
Date authors' conclusions section amended	Information not supplied by author
Contact address	A/Prof James F King Consultant in Perinatal Epidemiology Department of Perinatal Medicine Royal Women's Hospital Carlton Victoria 3053 AUSTRALIA E-mail: james.king@rwh.org.au Tel: +61 3 93442607 Fax: +61 3 93471761
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Editorial group code	HM-PREG

GRAPHS AND OTHER TABLES

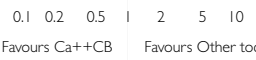
Analysis 01.01. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 01 Birth prior to 37 weeks gestation

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

Outcome: 01 Birth prior to 37 weeks gestation

Study	Ca++ CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ferguson 1990	24/33	19/33		12.2	1.26 [0.88, 1.81]
Garcia-Velasco 1998	4/26	3/26		1.9	1.33 [0.33, 5.38]
Glock 1993	23/39	24/41		15.0	1.01 [0.70, 1.45]
Jannet 1997	4/43	12/43		7.7	0.33 [0.12, 0.95]
Papatsonis 1997	66/95	72/90		47.5	0.87 [0.73, 1.03]
Weerakul 2002	28/45	24/44		15.6	1.14 [0.80, 1.62]
Total (95% CI)	281	277		100.0	0.95 [0.83, 1.09]
Total events: 149 (Ca++ CB), 154 (Other tocolytic)					
Test for heterogeneity chi-square=8.68 df=5 p=0.12 I^2 =42.4%					
Test for overall effect z=0.77 p=0.4					



Analysis 01.02. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 02 Birth prior to 34 weeks gestation

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

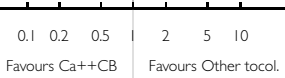
Outcome: 02 Birth prior to 34 weeks gestation

Study	Ca++ CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Glock 1993	15/39	13/41		10.1	1.21 [0.67, 2.21]
Jannet 1997	1/43	2/43		1.6	0.50 [0.05, 5.31]
Koks 1998	19/32	16/25		14.4	0.93 [0.62, 1.40]
Larmon 1999	5/57	8/65		6.0	0.71 [0.25, 2.06]
Papatsonis 1997	53/95	66/90		54.2	0.76 [0.61, 0.95]
Weerakul 2002	14/45	17/44		13.7	0.81 [0.45, 1.43]
Total (95% CI)	311	308		100.0	0.83 [0.69, 0.99]

Total events: 107 (Ca++ CB), 122 (Other tocolytic)

Test for heterogeneity chi-square=2.70 df=5 p=0.75 I^2 =0.0%

Test for overall effect z=2.03 p=0.04



Analysis 01.03. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 03 Birth within seven days of treatment

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

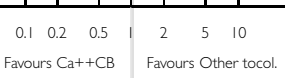
Outcome: 03 Birth within seven days of treatment

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Koks 1998	19/32	13/25		16.4	1.14 [0.71, 1.83]
Larmon 1999	2/57	6/65		6.3	0.38 [0.08, 1.81]
Papatsonis 1997	36/95	52/90		60.2	0.66 [0.48, 0.90]
Weerakul 2002	14/45	15/44		17.1	0.91 [0.50, 1.66]
Total (95% CI)	229	224		100.0	0.76 [0.60, 0.97]

Total events: 71 (Ca++CB), 86 (Other tocolytic)

Test for heterogeneity chi-square=4.80 df=3 p=0.19 I^2 =37.5%

Test for overall effect z=2.23 p=0.03



Analysis 01.04. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 04 Birth within 48 hours of treatment

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

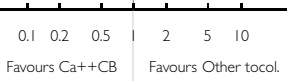
Outcome: 04 Birth within 48 hours of treatment

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ferguson 1990	6/33	10/33		11.3	0.60 [0.25, 1.46]
Garcia-Velasco 1998	3/26	2/26		2.3	1.50 [0.27, 8.25]
Glock 1993	3/39	3/41		3.3	1.05 [0.23, 4.90]
Koks 1998	15/32	6/24		7.7	1.88 [0.86, 4.11]
Kupferminc 1993	6/36	9/35		10.3	0.65 [0.26, 1.63]
Larmon 1999	2/57	3/65		3.2	0.76 [0.13, 4.39]
Papatsonis 1997	21/95	33/90		38.2	0.60 [0.38, 0.96]
Read 1986	4/20	11/20		12.4	0.36 [0.14, 0.95]
Weerakul 2002	14/45	10/44		11.4	1.37 [0.68, 2.75]
Total (95% CI)	383	378		100.0	0.80 [0.61, 1.05]

Total events: 74 (Ca++CB), 87 (Other tocolytic)

Test for heterogeneity chi-square=12.05 df=8 p=0.15 I^2 =33.6%

Test for overall effect z=1.59 p=0.1



Analysis 01.05. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 05 Pregnancy prolongation (days)

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

Outcome: 05 Pregnancy prolongation (days)

Study	Ca++CB N	Ca++CB Mean(SD)	Other tocolytic N	Other tocolytic Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Bracero 1991	23	28.00 (21.00)	19	21.00 (21.00)		8.7	7.00 [-5.76, 19.76]
Garcia-Velasco 1998	26	43.70 (21.58)	26	64.00 (36.80)		5.3	-20.30 [-36.70, -3.90]
Janky 1990	30	42.00 (21.90)	32	35.00 (15.61)		15.6	7.00 [-2.52, 16.52]
Larmon 1999	57	34.93 (25.90)	65	34.65 (22.40)		18.9	0.28 [-8.37, 8.93]
Papatsonis 1997	95	32.20 (23.80)	90	18.90 (22.40)		32.0	13.30 [6.64, 19.96]
Read 1986	20	36.30 (22.80)	20	25.10 (25.49)		6.3	11.20 [-3.79, 26.19]
Weerakul 2002	45	27.53 (24.14)	44	27.04 (25.68)		13.2	0.49 [-9.87, 10.85]
Total (95% CI)	296		296			100.0	5.71 [1.95, 9.47]

Test for heterogeneity chi-square=17.77 df=6 p=0.007 I^2 =66.2%

Test for overall effect z=2.97 p=0.003

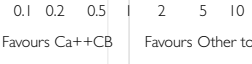
Analysis 01.06. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 06 Maternal adverse drug reaction

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

Outcome: 06 Maternal adverse drug reaction

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bracero 1991	4/26	12/23		7.2	0.29 [0.11, 0.79]
Ferguson 1990	5/33	18/33		10.2	0.28 [0.12, 0.66]
Glock 1993	5/39	13/41		7.2	0.40 [0.16, 1.03]
Jannet 1997	15/43	17/43		9.7	0.88 [0.51, 1.53]
Larmon 1999	5/57	16/65		8.5	0.36 [0.14, 0.91]
Papatsonis 1997	18/95	45/90		26.3	0.38 [0.24, 0.60]
Read 1986	2/20	13/20		7.4	0.15 [0.04, 0.60]
Weerakul 2002	2/45	41/44		23.6	0.05 [0.01, 0.19]
Total (95% CI)	358	359		100.0	0.32 [0.24, 0.41]



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Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Total events: 56 (Ca++CB), 175 (Other tocolytic)					
Test for heterogeneity chi-square=22.89 df=7 p=0.002 I^2 =69.4%					
Test for overall effect z=8.50 p<0.00001					

Analysis 01.07. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 07 Maternal drug reaction requiring cessation of treatment

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

Outcome: 07 Maternal drug reaction requiring cessation of treatment

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bracero 1991	0/26	2/23		8.0	0.18 [0.01, 3.52]
Ferguson 1990	0/33	4/33		13.7	0.11 [0.01, 1.98]
Garcia-Velasco 1998	0/26	1/26		4.6	0.33 [0.01, 7.82]
Glock 1993	0/39	4/41		13.3	0.12 [0.01, 2.10]
× Janky 1990	0/30	0/32		0.0	Not estimable
× Koks 1998	0/32	0/25		0.0	Not estimable
× Kupferminc 1993	0/36	0/35		0.0	Not estimable
Larmon 1999	1/57	0/65		1.4	3.41 [0.14, 82.18]
Papatsonis 1997	0/95	12/90		39.0	0.04 [0.00, 0.63]
Weerakul 2002	0/45	6/44		20.0	0.08 [0.00, 1.30]
Total (95% CI)	419	414		100.0	0.14 [0.05, 0.36]
Total events: 1 (Ca++CB), 29 (Other tocolytic)					
Test for heterogeneity chi-square=5.25 df=6 p=0.51 I^2 =0.0%					
Test for overall effect z=4.02 p=0.00006					

Analysis 01.08. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 08 Duration of maternal hospital stay (days)

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

Outcome: 08 Duration of maternal hospital stay (days)

Study	Ca++CB		Other tocolytic		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Garcia-Velasco 1998	26	3.87 (2.60)	26	3.69 (1.80)		100.0	0.18 [-1.04, 1.40]
Total (95% CI)	26		26			100.0	0.18 [-1.04, 1.40]
Test for heterogeneity: not applicable							
Test for overall effect z=0.29 p=0.8							

Analysis 01.09. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 09 Gestation at birth (completed weeks)

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

Outcome: 09 Gestation at birth (completed weeks)

Study	Ca++CB		Other tocolytic		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Bracero 1991	23	36.00 (3.00)	19	35.00 (4.00)		5.3	1.00 [-1.18, 3.18]
Jannet 1997	43	38.40 (1.70)	43	37.60 (2.10)		38.8	0.80 [-0.01, 1.61]
Koks 1998	35	32.50 (4.40)	28	32.90 (3.70)		6.3	-0.40 [-2.40, 1.60]
Larmon 1999	57	35.60 (3.70)	65	35.50 (3.20)		16.6	0.10 [-1.14, 1.34]
Papatsonis 1997	95	33.40 (4.50)	90	32.10 (4.10)		16.5	1.30 [0.06, 2.54]
Weerakul 2002	45	35.67 (2.90)	44	34.89 (3.07)		16.4	0.78 [-0.46, 2.02]
Total (95% CI)	298		289			100.0	0.70 [0.19, 1.20]
Test for heterogeneity chi-square=3.11 df=5 p=0.68 I^2 =0.0%							
Test for overall effect z=2.72 p=0.007							

Analysis 01.10. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 10 Birthweight (grams)

Review: Calcium channel blockers for inhibiting preterm labour

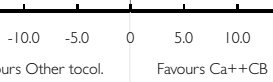
Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

Outcome: 10 Birthweight (grams)

Study	Ca++CB N	Ca++CB Mean(SD)	Other tocolytic N	Other tocolytic Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Garcia-Velasco 1998	26	2654.28 (943.72)	26	3100.00 (694.38)		4.4	-445.72 [-896.08, 4.64]
Glock 1993	39	2434.00 (716.00)	41	2508.00 (693.00)		9.4	-74.00 [-383.02, 235.02]
Jannet 1997	43	3131.00 (488.00)	43	3019.00 (494.00)		20.8	112.00 [-95.55, 319.55]
Koks 1998	35	1963.00 (844.00)	28	1935.00 (744.00)		5.8	28.00 [-364.59, 420.59]
Larmon 1999	57	2449.00 (729.00)	65	2475.00 (636.00)		15.0	-26.00 [-270.38, 218.38]
Papatsonis 1997	95	2120.00 (920.00)	90	1875.00 (707.00)		16.1	245.00 [9.29, 480.71]
Read 1986	20	3225.00 (432.00)	20	3020.00 (326.00)		15.9	205.00 [-32.19, 442.19]
Weerakul 2002	45	2649.78 (587.09)	44	2508.18 (683.67)		12.7	141.60 [-123.41, 406.61]
Total (95% CI)	360		357			100.0	84.42 [-10.13, 178.97]

Test for heterogeneity chi-square=10.22 df=7 p=0.18 I^2 =31.5%

Test for overall effect z=1.75 p=0.08



Analysis 01.11. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 11 Apgar score < 7 at five minutes

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

Outcome: 11 Apgar score < 7 at five minutes

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kupferminc 1993	2/42	2/40		15.7	0.95 [0.14, 6.44]
Larmon 1999	4/57	3/65		21.5	1.52 [0.36, 6.51]
Papatsonis 1997	4/95	8/90		62.9	0.47 [0.15, 1.52]
× Weerakul 2002	0/45	0/44		0.0	Not estimable
Total (95% CI)	239	239		100.0	0.77 [0.35, 1.71]

Total events: 10 (Ca++CB), 13 (Other tocolytic)

Test for heterogeneity chi-square=1.56 df=2 p=0.46 I^2 =0.0%

Test for overall effect z=0.63 p=0.5

Analysis 01.12. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 12 Admission to intensive care nursery

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

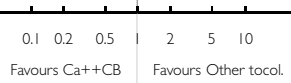
Outcome: 12 Admission to intensive care nursery

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bracero 1991	6/23	11/19		9.5	0.45 [0.20, 0.99]
Garcia-Velasco 1998	3/26	2/26		1.6	1.50 [0.27, 8.25]
× Janky 1990	0/30	0/32		0.0	Not estimable
Jannet 1997	5/43	7/43		5.5	0.71 [0.25, 2.08]
Koks 1998	16/35	10/28		8.8	1.28 [0.69, 2.37]
Kupferminc 1993	12/42	15/40		12.1	0.76 [0.41, 1.42]
Larmon 1999	15/57	11/65		8.1	1.56 [0.78, 3.11]
Papatsonis 1997	47/95	59/78		51.2	0.65 [0.51, 0.83]
Weerakul 2002	1/45	4/44		3.2	0.24 [0.03, 2.10]
Total (95% CI)	396	375		100.0	0.78 [0.64, 0.95]

Total events: 105 (Ca++CB), 119 (Other tocolytic)

Test for heterogeneity chi-square=11.97 df=7 p=0.10 I^2 =41.5%

Test for overall effect z=2.49 p=0.01



Analysis 01.13. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 13 Respiratory distress syndrome

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

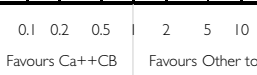
Outcome: 13 Respiratory distress syndrome

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bracero 1991	1/23	5/19		7.4	0.17 [0.02, 1.30]
Ferguson 1990	4/33	4/33		5.4	1.00 [0.27, 3.67]
Garcia-Velasco 1998	3/26	3/26		4.1	1.00 [0.22, 4.50]
× Janky 1990	0/30	0/32		0.0	Not estimable
Koks 1998	9/35	6/28		9.0	1.20 [0.49, 2.97]
Kupferminc 1993	4/42	8/40		11.1	0.48 [0.16, 1.46]
Larmon 1999	5/57	9/65		11.4	0.63 [0.23, 1.78]
Papatsonis 1997	20/95	33/90		46.0	0.57 [0.36, 0.92]
Weerakul 2002	2/45	4/44		5.5	0.49 [0.09, 2.53]
Total (95% CI)	386	377		100.0	0.63 [0.46, 0.88]

Total events: 48 (Ca++CB), 72 (Other tocolytic)

Test for heterogeneity chi-square=4.89 df=7 p=0.67 I^2 =0.0%

Test for overall effect z=2.74 p=0.006



Analysis 01.14. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 14 Neonatal jaundice

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

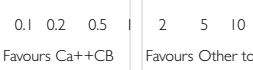
Outcome: 14 Neonatal jaundice

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bracero 1991	2/23	6/19		9.6	0.28 [0.06, 1.21]
Papatsonis 1997	49/95	60/90		90.4	0.77 [0.61, 0.99]
Total (95% CI)	118	109		100.0	0.73 [0.57, 0.93]

Total events: 51 (Ca++CB), 66 (Other tocolytic)

Test for heterogeneity chi-square=1.91 df=1 p=0.17 I^2 =47.7%

Test for overall effect z=2.58 p=0.01



Analysis 01.15. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 15 Neonatal sepsis

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

Outcome: 15 Neonatal sepsis

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bracero 1991	0/23	2/19		8.0	0.17 [0.01, 3.27]
Janky 1990	5/30	4/32		11.3	1.33 [0.39, 4.50]
Papatsonis 1997	19/95	25/90		74.9	0.72 [0.43, 1.21]
Weerakul 2002	1/45	2/44		5.9	0.49 [0.05, 5.20]
Total (95% CI)	193	185		100.0	0.73 [0.46, 1.16]
Total events: 25 (Ca++CB), 33 (Other tocolytic)					
Test for heterogeneity chi-square=2.00 df=3 p=0.57 I^2 =0.0%					
Test for overall effect z=1.33 p=0.2					

Analysis 01.16. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 16 Necrotising enterocolitis

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

Outcome: 16 Necrotising enterocolitis

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bracero 1991	0/26	1/23		17.2	0.30 [0.01, 6.94]
Papatsonis 1997	1/95	5/90		55.5	0.19 [0.02, 1.59]
Weerakul 2002	0/45	2/44		27.3	0.20 [0.01, 3.96]
Total (95% CI)	166	157		100.0	0.21 [0.05, 0.96]
Total events: 1 (Ca++CB), 8 (Other tocolytic)					
Test for heterogeneity chi-square=0.06 df=2 p=0.97 I^2 =0.0%					
Test for overall effect z=2.02 p=0.04					

Analysis 01.17. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 17 Intraventricular haemorrhage

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

Outcome: 17 Intraventricular haemorrhage

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ferguson 1990	2/33	1/33		3.1	2.00 [0.19, 21.00]
Papatsonis 1997	17/95	28/90		89.1	0.58 [0.34, 0.98]
Weerakul 2002	0/45	2/44		7.8	0.20 [0.01, 3.96]
Total (95% CI)	173	167		100.0	0.59 [0.36, 0.98]

Total events: 19 (Ca++CB), 31 (Other tocolytic)

Test for heterogeneity chi-square=1.56 df=2 p=0.46 I^2 =0.0%

Test for overall effect z=2.06 p=0.04

Analysis 01.18. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 18 Intraventricular haemorrhage grades three or four

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

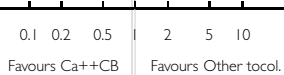
Outcome: 18 Intraventricular haemorrhage grades three or four

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Ferguson 1990	0/33	0/33		0.0	Not estimable
Papatsonis 1997	4/95	6/90		70.9	0.63 [0.18, 2.16]
Weerakul 2002	0/45	2/44		29.1	0.20 [0.01, 3.96]
Total (95% CI)	173	167		100.0	0.50 [0.16, 1.55]

Total events: 4 (Ca++CB), 8 (Other tocolytic)

Test for heterogeneity chi-square=0.51 df=1 p=0.48 I^2 =0.0%

Test for overall effect z=1.20 p=0.2



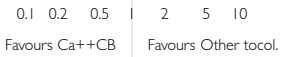
Analysis 01.19. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 19 Retinopathy of prematurity

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

Outcome: 19 Retinopathy of prematurity

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Papatsonis 1997	0/95	4/90		100.0	0.11 [0.01, 1.93]
Total (95% CI)	95	90		100.0	0.11 [0.01, 1.93]
Total events: 0 (Ca++CB), 4 (Other tocolytic)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.52 p=0.1					



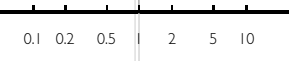
Analysis 01.20. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 20 Perinatal mortality

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

Outcome: 20 Perinatal mortality

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bracero 1991	1/23	0/19		6.0	2.50 [0.11, 58.06]
Ferguson 1990	3/33	0/33		5.5	7.00 [0.38, 130.41]
× Garcia-Velasco 1998	0/26	0/26		0.0	Not estimable
Glock 1993	2/29	0/41		4.5	7.00 [0.35, 140.60]
× Janky 1990	0/30	0/32		0.0	Not estimable
Kupferminc 1993	0/42	1/40		16.8	0.32 [0.01, 7.58]
× Larmon 1999	0/57	0/65		0.0	Not estimable
Papatsonis 1997	7/95	6/90		67.3	1.11 [0.39, 3.16]
× Read 1986	0/20	0/20		0.0	Not estimable
× Weerakul 2002	0/45	0/44		0.0	Not estimable
Total (95% CI)	400	410		100.0	1.65 [0.74, 3.64]
Total events: 13 (Ca++CB), 7 (Other tocolytic)					
Test for heterogeneity chi-square=3.49 df=4 p=0.48 I^2 =0.0%					
Test for overall effect z=1.23 p=0.2					



Analysis 01.21. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 21 Perinatal mortality excluding congenital abnormality

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

Outcome: 21 Perinatal mortality excluding congenital abnormality

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Bracero 1991	0/23	0/19		0.0	Not estimable
Ferguson 1990	2/33	0/33		5.8	5.00 [0.25, 100.32]
× Garcia-Velasco 1998	0/26	0/26		0.0	Not estimable
Glock 1993	2/39	0/41		5.6	5.25 [0.26, 106.01]
× Janky 1990	0/30	0/32		0.0	Not estimable
Kupferminc 1993	0/42	1/40		17.7	0.32 [0.01, 7.58]
× Larmon 1999	0/57	0/65		0.0	Not estimable
Papatsonis 1997	7/95	6/90		70.9	1.11 [0.39, 3.16]
× Read 1986	0/20	0/20		0.0	Not estimable
× Weerakul 2002	0/45	0/44		0.0	Not estimable
Total (95% CI)	410	410		100.0	1.42 [0.61, 3.31]

Total events: 11 (Ca++CB), 7 (Other tocolytic)

Test for heterogeneity chi-square=2.48 df=3 p=0.48 I^2 =0.0%

Test for overall effect z=0.82 p=0.4

Analysis 01.22. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 22 Fetal death

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

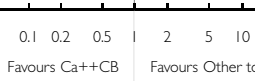
Outcome: 22 Fetal death

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Bracero 1991	0/23	0/19		0.0	Not estimable
Ferguson 1990	1/33	0/33		100.0	3.00 [0.13, 71.07]
× Garcia-Velasco 1998	0/26	0/26		0.0	Not estimable
× Glock 1993	0/39	0/41		0.0	Not estimable
× Janky 1990	0/30	0/32		0.0	Not estimable
× Kupferminc 1993	0/42	0/40		0.0	Not estimable
× Larmon 1999	0/57	0/65		0.0	Not estimable
× Papatsonis 1997	0/95	0/90		0.0	Not estimable
× Read 1986	0/20	0/20		0.0	Not estimable
× Weerakul 2002	0/45	0/44		0.0	Not estimable
Total (95% CI)	410	410		100.0	3.00 [0.13, 71.07]

Total events: 1 (Ca++CB), 0 (Other tocolytic)

Test for heterogeneity: not applicable

Test for overall effect z=0.68 p=0.5



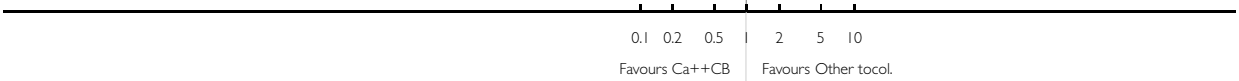
Analysis 01.23. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 23 Fetal death excluding congenital abnormality

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

Outcome: 23 Fetal death excluding congenital abnormality

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Bracero 1991	0/23	0/19		0.0	Not estimable
× Ferguson 1990	0/33	0/33		0.0	Not estimable
× Garcia-Velasco 1998	0/26	0/26		0.0	Not estimable
× Glock 1993	0/39	0/41		0.0	Not estimable
× Janky 1990	0/30	0/32		0.0	Not estimable
× Kupferminc 1993	0/42	0/40		0.0	Not estimable
× Larmon 1999	0/57	0/65		0.0	Not estimable
× Papatsonis 1997	0/95	0/90		0.0	Not estimable
× Read 1986	0/20	0/20		0.0	Not estimable
× Weerakul 2002	0/45	0/44		0.0	Not estimable
Total (95% CI)	410	410		0.0	Not estimable
Total events: 0 (Ca++CB), 0 (Other tocolytic)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 01.24. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 24 Neonatal death

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

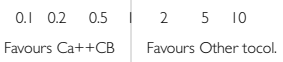
Outcome: 24 Neonatal death

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bracero 1991	1/23	0/19		5.3	2.50 [0.11, 58.06]
Ferguson 1990	2/33	0/33		4.8	5.00 [0.25, 100.32]
× Garcia-Velasco 1998	0/26	0/26		0.0	Not estimable
Glock 1993	2/39	0/41		4.7	5.25 [0.26, 106.01]
× Janky 1990	0/30	0/32		0.0	Not estimable
Koks 1998	3/35	1/28		10.7	2.40 [0.26, 21.83]
Kupferminc 1993	0/42	1/40		14.8	0.32 [0.01, 7.58]
× Larmon 1999	0/57	0/65		0.0	Not estimable
Papatsonis 1997	7/95	6/90		59.6	1.11 [0.39, 3.16]
× Read 1986	0/20	0/20		0.0	Not estimable
× Weerakul 2002	0/45	0/44		0.0	Not estimable
Total (95% CI)	445	438		100.0	1.58 [0.74, 3.39]

Total events: 15 (Ca++CB), 8 (Other tocolytic)

Test for heterogeneity chi-square=2.83 df=5 p=0.73 I^2 =0.0%

Test for overall effect z=1.19 p=0.2



Analysis 01.25. Comparison 01 Any calcium channel blocker compared with any other tocolytic agent, Outcome 25 Neonatal death excluding congenital abnormality

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 01 Any calcium channel blocker compared with any other tocolytic agent

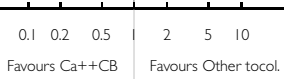
Outcome: 25 Neonatal death excluding congenital abnormality

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Bracero 1991	0/23	0/19		0.0	Not estimable
Ferguson 1990	2/33	0/33		5.8	5.00 [0.25, 100.32]
× Garcia-Velasco 1998	0/26	0/26		0.0	Not estimable
Glock 1993	2/39	0/41		5.6	5.25 [0.26, 106.01]
× Janky 1990	0/30	0/32		0.0	Not estimable
Kupferminc 1993	0/42	1/40		17.7	0.32 [0.01, 7.58]
× Larmon 1999	0/57	0/65		0.0	Not estimable
Papatsonis 1997	7/95	6/90		70.9	1.11 [0.39, 3.16]
× Read 1986	0/20	0/20		0.0	Not estimable
× Weerakul 2002	0/45	0/44		0.0	Not estimable
Total (95% CI)	410	410		100.0	1.42 [0.61, 3.31]

Total events: 11 (Ca++CB), 7 (Other tocolytic)

Test for heterogeneity chi-square=2.48 df=3 p=0.48 I^2 =0.0%

Test for overall effect z=0.82 p=0.4



Analysis 02.01. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 01 Birth prior to 37 weeks gestation

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 01 Birth prior to 37 weeks gestation

Study	Ca++ CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ferguson 1990	24/33	19/33		17.6	1.26 [0.88, 1.81]
Garcia-Velasco 1998	4/26	3/26		2.8	1.33 [0.33, 5.38]
Jannet 1997	4/43	12/43		11.1	0.33 [0.12, 0.95]
Papatsonis 1997	66/95	72/90		68.5	0.87 [0.73, 1.03]
Total (95% CI)	197	192		100.0	0.89 [0.76, 1.05]

Total events: 98 (Ca++ CB), 106 (Other tocolytic)

Test for heterogeneity chi-square=7.39 df=3 p=0.06 I^2 =59.4%

Test for overall effect z=1.40 p=0.2

Analysis 02.02. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 02 Birth prior to 34 weeks gestation

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

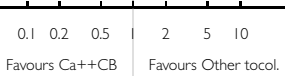
Outcome: 02 Birth prior to 34 weeks gestation

Study	Ca++ CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Jannet 1997	1/43	2/43		2.3	0.50 [0.05, 5.31]
Koks 1998	19/32	16/25		20.5	0.93 [0.62, 1.40]
Papatsonis 1997	53/95	66/90		77.2	0.76 [0.61, 0.95]
Total (95% CI)	170	158		100.0	0.79 [0.65, 0.96]

Total events: 73 (Ca++ CB), 84 (Other tocolytic)

Test for heterogeneity chi-square=0.85 df=2 p=0.65 I^2 =0.0%

Test for overall effect z=2.40 p=0.02



Analysis 02.03. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 03 Birth within seven days of treatment

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 03 Birth within seven days of treatment

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Koks 1998	19/32	13/25		21.5	1.14 [0.71, 1.83]
Papatsonis 1997	36/95	52/90		78.5	0.66 [0.48, 0.90]
Total (95% CI)	127	115		100.0	0.76 [0.59, 0.99]

Total events: 55 (Ca++CB), 65 (Other tocolytic)

Test for heterogeneity chi-square=3.70 df=1 p=0.05 I^2 =73.0%

Test for overall effect z=2.07 p=0.04

Analysis 02.04. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 04 Birth within 48 hours of treatment

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 04 Birth within 48 hours of treatment

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ferguson 1990	6/33	10/33		13.7	0.60 [0.25, 1.46]
Garcia-Velasco 1998	3/26	2/26		2.7	1.50 [0.27, 8.25]
Koks 1998	15/32	6/24		9.4	1.88 [0.86, 4.11]
Kupferminc 1993	6/36	9/35		12.5	0.65 [0.26, 1.63]
Papatsonis 1997	21/95	33/90		46.5	0.60 [0.38, 0.96]
Read 1986	4/20	11/20		15.1	0.36 [0.14, 0.95]
Total (95% CI)	242	228		100.0	0.72 [0.53, 0.97]

Total events: 55 (Ca++CB), 71 (Other tocolytic)

Test for heterogeneity chi-square=9.13 df=5 p=0.10 I^2 =45.2%

Test for overall effect z=2.14 p=0.03

Analysis 02.05. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 05 Pregnancy prolongation (days)

Review: Calcium channel blockers for inhibiting preterm labour

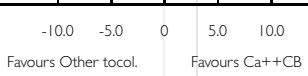
Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 05 Pregnancy prolongation (days)

Study	Ca++CB N	Ca++CB Mean(SD)	Other tocolytic N	Other tocolytic Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Bracero 1991	23	28.00 (21.00)	19	21.00 (21.00)		12.8	7.00 [-5.76, 19.76]
Garcia-Velasco 1998	26	43.70 (21.58)	26	64.00 (36.80)		7.8	-20.30 [-36.70, -3.90]
Janky 1990	30	42.00 (21.90)	32	35.00 (15.61)		23.0	7.00 [-2.52, 16.52]
Papatsonis 1997	95	32.20 (23.80)	90	18.90 (22.40)		47.1	13.30 [6.64, 19.96]
Read 1986	20	36.30 (22.80)	20	25.10 (25.68)		9.2	11.20 [-3.85, 26.25]
Total (95% CI)	194		187			100.0	8.24 [3.67, 12.81]

Test for heterogeneity chi-square=14.11 df=4 p=0.007 I^2 =71.6%

Test for overall effect z=3.53 p=0.0004



Analysis 02.06. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 06 Maternal adverse drug reaction

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 06 Maternal adverse drug reaction

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bracero 1991	4/26	12/23		11.9	0.29 [0.11, 0.79]
Ferguson 1990	5/33	18/33		16.8	0.28 [0.12, 0.66]
Jannet 1997	15/43	17/43		15.9	0.88 [0.51, 1.53]
Papatsonis 1997	18/95	45/90		43.2	0.38 [0.24, 0.60]
Read 1986	2/20	13/20		12.2	0.15 [0.04, 0.60]
Total (95% CI)	217	209		100.0	0.40 [0.30, 0.55]
Total events: 44 (Ca++CB), 105 (Other tocolytic)					
Test for heterogeneity chi-square=10.86 df=4 p=0.03 I^2 =63.2%					
Test for overall effect z=5.94 p<0.00001					

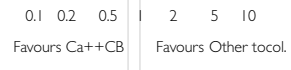
Analysis 02.07. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 07 Maternal drug reaction requiring cessation of treatment

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 07 Maternal drug reaction requiring cessation of treatment

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bracero 1991	0/26	2/23		12.3	0.18 [0.01, 3.52]
Ferguson 1990	0/33	4/33		20.9	0.11 [0.01, 1.98]
Garcia-Velasco 1998	0/26	1/26		7.0	0.33 [0.01, 7.82]
× Janky 1990	0/30	0/32		0.0	Not estimable
× Koks 1998	0/32	0/25		0.0	Not estimable
× Kupferminc 1993	0/36	0/35		0.0	Not estimable
Papatsonis 1997	0/95	12/90		59.7	0.04 [0.00, 0.63]
Total (95% CI)	278	264		100.0	0.09 [0.02, 0.38]
Total events: 0 (Ca++CB), 19 (Other tocolytic)					
Test for heterogeneity chi-square=1.23 df=3 p=0.75 I^2 =0.0%					
Test for overall effect z=3.27 p=0.001					



Analysis 02.08. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 08 Duration of maternal hospital stay (days)

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 08 Duration of maternal hospital stay (days)

Study	Ca++CB		Other tocolytic		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Garcia-Velasco 1998	26	3.87 (2.60)	26	3.69 (1.80)		100.0	0.18 [-1.04, 1.40]
Total (95% CI)	26		26			100.0	0.18 [-1.04, 1.40]
Test for heterogeneity: not applicable							
Test for overall effect z=0.29 p=0.8							

Analysis 02.09. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 09 Gestation at birth (completed weeks)

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 09 Gestation at birth (completed weeks)

Study	Ca++CB		Other tocolytic		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
Bracero 1991	23	36.00 (3.00)	19	35.00 (4.00)		8.0	1.00 [-1.18, 3.18]
Jannet 1997	43	38.40 (1.70)	43	37.60 (2.10)		58.0	0.80 [-0.01, 1.61]
Koks 1998	35	32.50 (4.40)	28	32.90 (3.70)		9.4	-0.40 [-2.40, 1.60]
Papatsonis 1997	95	33.40 (4.50)	90	32.10 (4.10)		24.6	1.30 [0.06, 2.54]
Total (95% CI)	196		180			100.0	0.83 [0.21, 1.44]
Test for heterogeneity chi-square=2.03 df=3 p=0.57 I^2 =0.0%							
Test for overall effect z=2.63 p=0.008							

Analysis 02.10. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 10 Birthweight (grams)

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 10 Birthweight (grams)

Study	Ca++CB N	Ca++CB Mean(SD)	Other tocolytic N	Other tocolytic Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Garcia-Velasco 1998	26	2654.28 (943.72)	26	3100.00 (694.38)		7.0	-445.72 [-896.08, 4.64]
Jannet 1997	43	3131.00 (488.00)	43	3019.00 (494.00)		33.0	112.00 [-95.55, 319.55]
Koks 1998	35	1963.00 (844.00)	28	1935.00 (744.00)		9.2	28.00 [-364.59, 420.59]
Papatsonis 1997	95	2120.00 (920.00)	90	1875.00 (707.00)		25.6	245.00 [9.29, 480.71]
Read 1986	20	3225.00 (432.00)	20	3020.00 (326.00)		25.2	205.00 [-32.19, 442.19]
Total (95% CI)	219		207			100.0	122.68 [3.51, 241.86]

Test for heterogeneity chi-square=7.85 df=4 p=0.10 I^2 =49.0%

Test for overall effect z=2.02 p=0.04

Analysis 02.11. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 11 Apgar score < 7 at five minutes

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 11 Apgar score < 7 at five minutes

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Kupferminc 1993	2/42	2/40		20.0	0.95 [0.14, 6.44]
Papatsonis 1997	4/95	8/90		80.0	0.47 [0.15, 1.52]
Total (95% CI)	137	130		100.0	0.57 [0.21, 1.52]

Total events: 6 (Ca++CB), 10 (Other tocolytic)

Test for heterogeneity chi-square=0.37 df=1 p=0.54 I^2 =0.0%

Test for overall effect z=1.12 p=0.3

Analysis 02.12. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 12 Admission to intensive care nursery

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

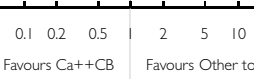
Outcome: 12 Admission to intensive care nursery

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bracero 1991	6/23	11/19		9.9	0.45 [0.20, 0.99]
Garcia-Velasco 1998	3/26	2/26		1.6	1.50 [0.27, 8.25]
× Janky 1990	0/30	0/32		0.0	Not estimable
Jannet 1997	5/43	7/43		5.8	0.71 [0.25, 2.08]
Koks 1998	16/35	10/28		9.1	1.28 [0.69, 2.37]
Kupferminc 1993	12/42	15/40		12.6	0.76 [0.41, 1.42]
Papatsonis 1997	65/95	72/90		60.9	0.86 [0.72, 1.02]
Total (95% CI)	294	278		100.0	0.84 [0.71, 1.00]

Total events: 107 (Ca++CB), 117 (Other tocolytic)

Test for heterogeneity chi-square=4.86 df=5 p=0.43 I^2 =0.0%

Test for overall effect z=1.93 p=0.05



Analysis 02.13. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 13 Respiratory distress syndrome

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

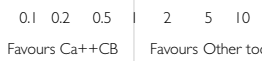
Outcome: 13 Respiratory distress syndrome

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bracero 1991	1/23	5/19		8.9	0.17 [0.02, 1.30]
Ferguson 1990	4/33	4/33		6.5	1.00 [0.27, 3.67]
Garcia-Velasco 1998	3/26	3/26		4.9	1.00 [0.22, 4.50]
× Janky 1990	0/30	0/32		0.0	Not estimable
Koks 1998	9/35	6/28		10.9	1.20 [0.49, 2.97]
Kupferminc 1993	4/42	8/40		13.4	0.48 [0.16, 1.46]
Papatsonis 1997	20/95	33/90		55.4	0.57 [0.36, 0.92]
Total (95% CI)	284	268		100.0	0.64 [0.45, 0.91]

Total events: 41 (Ca++CB), 59 (Other tocolytic)

Test for heterogeneity chi-square=4.77 df=5 p=0.44 I^2 =0.0%

Test for overall effect z=2.46 p=0.01



Analysis 02.14. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 14 Neonatal jaundice

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

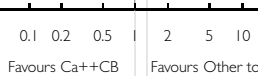
Outcome: 14 Neonatal jaundice

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bracero 1991	2/23	6/19		9.6	0.28 [0.06, 1.21]
Papatsonis 1997	49/95	60/90		90.4	0.77 [0.61, 0.99]
Total (95% CI)	118	109		100.0	0.73 [0.57, 0.93]

Total events: 51 (Ca++CB), 66 (Other tocolytic)

Test for heterogeneity chi-square=1.91 df=1 p=0.17 I^2 =47.7%

Test for overall effect z=2.58 p=0.01



Analysis 02.15. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 15 Neonatal sepsis

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 15 Neonatal sepsis

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bracero 1991	0/23	2/19		8.5	0.17 [0.01, 3.27]
Janky 1990	5/30	4/32		12.0	1.33 [0.39, 4.50]
Papatsonis 1997	19/95	25/90		79.6	0.72 [0.43, 1.21]
Total (95% CI)	148	141		100.0	0.75 [0.47, 1.19]
Total events: 24 (Ca++CB), 31 (Other tocolytic)					
Test for heterogeneity chi-square=1.87 df=2 p=0.39 I^2 =0.0%					
Test for overall effect z=1.22 p=0.2					

Analysis 02.16. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 16 Necrotising enterocolitis

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 16 Necrotising enterocolitis

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bracero 1991	0/26	1/23		23.6	0.30 [0.01, 6.94]
Papatsonis 1997	1/95	5/90		76.4	0.19 [0.02, 1.59]
Total (95% CI)	121	113		100.0	0.21 [0.04, 1.25]
Total events: 1 (Ca++CB), 6 (Other tocolytic)					
Test for heterogeneity chi-square=0.05 df=1 p=0.82 I^2 =0.0%					
Test for overall effect z=1.71 p=0.09					

Analysis 02.17. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 17 Intraventricular haemorrhage

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 17 Intraventricular haemorrhage

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Ferguson 1990	2/33	1/33		3.4	2.00 [0.19, 21.00]
Papatsonis 1997	17/95	28/90		96.6	0.58 [0.34, 0.98]
Total (95% CI)	128	123		100.0	0.62 [0.37, 1.04]
Total events: 19 (Ca++CB), 29 (Other tocolytic)					
Test for heterogeneity chi-square=1.03 df=1 p=0.31 I^2 =3.2%					
Test for overall effect z=1.81 p=0.07					

Analysis 02.18. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 18 Intraventricular haemorrhage grades three or four

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 18 Intraventricular haemorrhage grades three or four

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Ferguson 1990	0/33	0/33		0.0	Not estimable
Papatsonis 1997	4/95	6/90		100.0	0.63 [0.18, 2.16]
Total (95% CI)	128	123		100.0	0.63 [0.18, 2.16]
Total events: 4 (Ca++CB), 6 (Other tocolytic)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.73 p=0.5					

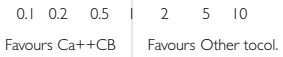
Analysis 02.19. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 19 Retinopathy of prematurity

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 19 Retinopathy of prematurity

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Papatsonis 1997	0/95	4/90		100.0	0.11 [0.01, 1.93]
Total (95% CI)	95	90		100.0	0.11 [0.01, 1.93]
Total events: 0 (Ca++CB), 4 (Other tocolytic)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.52 p=0.1					



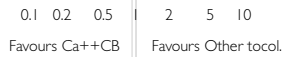
Analysis 02.20. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 20 Perinatal mortality

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 20 Perinatal mortality

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bracero 1991	1/23	0/19		6.2	2.50 [0.11, 58.06]
Ferguson 1990	3/33	0/33		5.7	7.00 [0.38, 130.41]
× Garcia-Velasco 1998	0/26	0/26		0.0	Not estimable
× Janky 1990	0/30	0/32		0.0	Not estimable
Kupferminc 1993	0/42	1/40		17.6	0.32 [0.01, 7.58]
Papatsonis 1997	7/95	6/90		70.5	1.11 [0.39, 3.16]
× Read 1986	0/20	0/20		0.0	Not estimable
Total (95% CI)	269	260		100.0	1.39 [0.60, 3.24]
Total events: 11 (Ca++CB), 7 (Other tocolytic)					
Test for heterogeneity chi-square=2.32 df=3 p=0.51 I^2 =0.0%					
Test for overall effect z=0.76 p=0.4					



Analysis 02.21. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 21 Perinatal mortality excluding congenital abnormality

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

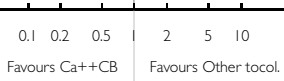
Outcome: 21 Perinatal mortality excluding congenital abnormality

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Bracero 1991	0/23	0/19		0.0	Not estimable
Ferguson 1990	2/33	0/33		6.1	5.00 [0.25, 100.32]
× Garcia-Velasco 1998	0/26	0/26		0.0	Not estimable
× Janky 1990	0/30	0/32		0.0	Not estimable
Kupferminc 1993	0/42	1/40		18.7	0.32 [0.01, 7.58]
Papatsonis 1997	7/95	6/90		75.2	1.11 [0.39, 3.16]
× Read 1986	0/20	0/20		0.0	Not estimable
Total (95% CI)	269	260		100.0	1.20 [0.49, 2.94]

Total events: 9 (Ca++CB), 7 (Other tocolytic)

Test for heterogeneity chi-square=1.57 df=2 p=0.46 I^2 =0.0%

Test for overall effect z=0.39 p=0.7



Analysis 02.22. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 22 Fetal death

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 22 Fetal death

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Bracero 1991	0/23	0/19		0.0	Not estimable
Ferguson 1990	1/33	0/33		100.0	3.00 [0.13, 71.07]
× Garcia-Velasco 1998	0/26	0/26		0.0	Not estimable
× Janky 1990	0/30	0/32		0.0	Not estimable
× Kupferminc 1993	0/42	0/40		0.0	Not estimable
× Papatsonis 1997	0/95	0/90		0.0	Not estimable
× Read 1986	0/20	0/20		0.0	Not estimable
Total (95% CI)	269	260		100.0	3.00 [0.13, 71.07]

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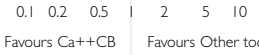
Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Total events: 1 (Ca++CB), 0 (Other tocolytic)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.68 p=0.5					



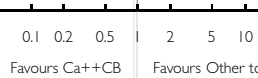
Analysis 02.23. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 23 Fetal death excluding congenital abnormality

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 23 Fetal death excluding congenital abnormality

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Bracero 1991	0/23	0/19		0.0	Not estimable
× Ferguson 1990	0/33	0/33		0.0	Not estimable
× Garcia-Velasco 1998	0/26	0/26		0.0	Not estimable
× Janky 1990	0/30	0/32		0.0	Not estimable
× Kupferminc 1993	0/42	0/40		0.0	Not estimable
× Papatsonis 1997	0/95	0/90		0.0	Not estimable
× Read 1986	0/20	0/20		0.0	Not estimable
Total (95% CI)	269	260		0.0	Not estimable
Total events: 0 (Ca++CB), 0 (Other tocolytic)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 02.25. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 25 Neonatal death

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 25 Neonatal death

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Bracero 1991	1/23	0/19		5.5	2.50 [0.11, 58.06]
Ferguson 1990	2/33	0/33		5.1	5.00 [0.25, 100.32]
× Garcia-Velasco 1998	0/26	0/26		0.0	Not estimable
× Janky 1990	0/30	0/32		0.0	Not estimable
Koks 1998	3/35	1/28		11.3	2.40 [0.26, 21.83]
Kupferminc 1993	0/42	1/40		15.6	0.32 [0.01, 7.58]
Papatsonis 1997	7/95	6/90		62.5	1.11 [0.39, 3.16]
× Read 1986	0/20	0/20		0.0	Not estimable
Total (95% CI)	304	288		100.0	1.40 [0.63, 3.12]

Total events: 13 (Ca++CB), 8 (Other tocolytic)

Test for heterogeneity chi-square=2.09 df=4 p=0.72 I^2 =0.0%

Test for overall effect z=0.83 p=0.4

Analysis 02.26. Comparison 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent, Outcome 26 Neonatal death excluding congenital abnormality

Review: Calcium channel blockers for inhibiting preterm labour

Comparison: 02 Any dihydropyridine calcium channel blocker compared with any betamimetic agent

Outcome: 26 Neonatal death excluding congenital abnormality

Study	Ca++CB n/N	Other tocolytic n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
× Bracero 1991	0/23	0/19		0.0	Not estimable
Ferguson 1990	2/33	0/33		6.1	5.00 [0.25, 100.32]
× Garcia-Velasco 1998	0/26	0/26		0.0	Not estimable
× Janky 1990	0/30	0/32		0.0	Not estimable
Kupferminc 1993	0/42	1/40		18.7	0.32 [0.01, 7.58]
Papatsonis 1997	7/95	6/90		75.2	1.11 [0.39, 3.16]
× Read 1986	0/20	0/20		0.0	Not estimable
Total (95% CI)	269	260		100.0	1.20 [0.49, 2.94]

Total events: 9 (Ca++CB), 7 (Other tocolytic)

Test for heterogeneity chi-square=1.57 df=2 p=0.46 I^2 =0.0%

Test for overall effect z=0.39 p=0.7