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Comparative effectiveness and safety of nifedipine and magnesium sulfate as treatment options for preterm birth: a systematic review and meta-analysis

Jianing Fan , Qianqian Lu, Jie Chen, Pingping Lin, Chong Fan , Juan Lyv, Yuhan Zhang, Xinyan Wang

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JF and QL contributed equally.

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Women's Hospital of Nanjing Medical University, Nanjing Women and Children's Healthcare Hospital, Nanjing, Jiangsu, China

Correspondence to
Dr Xinyan Wang; maymay0512@njmu.edu.cn and Dr Yuhan Zhang; yuhanzhang123@outlook.com

ABSTRACT

Objectives Preterm birth (PTB) is a major cause of neonatal morbidity and mortality worldwide. Effective use of tocolytic agents may improve perinatal outcomes. This study aims to compare the effectiveness and safety of nifedipine and magnesium sulfate in the treatment of PTB.

Design A systematic review and meta-analysis.

Data sources China National Knowledge Infrastructure, China Science and Technology Journal Database, WanFang, PubMed, Embase, Web of Science and Cochrane were searched from inception to 1 December 2024.

Eligibility criteria We included randomised controlled trials (RCTs) and cohort studies that compare the efficacy and safety of magnesium sulfate versus nifedipine in treating PTB.

Data extraction and synthesis Two researchers independently screened studies and extracted data. Risk of bias was assessed using the Cochrane risk-of-bias assessment tool for RCTs and the modified Newcastle-Ottawa Scale for non-randomised studies. Meta-analysis was conducted using Review Manager V.5.4.

Results In all, 50 articles were included in this review, comprising 6072 cases (n=3014 for the magnesium sulfate group; n=3058 for the nifedipine group). Compared with the magnesium sulfate group, the nifedipine group was more favourable in terms of time to onset of action and prolongation of days of gestation, as well as higher neonatal 1 min Apgar scores. The use of magnesium sulfate was associated with a higher incidence of maternal side effects, specifically tachycardia, flushing, palpitations, dizziness and nausea. In addition, the magnesium sulfate group also showed a higher incidence of neonatal respiratory distress syndrome than the nifedipine group.

Conclusion Compared with magnesium sulfate, nifedipine is more effective with a faster onset of action and a longer prolonging pregnancy. Additionally, nifedipine may be safer for fewer maternal side effects and better neonatal outcomes. Further studies are needed to confirm the long-term safety and efficacy of these treatments.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The study conducted an extensive search across multiple databases without language restrictions, capturing a wide range of relevant studies.
⇒ Both maternal side effects and neonatal safety were evaluated, offering a comprehensive safety profile.
⇒ The inclusion of both randomised controlled trials and cohort studies enriched the data but may have introduced publication bias.
⇒ The included studies varied geographically, which could introduce discrepancies in the diagnostic criteria for preterm birth and treatment protocols.

INTRODUCTION

Preterm birth (PTB) refers to delivery before 37 weeks of gestation.[1] The estimated PTB rate worldwide in 2020 was expected to be 9.9%.[2] Complications associated with PTB include impaired health and growth, cognitive and psychological impairments, and early onset of chronic illnesses. They are the most prevalent cause of neonatal mortality and the primary contributor to death among children under the age of 5, accounting for 36.1% and 17.7%, respectively.[3] Additionally, the high cost of treating PTB poses a significant economic burden for families and societies.[4] Therefore, timely intervention and medication are critical for the prevention and management of PTB as they are essential in reducing maternal and neonatal mortality rates and related complications.

Tocolytics, including nifedipine and magnesium sulfate, are commonly used to prolong gestational age of pregnancy after the diagnosis of PTB clinically.[5] This provides an opportunity for women with imminent PTB to receive corticosteroids and magnesium sulfate, which can improve neonatal outcomes and protect fetal neurodevelopment.[6]

Nifedipine, a calcium channel blocker, has been shown to reduce the likelihood of delivery within 7 days of treatment initiation and before 34 weeks of gestation, and may also reduce adverse neonatal outcomes.[7] However, separate research found that while nifedipine may extend gestation for 48 hours

or 7 days, it does not effectively prevent delivery prior to 37 weeks of gestation. Furthermore, there was no significant improvement in neonatal outcomes.[8] Magnesium sulfate is widely regarded as the preferred tocolytic agent by many obstetricians and perinatologists due to its positive effects on achieving uterine quiescence rapidly, especially at higher doses.[9] However, some researchers have questioned magnesium sulfate's effectiveness as a tocolytic agent and raised concerns about its potential association with fetal and neonatal deaths.[10] Nevertheless, magnesium sulfate remains a widely used tocolytic agent. According to recent research, the results do not establish significant correlations between prenatal magnesium sulfate and adverse neonatal outcomes.[11]

Despite the widespread use of nifedipine and magnesium sulfate in the management of PTB, there remains uncertainty regarding their relative effectiveness and safety. Although both agents have been studied with other tocolytic drugs, no comprehensive review has directly compared them in terms of the efficacy of treatment and maternal and neonatal outcomes. Therefore, this review is needed to clarify the benefits and risks of each treatment and provide guidance for clinical decision-making. By synthesising existing evidence, this study aims to offer comprehensive and valuable insights into the use of these tocolytic agents in the management of PTB and compare their effectiveness and safety in treating PTB, specifically in prolonging pregnancy and evaluating associated maternal and fetal outcomes.

METHODS

This systematic review and meta-analysis were conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[12] and the Meta-Analyses of Observational Studies in Epidemiology checklist.[13] The research project has been registered on the PROSPERO platform (registration number: CRD42023481966).

Literature search and selection criteria

We carried out an extensive search of the literature in multiple databases, including China National Knowledge Infrastructure, China Science and Technology Journal Database, WanFang, PubMed, Embase, Web of Science and Cochrane. The initial search was conducted from inception to May 2023, then was updated in December 2024 to include the most recent publications. No language restrictions were applied. The search aimed to identify relevant studies on women with PTB. The search terms used included "nifedipine", "cordipin", "procardia", "nifangin", "vascard", "Magnesium Sulfate", "Heptahydrate Magnesium Sulfate", "preterm labor", "Labor, Preterm", "Premature Labor" and "Obstetric Labor, Premature" The search strategies are shown in online supplemental table S1.

We included randomised controlled trials (RCTs) and cohort studies that met the following criteria: (1) the study population consisted of pregnant women diagnosed with PTB; (2) studies that compared magnesium sulfate with nifedipine as tocolytic agents; (3) studies that reported on the efficacy and safety profiles of both agents; (4) only RCTs and cohort studies were included; observational studies, conference articles, letters, reviews with insufficient data or lack of clear outcome reporting were excluded.

Data extraction

The initial screening of literature titles and abstracts, as well as the subsequent assessment of potential eligibility, was conducted independently by two reviewers (JF and QL). Duplicate publications were eliminated using EndNote software. Data extraction from each eligible study was performed using a standardised form. The data extracted encompassed various aspects of the study, such as the randomisation procedure, blinding methods for providers, patients and outcome assessors, exclusions and the method used for concealing allocation. Additionally, the details of the participants were included, such as the criteria for inclusion and exclusion, the definition of PTB, the gestational age at which the participants entered the trial and the total number of women involved. The specifics of the intervention were also documented, including the loading and maintenance dose, route of administration, duration of treatment, possibility of retreatment and use of alternative tocolytic therapy. Lastly, the outcome indicators were recorded as well. Any inconsistencies that emerged throughout the procedure were addressed through deliberation, and in the event of necessity, two additional (PL and JC) evaluators were consulted.

Quality evaluation and risk-of-bias assessment

The included literature in this analysis comprised RCTs or cohort studies. The risk of bias in cohort studies was evaluated using the modified Newcastle-Ottawa Scale (NOS), which is specifically designed to assess the quality of non-randomised studies based on three domains: study population selection, comparability and exposure (outcome).[14] The NOS assigns a maximum score of 9 points, with higher scores indicating a lower risk of bias and higher study quality, scores between 4 and 6 suggest moderate quality and scores below 3 indicate poor quality. A score of 7 or above is typically considered to indicate a study with high quality, while scores 4–6 suggest a moderate quality and <3 indicate poor quality. For the RCTs, the Cochrane risk-of-bias assessment tool was employed to evaluate potential bias.[15] This tool assesses various domains, including selection, performance, detection, attrition, reporting and other bias. Risk of bias for each domain was categorised as low, high or unclear.

Statistical analysis

Data analysis was executed using Review Manager (RevMan) V.5.4 (The Nordic Cochrane Centre, Copenhagen, Denmark). For the presentation of quantitative

data from individual studies, we used summary relative risk (RR) for dichotomous data and mean difference (MD) for continuous data, along with their corresponding 95% CIs.

Heterogeneity of the results among studies was tested with the quantity I^2 values, with $I^2 \geq 50\%$ considered to indicate significant heterogeneity. Summary estimates were computed using random-effects models. If no substantial statistical heterogeneity was found, data were combined using fixed-effects models.

Outcomes

The outcomes were treatment efficacy, including time to drug onset, whether prolongation of gestational age was more than 48 hours or 7 days, prolongation age of pregnancy; maternal adverse effects, including tachycardia, hypotension, flushing, palpitations, dizziness, nausea, headache, gastrointestinal upset; and neonatal safety profiles, such as birth weight; neonatal pneumonia; neonatal sepsis; necrotising enterocolitis (NEC); intraventricular haemorrhage (IVH); respiratory distress syndrome (RDS) and Apgar score.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

Study selection

The findings from the search strategy, including sources of identified studies, exclusion process and final inclusion, are presented in figure 1. In total, 1163 records were obtained from the computerised database search, with 267 of them being recognised as duplicates. After reviewing the titles and abstracts, 683 papers were excluded, resulting in 213 studies that underwent a secondary screening for eligibility. The final analysis included 52 studies.[16–67]

Study characteristics

The comprehensive attributes of the studies that were incorporated in the analysis are listed in online supplemental table S2 . Out of the included studies, 14 (27%) were retrospective cohort studies, while 38 (73%) were RCTs. Among these studies, 39 (75%) were conducted in China, 5 (10%) in the USA, 5 (10%) in Iran and the remaining 3 were conducted in Pakistan, India and Israel. The gestational age at study entry ranged from 20 to 37 weeks, and sample sizes varied between 20 and 400, with a total of 6072 participants. Participants' ages ranged from 18 to 45 years. Magnesium sulfate was commonly delivered via an initial intravenous bolus followed by continuous infusion, while nifedipine was given an oral dose followed by maintenance therapy. Diagnostic criteria for PTB typically involved uterine contractions and cervical changes (≥2 cm dilation or ≥50% effacement). Treatment efficacy was generally

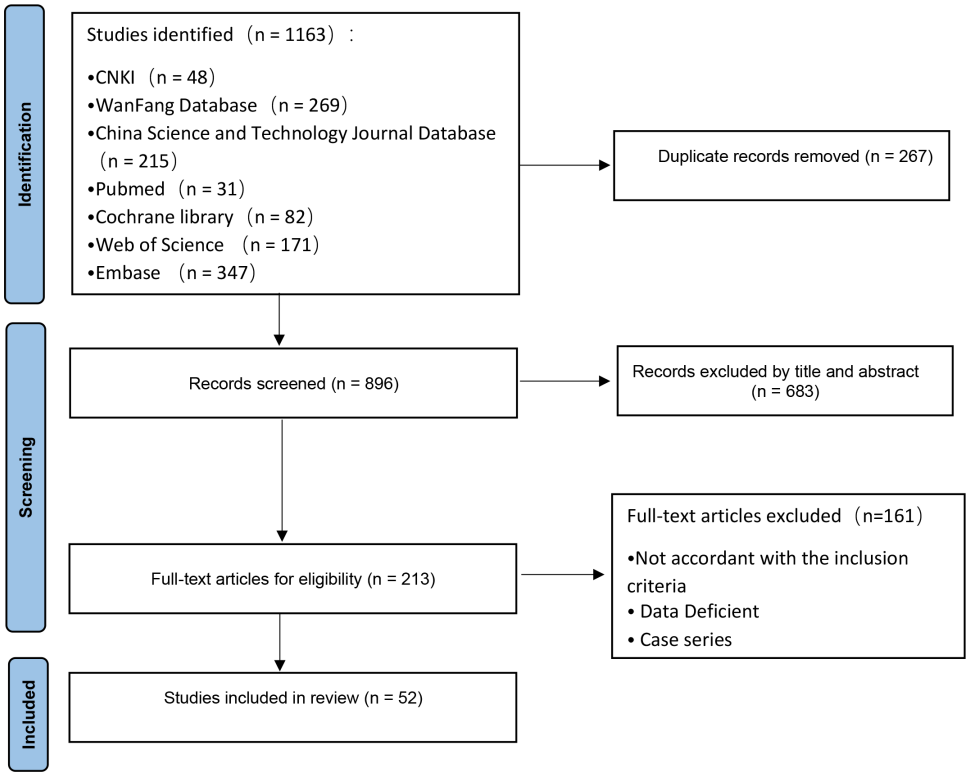

Figure 1 The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study screening and selection. CNKI, China National Knowledge Infrastructure.

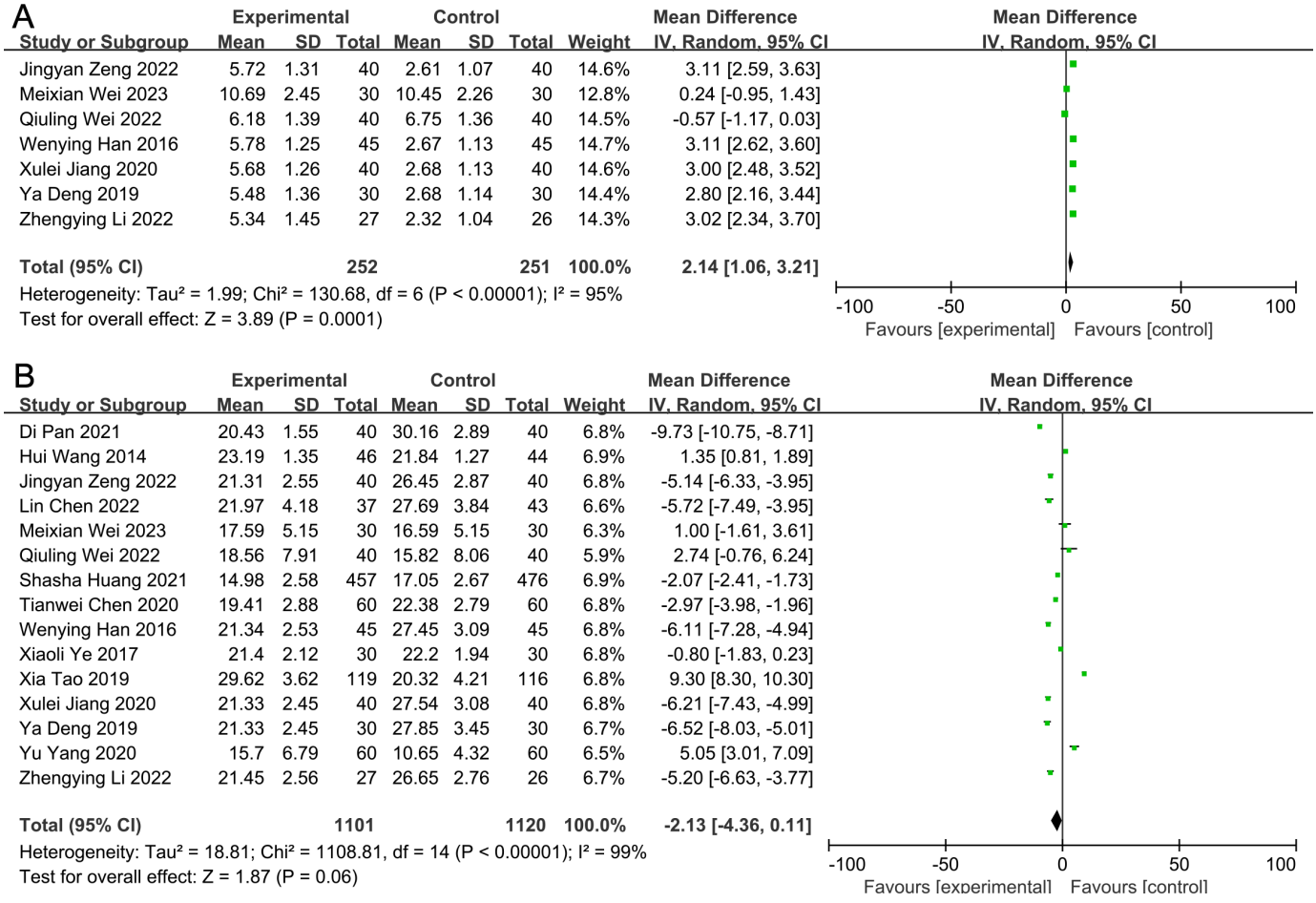

Figure 2 Forest plots showing the (A)mean difference for the onset time of drugs and (B) risk ratios for the days of prolonged pregnancy. IV, inverse-variance test.

reported as successful in prolonging pregnancy by 48 hours or 7 days or more.

Study quality

The risk-of-bias assessment for the 38 included RCTs is detailed in online supplemental figure S1, with most studies having a low risk for randomisation but higher risks for allocation concealment and blinding. For the 14 cohort studies, the NOS quality assessment scores ranged from 6 to 8, with strong selection methods but some weaknesses in exposure assessment and follow-up, as detailed in online supplemental Table S3. Overall, most studies were of moderate to high quality, though certain biases need cautious interpretation.

Meta-analysis results

The onset time of drugs was longer in the magnesium sulfate group compared with the nifedipine group (MD 2.14; 95% CI 1.06 to 3.21; p<0.0001), with considerable heterogeneity among the seven included studies (I^2 = 95%) (figure 2A).[21 23 29–31 51 67] Based on 20 papers (I^2=49%),[17 27 36 40 41 43 45 46 48–51 53–56 59 61 62 65] no significant difference was observed in the number of individuals with pregnancy prolongation of 48 hours or more between the magnesium sulfate and nifedipine groups (RR 0.99; 95% CI 0.95 to 1.04; p=0.66) (figure 3). This finding also applied to the number of people with a prolongation of pregnancy for 7 days or more (RR 0.94; 95% CI 0.84 to 1.05; p=0.28) among 13 included studies (I^2=0%) (figure 3).[36 40 42 43 45 46 48–51 53 54 62] The days of prolonged pregnancy were shorter in the magnesium sulfate group compared with the nifedipine group (MD −2.13, 95% CI −4.36 to 0.11, p=0.06) (figure 2B), with significant heterogeneity observed among the 15 included papers (I^2=99%).[17 19–21 23 27–31 37 42 47 51 67]

The administration of nifedipine was observed to be correlated with a notable decrease in maternal side effects. The most notable result to emerge from 30 studies[16 17 19 21 24–27 29–34 37–39 42 44 47 48 51 52 54 57 59 61 63 64 66] indicated that women in the magnesium sulfate group were more likely to experience side effects compared with those in the nifedipine group. This difference was statistically significant with regard to tachycardia (RR 1.9; 95% CI 1.14 to 2.51; p=0.009), hypotension (RR 0.60; 95% CI 0.38 to 0.95; p=0.03), flushing (RR 3.84; 95% CI 2.63 to 5.61; p<0.00001), palpitation (RR 3.16; 95% CI 1.57 to 6.38; p=0.001), dizziness (RR 3.41; 95% CI 1.82 to 6.38; p=0.0001) and nausea (RR 4.73; 95% CI 2.49 to 8.98; p<0.00001). Nevertheless, there was no substantial difference in relation to headache (RR 0.83; 95% CI 0.85 to 1.11; p=0.22) and gastrointestinal distress (RR 2.57; 95% CI 0.61 to 10.77; p=0.20) (figure 4).

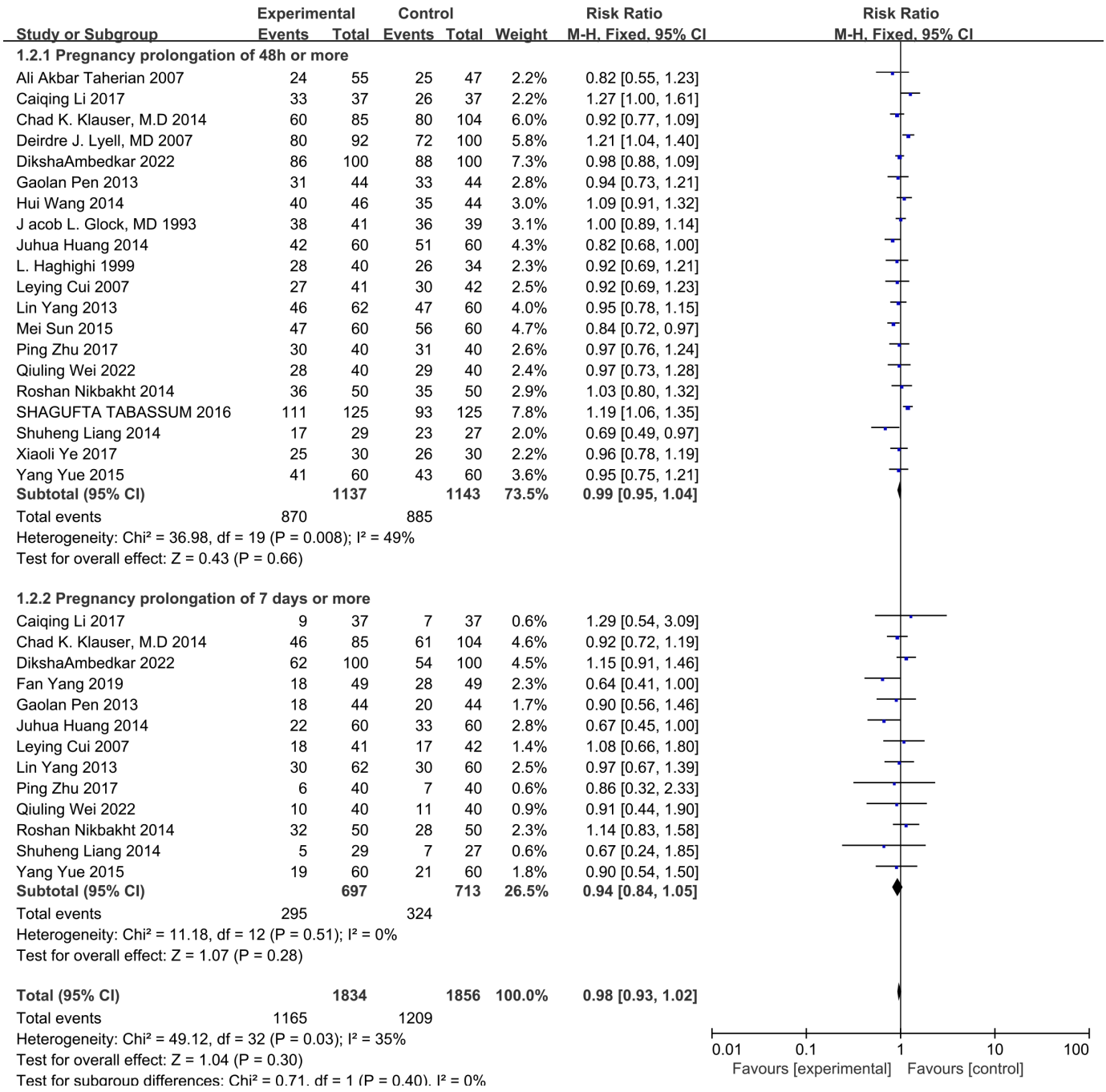

Figure 3 Forest plots showing the risk ratios for prolongation of pregnancy for more than 48 hours or 7 days. M-H, Mantel-Haenszel test.

Furthermore, our analysis using a random-effects model revealed that there was no statistically significant difference seen between the two groups regarding birth weight (MD −163.79; 95% CI −467.48 to 139.91, p=0.27) (online supplemental figure S2). The group administered with magnesium sulfate exhibited a statistically significant decrease in Apgar score at 1 min compared with the group treated with nifedipine (MD −0.54; 95% CI −0.83 to −0.25, p=0.0002) (figure 5A). The administration of magnesium sulfate was found to be correlated with a heightened susceptibility to a higher risk of RDS (RR 1.73; 95% CI 1.24 to 2.41, p=0.001) (figure 5B). There were no statistically significant differences observed between the group administered with magnesium sulfate and nifedipine in relation to neonatal pneumonia, neonatal sepsis, NEC, IVH, Apgar score 5 min (figure 5B and online supplemental figure S3).

DISCUSSION

Magnesium, a calcium antagonist, affects uterine contractility by inhibiting extracellular calcium influx and intracellular calcium release, thereby reducing both spontaneous and induced myometrial contractions.[68] Besides

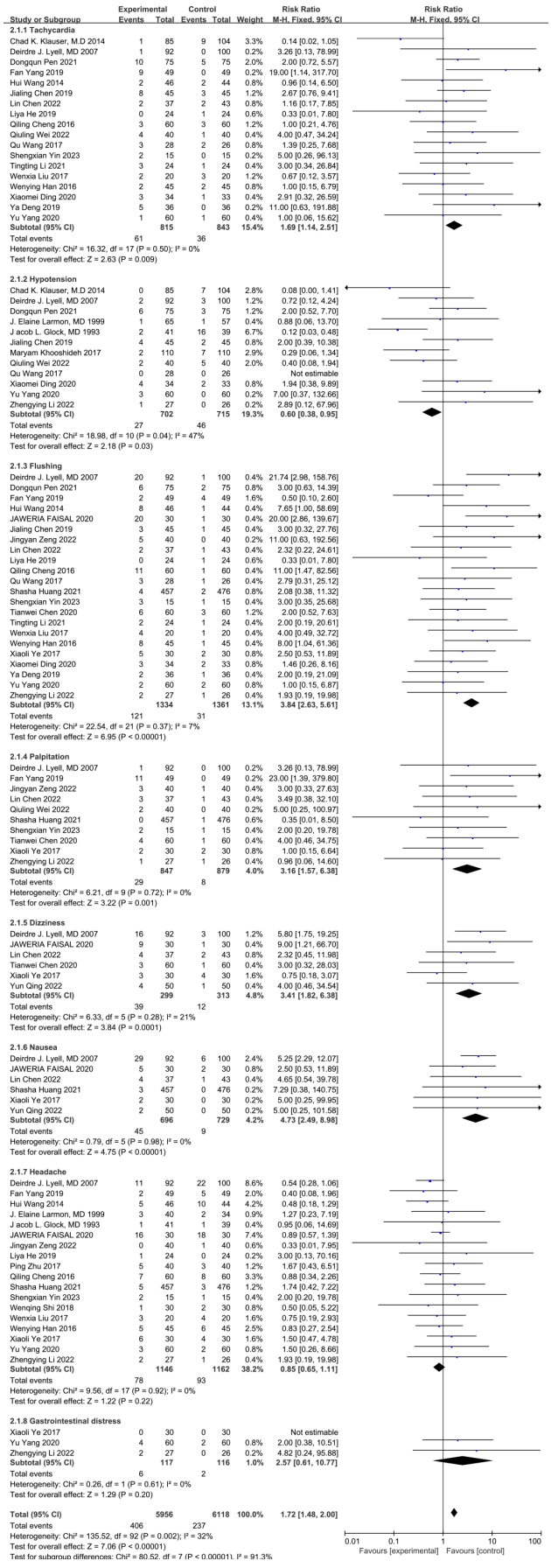

Figure 4 Forest plots showing the risk ratios for maternal side effects. M-H, Mantel-Haenszel test.

its neuroprotective effect on the fetus, magnesium sulfate is commonly used as a tocolytic agent for PTB in obstetric practice. As indicated by a 2008 questionnaire of American obstetricians-gynaecologists, the drug is frequently used due to its favourable adverse outcome profile.[69] Nevertheless, it is crucial to note that administration of magnesium sulfate during tocolytic therapy can lead to significant hypocalcaemia.[70] Furthermore, overdose of magnesium sulfate can result in respiratory depression and subsequent arrest due to its narrow therapeutic and toxic dose range.[71] Currently, most international guidelines recommend nifedipine as the first-line tocolytic agent for PTB.[72] Nifedipine is believed to inhibit myometrial contractions through the inhibition of voltage-dependent L-type calcium channels, leading to reduced intracellular calcium availability. Moreover, nifedipine is clinically used to improve circulation and treat hypertension and other cardiovascular diseases.[73] However, nifedipine can cause cardiac depression in healthy adults due to its inotropic and chronotropic effects, resulting from the inhibition of extracellular calcium influx.[74] Severe maternal side effects have been documented in preterm pregnant women receiving nifedipine for tocolysis, including acute pulmonary oedema, myocardial infarction, atrial fibrillation and profound hypotension.[75 76] One study suggested that short-term nifedipine administration significantly increases fetal middle cerebral artery and maternal uterine artery blood flow when used to treat PTB.[77]

Unlike magnesium, which exerts its effect through a more indirect mechanism, nifedipine acts directly by blocking calcium channels and altering their structure. This difference may explain why magnesium sulfate has a longer onset time but shorter duration of efficacy compared with nifedipine in PTB cases. It is important to note that magnesium can cross the placental barrier and be transmitted to the fetus, leading to a high correlation between maternal serum and umbilical cord magnesium levels, with a nearly 1:1 ratio.[78] This might explain why the administration of magnesium sulfate is correlated with a heightened incidence of RDS compared with nifedipine. High doses of magnesium can inhibit the respiratory centre, resulting in respiratory depression. Therefore, there exists a potential for magnesium sulfate to have a pronounced depressive impact on the neonatal muscular tone and respiratory function of neonates, which is associated with antenatal exposure to magnesium sulfate. Previous research has demonstrated a correlation between antenatal exposure to magnesium sulfate and NICU admission among preterm infants in a dose-dependent manner.[79]

Either magnesium sulfate or nifedipine can be employed as tocolytic agents to transiently extend the duration of pregnancy, hence allowing for the use of neuroprotective therapies such as corticosteroids. Prolonging pregnancy helps further develop and mature fetal organs and systems, reducing the risk of neonatal mortality and long-term health problems.[4] However, tocolytics alone cannot

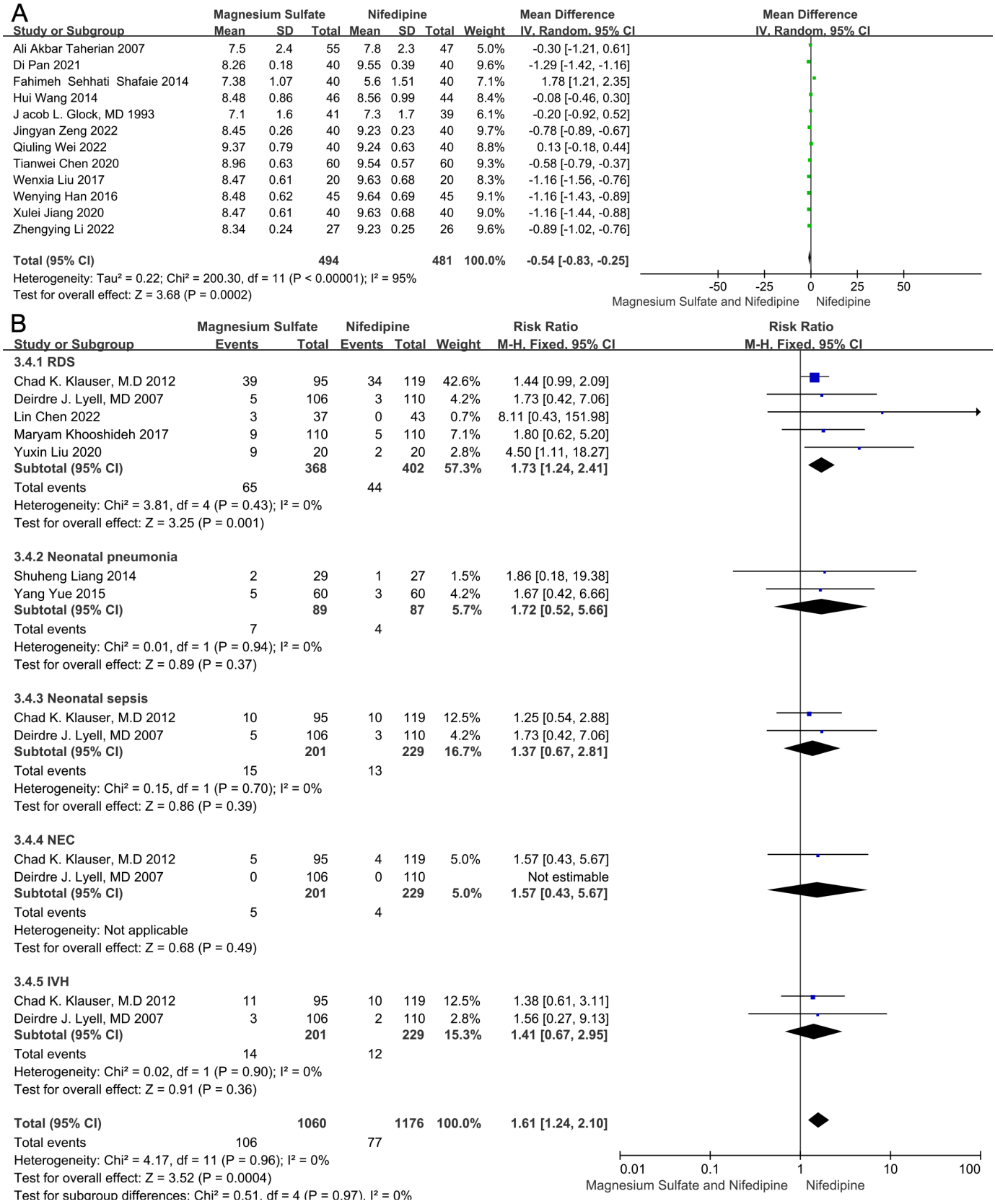

Figure 5 Forest plots showing the (A) mean difference for 1 min Apgar score and (B) risk ratios for neonatal side effects. IV, inverse-variance test; M-H, Mantel-Haenszel test.

significantly prevent PTB or enhance perinatal outcomes. The available evidence is inadequate to establish any discernible distinction between magnesium maintenance therapy and placebo or alternative therapies in terms of their efficacy in preventing PTB.[80] Similarly, in individuals diagnosed with threatened PTB, the utilisation of nifedipine for maintenance did not yield a statistically significant decrease in adverse perinatal outcomes compared with the administration of placebo.[81] The results of our analysis indicated that there was no statistically significant distinction between magnesium sulfate and nifedipine on neonatal adverse outcomes. Nevertheless, it is important to acknowledge that the number of included studies was limited, and not all studies evaluated adverse neonatal outcomes. Therefore, our study had limited ability to detect differences in adverse neonatal outcomes, such as neonatal pneumonia, sepsis, NEC and IVH. Therefore, it cannot conclude that nifedipine is significantly superior to magnesium sulfate in terms of safety for the treatment of PTB.

Compared with magnesium sulfate alone, the combined therapy of magnesium sulfate and nifedipine has shown significant improvements in the success rate of fertility preservation and the prolongation of pregnancy. Therefore, there is potential to consider promoting this combination therapy in clinical practice.[82] However, it is crucial to acknowledge that the incidence of adverse effects on both maternal and fetal outcomes after combination therapy was not clarified in the available literature. Hence, it is recommended that future studies assess both the effectiveness and safety of combination therapy in contrast to the individual administration of each drug, which could focus on the efficacy and side effects of combination therapy compared with those after using the drug alone.

There are some limitations in our study, one being the geographical variability due to the inclusion of studies from multiple regions, which could explain discrepancies in the diagnostic criteria for PTB and treatment protocols. Moreover, not all of the included research were conducted in a blinded method, potentially impacting the assessment of patients' symptoms by medical staff. The lack of long-term follow-up on maternal and neonatal outcomes in the studies we included also limits the generalisability of our findings. Therefore, we recommend that future researchers undertake high-quality and large-scale clinical trials with comprehensive follow-up of maternal and neonatal outcomes to further assess the safety and effectiveness of nifedipine with magnesium sulfate in the treatment of PTB, as well as elucidate any disparities in neonatal outcomes between the two drugs.

CONCLUSIONS

Nifedipine demonstrates superior efficacy as a tocolytic agent compared with magnesium sulfate, with a rapid onset and extended period of gestation. However, no substantial difference was observed between magnesium sulfate and nifedipine in their ability to extend pregnancy for 48 hours or 7 days or longer. Furthermore, nifedipine has been shown to have a lower incidence of maternal side effects compared with magnesium sulfate. Regarding neonatal outcomes, magnesium sulfate is associated with a significantly higher risk of neonatal RDS and a lower Apgar score at 1 min compared with nifedipine. However, no significant differences were observed in other neonatal adverse effects. To provide more informed recommendations for the treatment of PTB, more future research is needed to evaluate the safety and effectiveness of these two tocolytic agents.

Contributors Data curation: JF, PL. Formal analysis: JC, QL. Investigation: PL. Methodology: JF, PL, QL. Software: JC, PL. Supervision: CF, JL. Writing—original draft: JF, YZ. Writing—review and editing: JF, PL, YZ, XW. All authors have read and agreed to the published version of the manuscript. CF acted as guarantor.

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Competing interests None declared.

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ORCID iDs

Jianing Fan http://orcid.org/0009-0000-5279-6993
Chong Fan http://orcid.org/0000-0001-6331-1832

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