Taiwanese Journal of Obstetrics & Gynecology 55 (2016) 399–404

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Progesterone and nifedipine for maintenance tocolysis after arrested preterm labor: A systematic review and meta-analysis of randomized controlled trial

Ming-Xia Ding [a], Xin Luo [a], Xue-Mei Zhang [a], Bing Bai [a], Ju-Xiang Sun [b], Hong-Bo Qi [a, *]

[a] Department of Obstetrics and Gynecology, First Affiliated Hospital of Chongqing Medical University, Chongqing, China
[b] Department of Obstetrics and Gynecology, Linyi People's Hospital, Linyi, China

ARTICLE INFO

Article history:
Accepted 30 July 2015

Keywords:
meta-analysis
nifedipine
progesterone
systematic review
tocolysis

ABSTRACT

Objective: No treatment is recommended for routine maintenance tocolysis after an arrested preterm birth. Our present study aimed to evaluate the effect of progesterone and nifedipine as maintenance tocolysis therapy after an arrested preterm birth.
Materials and Methods: For relevant studies, we systematically searched the literature in databases of PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) in the Cochrane Library. Only randomized controlled trials were included.
Results: Nine trials were included in our review. Nifedipine and progesterone were used for maintenance tocolysis. Compared to placebo treatment or no treatment, maintenance tocolysis with progesterone could significantly prolong the delivery gestational weeks [standard mean difference (SMD) 1.64; 95% confidence interval (CI), 1.21, 2.07; $p < 0.00001$], reduce the proportion of patients with delivery before 37 weeks (risk ratio 0.63; 95% CI, 0.47, 0.83; $p = 0.001$), and increase the birth weight (SMD 317.71; 95% CI, 174.89, 460.53; $p < 0.0001$). However, no such benefits were observed after maintenance tocolysis with nifedipine. Both nifedipine and progesterone had no significant influences on the following outcomes: neonatal intensive care unit stay, proportion of neonatal intensive care unit admission, neonatal mortality, and incidence of respiratory distress syndrome.
Conclusion: Our results with maintenance tocolysis with progesterone may be useful for patients who had an episode of threatened preterm labor successfully treated with acute tocolytic therapy.

Introduction

A common cause of neonatal morbidity and mortality is preterm birth. Nearly 75% of perinatal deaths occur in infants born before 37 weeks' gestation [1,2].

After arrested preterm labor with acute tocolysis, maintenance tocolysis should be continued with the goals of prolonging gestation and improving neonatal outcome. There are several reasons to consider maintenance tocolysis. First, perinatal morbidity and mortality are inversely related to gestational age [3], therefore delaying delivery may improve perinatal outcome. Second, after an episode of preterm labor, the stimulus for preterm labor may remain and the patient remains at increased risk for preterm delivery. Prostaglandins, which are increased with contractions, can upregulate oxytocin receptors and potentially increase the risk for preterm delivery [4].

However, the effectiveness of maintenance tocolysis is unclear. Our present study aimed to evaluate the effect of progesterone and nifedipine as the maintenance tocolysis therapy after arrested preterm birth.

Methods

Eligibility criteria

Randomized controlled trials that enrolled participants who had been in active preterm labor, as defined by contractions with cervical change, and had their preterm labor successfully arrested

* Corresponding author. Department of Obstetrics and Gynecology, First Affiliated Hospital of Chongqing Medical University, Youyi Road Number 1, Yuzhong District, Chongqing 400016, China.
E-mail address: cqqhb2012@126.com (H.-B. Qi).

http://dx.doi.org/10.1016/j.tjog.2015.07.005

were eligible for inclusion. Maintenance tocolysis with progesterone or nifedipine were administered.

The following outcomes were measured: delivery gestational weeks, pregnancy prolongation, and proportion of patients with delivery at <37 weeks, birth weight, proportion of neonatal intensive care unit admissions, neonatal mortality, and incidence of respiratory distress syndrome.

Literature search

Studies were identified by searching electronic databases and scanning the reference lists of the articles. This search was applied to PubMed (years 1980–2014), and adapted for Embase (years 1980–2014). Cochrane databases were also reviewed. The last search was performed on December 31, 2014.

Search strategy and study selection

Keywords combined with Medical Subject Headings (MESH) terms such as “nifedipine” and “progesterone” were used for the search. Eligibility assessment was performed independently in an unblended standardized manner by two reviewers. Disagreements between reviewers were resolved by consensus. One review author extracted the data from the included studies and the second author checked the extracted data. Information on the characteristics of a trial was extracted from each included trial.

Risk of bias in individual studies

The risk of bias assessment was performed independently by two investigators. Disagreements were resolved by discussion. The risk of bias was assessed, as described in the Cochrane handbook [5], by recording the methods used to generate the randomization schedule and conceal allocation; by whether blinding was implemented for participants, staff, and outcome assessment; by the proportion of patients who completed follow up; and by whether there was evidence of selective reporting of outcomes.

Statistics

The risk ratio (RR) with 95% confidence interval (CI) was calculated for dichotomous variables. For continuous outcomes, we pooled the study results using the standard mean difference (SMD). The SMD calculation requires a mean value and standard deviation for each group. Differences in the means were significant at $p < 0.05$. Heterogeneity between studies was assessed using the I^2 statistic with a cut-off value of $\geq$50%, and the χ^2 test with a $p < 0.10$ was used to define a significant degree of heterogeneity [6].

Results

Based on the search strategy (Figure 1), 10 trials were included in our study [7–16]. Of these, five trials evaluated the effect of nifedipine for maintenance tocolysis after arrested preterm labor, compared to a placebo treatment or no treatment [10,13–16]. Another four studies evaluated the effect of progesterone for maintenance tocolysis after arrested preterm labor, compared to placebo or no treatment [7–9,11]. The remaining trial evaluated the relative effect of progesterone versus as maintenance tocolysis after arrested preterm labor [12]. The main characteristics are presented in Table 1. Most included trials were of high or moderate methodological quality.

Meta-analysis

The items for delivery outcomes and neonatal outcomes reported in every trial were somewhat different. The outcomes that were mostly reported were therefore chosen for quantitative analyses.

Gestational weeks at delivery and pregnancy prolongation (in days)

The outcome of gestational weeks at delivery was reported in all included trials. The overall pooled results from the meta-analysis demonstrated that, compared to placebo or no treatment, maintenance tocolysis therapy with progesterone could significantly prolong the number of gestational weeks at delivery (SMD, 1.64; 95% CI, 1.21, 2.07; $p < 0.00001$; Figure 2A). In addition, progesterone was more effective than nifedipine in maintenance tocolysis therapy after arrested preterm birth (SMD, 2.60; 95% CI, 1.71, 3.49; $p < 0.00001$; Figure 2B). However, no significant benefit was observed after maintenance tocolysis therapy with nifedipine, compared to placebo or no treatment (SMD, 0.31; 95% CI, -0.60, 1.22; $p = 0.50$; Figure 2C).

The outcome of pregnancy prolongation was also reported in all included trials. Similar pooled results were obtained after meta-analyses, as shown in Figure 2. Patients in the progesterone group had a longer latency until delivery than patients in the placebo group (SMD, 11.05; 95% CI, 4.76, 17.33; $p = 0.0006$; Figure 3A) or patients in the nifedipine group (SMD, 23.50; 95% CI, 18.40, 28.60; $p < 0.00001$; Figure 3B). However, there was no significant difference between the nifedipine group and the placebo group (SMD, 2.21; 95% CI, -3.63, 8.05; $p = 0.46$; Figure 3C).

The proportion of patients with delivery at <37 weeks

The outcome of the proportion of patients with delivery at <37 weeks was reported in seven trials. The proportion of patients with delivery at <37 weeks was 41% in the progesterone group, 64% in the placebo/no treatment group, and 67% in the nifedipine group. Significantly fewer patients in the progesterone group delivered after 37 weeks, compared to the placebo or no treatment groups (RR, 0.63; 95% CI, 0.47, 0.83; $p = 0.001$; Figure 4A), and nifedipine group (RR, 0.43; 95% CI, 0.30, 0.62; $p < 0.00001$; Figure 4B). However, there was no difference between the nifedipine group and the placebo or no treatment group in the proportion of patients with delivery at <37 weeks (RR, 0.97; 95% CI, 0.87, 1.09; $p = 0.64$; Figure 4C).

Neonatal outcomes

The outcome of birth weight was reported in nine trials. The overall pooled results demonstrated that maintenance tocolysis therapy with progesterone could significantly improve birth weight, compared to placebo or no treatment. (SMD, 317.71; 95% CI, 174.89, 460.53; $p < 0.00001$; Figure 5A). However, there was no significant difference between the nifedipine group and the placebo group (SMD, 5.58; 95% CI, -103.28, 114.43; $p = 0.92$; Figure 5B).

The outcomes of the proportion of neonatal intensive care unit admissions, neonatal intensive care unit stay, mortality rate, and incidence of respiratory distress syndrome were not significantly different, based on the comparison of progesterone versus placebo or no treatment, and the comparison of nifedipine versus placebo or no treatment.

Discussion

Our present meta-analysis systematically reviewed maintenance tocolysis therapy with progesterone and nifedipine after

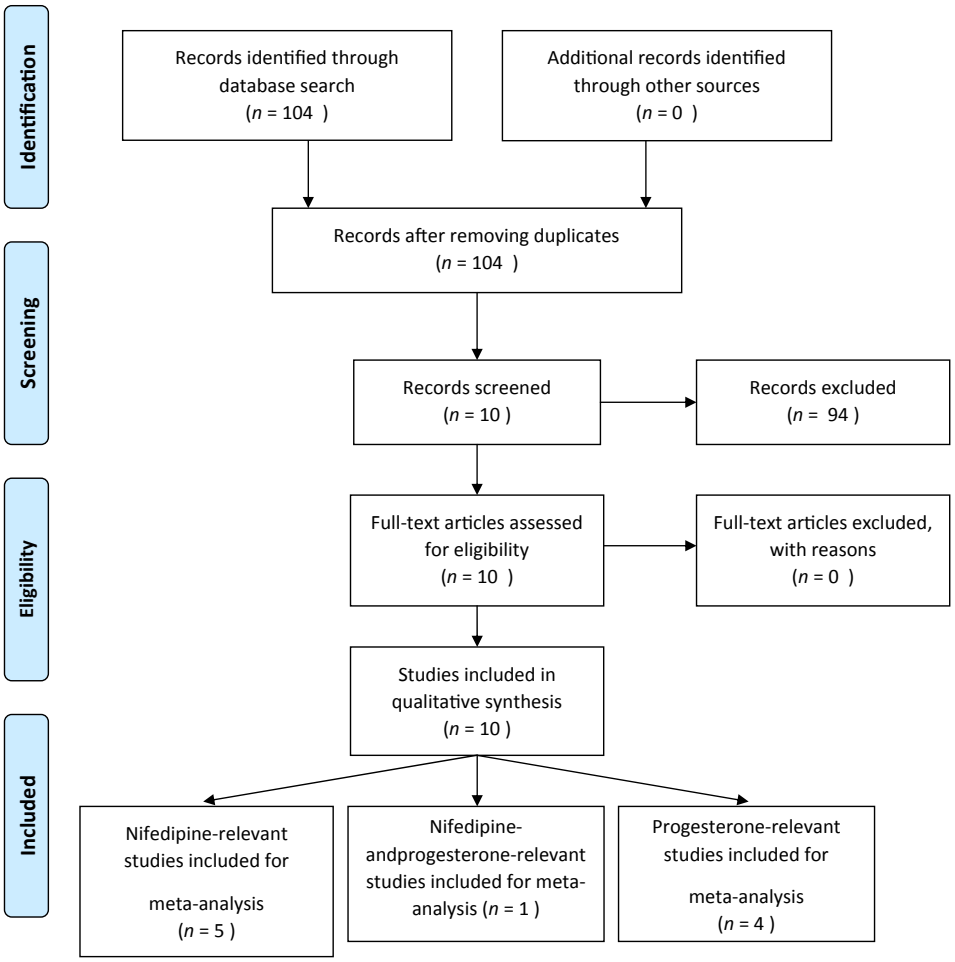

Figure 1. Flow chart of the study selection.

Table 1
The main characteristics of the included trials.

Study	Country	Mean age	Age (mean)	Gestation weeks	Treatment intervention	Control intervention
Carr 1999 [10]	USA	37/37	22.7/22.8	24–34	Nifedipine	No treatment
Sayin 2004 [16]	Turkey	37/36	26.6/27.3	Not reported	Nifedipine	No treatment
Lyell 2008 [13]	USA	33/35	28.4/28.1	24–34	Nifedipine	Placebo
Roos 2013 [15]	Netherlands	201/205	30.2/30.2	26–32	Nifedipine	Placebo
Parry 2014 [14]	New Zealand	29/31	29.0/29.7	24–34	Nifedipine	Placebo
Kamat 2014 [12]	India	49/51	Not reported	<37	Progesterone	Nifedipine
Borna 2008 [9]	Iran	37/33	26.1/25.5	24–34	Progesterone	No treatment
Arikan 2011 [8]	Turkey	43/40	Not reported	24–34	Progesterone	No treatment
Areia 2013 [7]	Portugal	26/26	30.1/28.38	24–34	Progesterone	No treatment or placebo
Choudhary 2014 [11]	India	45/45	24.1/23.7	24–34	Progesterone	Placebo

arrested preterm birth. The use of maintenance tocolytic therapy after an initial episode of preterm labor is controversial. Our results altogether demonstrated that maintenance tocolysis with progesterone may be useful for patients who had an episode of threatened preterm labor that was successfully treated by acute tocolytic therapy; however, there are no benefits in maintenance tocolysis therapy with nifedipine.

Progesterone has been studied extensively for the prevention of preterm labor in high-risk patients such as women with a history of preterm labor and women with a short cervix in the current pregnancy [17,18]. However, the mechanism of action of progesterone in prolonging pregnancy is not well known. Until recently, several trials evaluating the effect of progesterone for maintenance tocolysis treatment after arrested preterm labor had been published [7–9,11]. Vaginal progesterone was used in three of these trials [7–9], and oral micronized progesterone was administered in the remaining study [11]. The dosage of progesterone was 200 mg or 400 mg. From these studies, we found that vaginal and oral progesterone were both effective in prolonging the latency period and increasing the birth weight of neonates, and that 200 mg and 400 mg of progesterone were effective. Furthermore, the use of progesterone did not increase the incidence rate of adverse events. We provided robust evidence that progesterone was effective for maintenance tocolysis treatment after arrested preterm labor. In

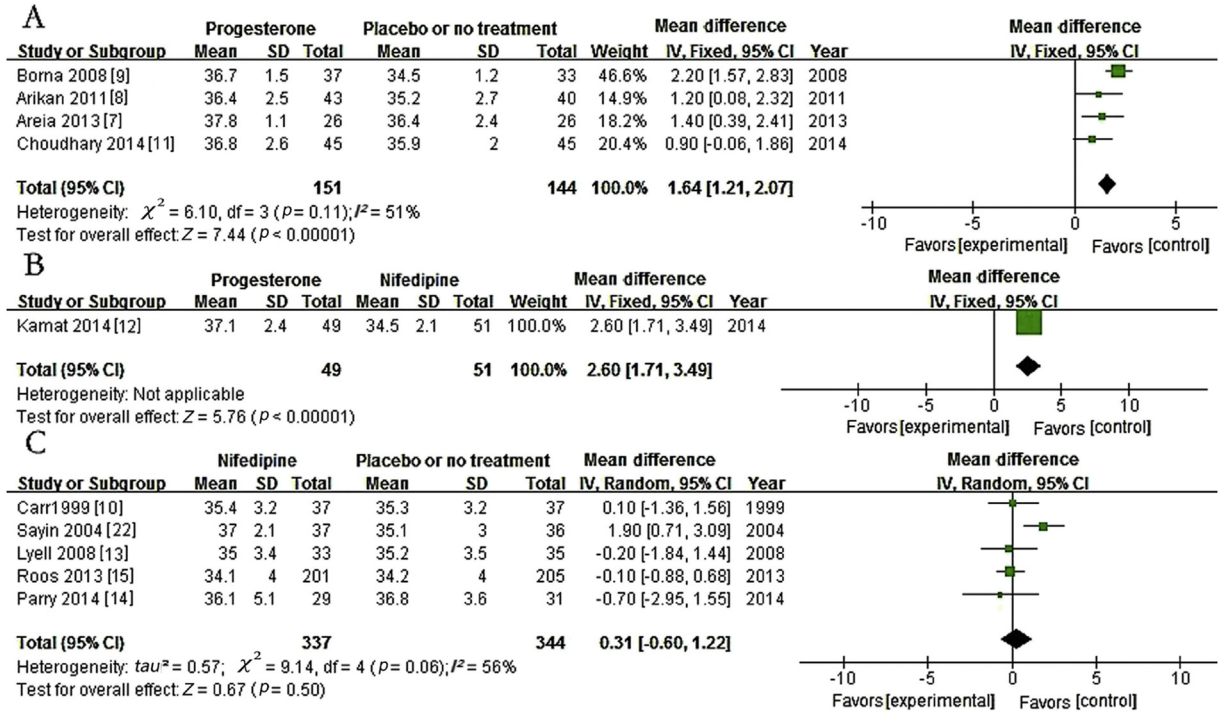

Figure 2. Meta-analysis for the outcome of the gestational age at delivery (weeks). (A) Progesterone versus placebo or no treatment. (B) Progesterone versus nifedipine. (C) Nifedipine versus placebo or no treatment. CI = confidence interval; IV = inverse variance; SD = standard deviation.

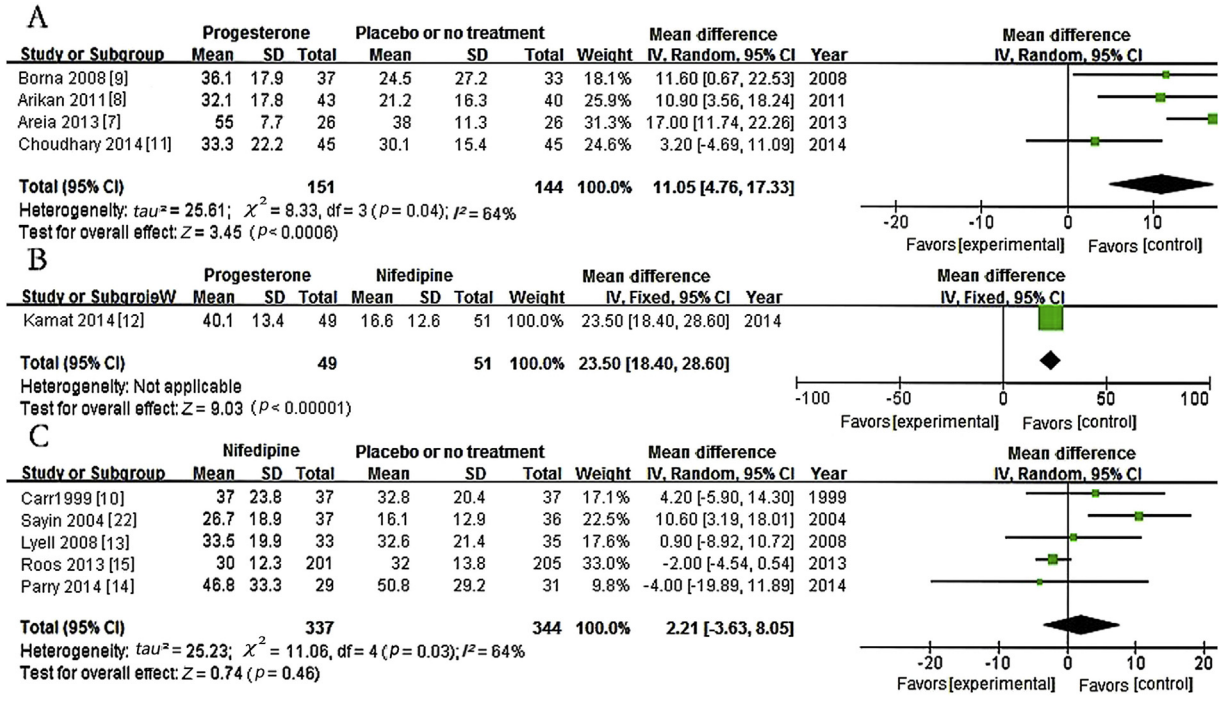

Figure 3. Meta-analysis for the outcome of pregnancy prolongation (days). (A) Progesterone versus placebo or no treatment. (B) Progesterone versus nifedipine. (C) Nifedipine versus placebo or no treatment. CI = confidence interval; IV = inverse variance; SD = standard deviation.

addition, one trial [12] of the included trials compared progesterone with nifedipine for maintenance tocolysis after arrested preterm labor, with results in favor of progesterone. Several relevant reviews have recently been published. In 2012, Haas et al [19] found that prostaglandin inhibitors and calcium channel blockers had the highest probability of delaying delivery and improving neonatal and maternal outcomes. In 2015, Suhag et al [20] in a meta-analysis of randomized controlled trials evaluated the efficacy of maintenance tocolysis with vaginal progesterone, compared to the control group (i.e., placebo or no treatment) in singleton gestations with

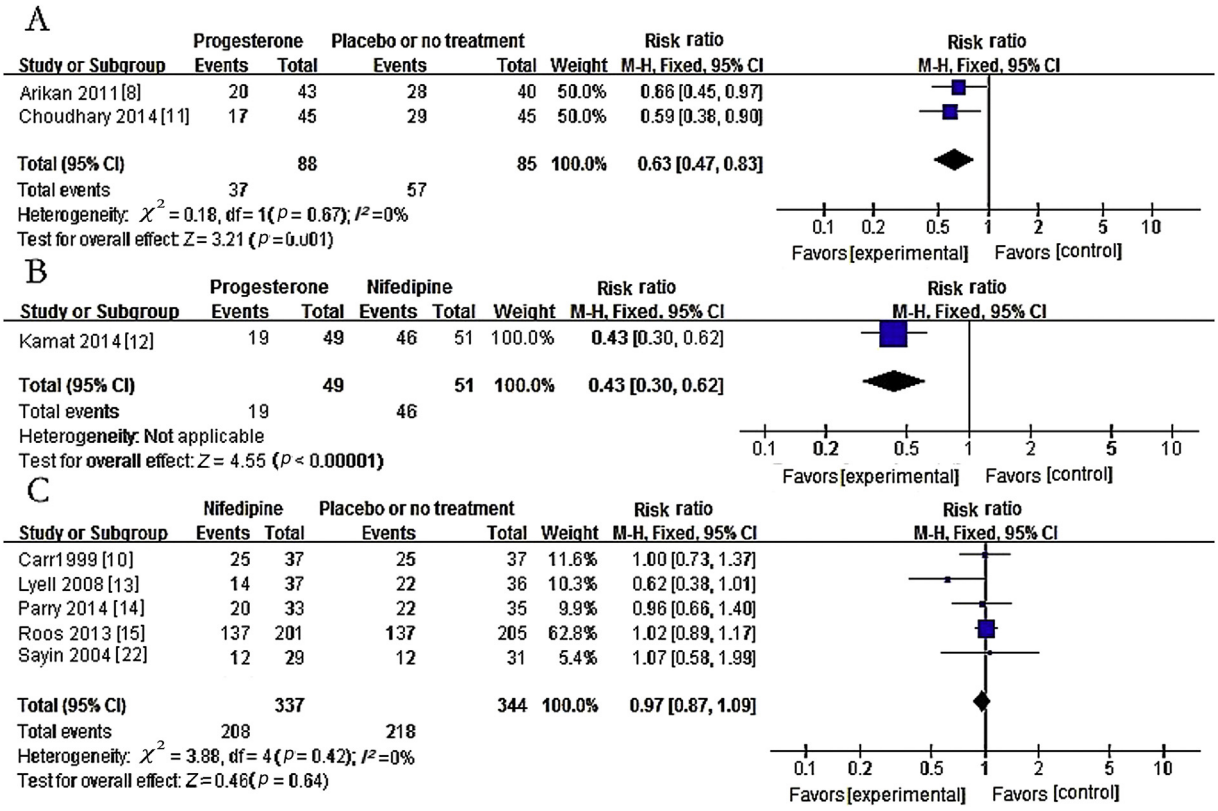

Figure 4. Meta-analysis for the outcome of the proportion of patients with delivery at <37 weeks. (A) Progesterone versus placebo or no treatment. (B) Progesterone versus nifedipine. (C) Nifedipine versus placebo or no treatment. CI = confidence interval; IV = inverse variance; SD = standard deviation.

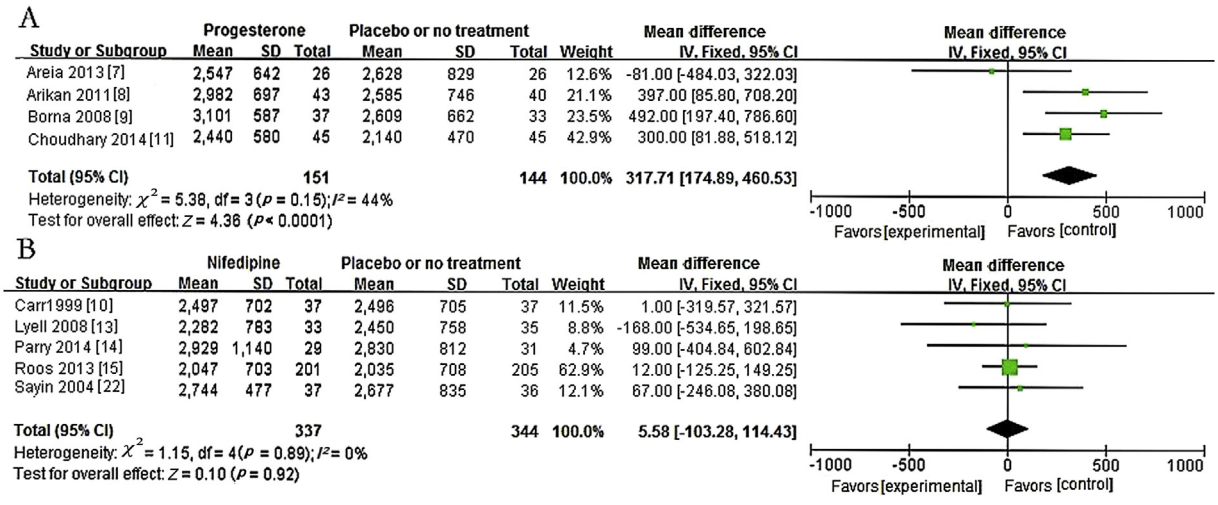

Figure 5. Meta-analysis for the outcome of birth weight. (A) Progesterone versus placebo or no treatment. (B) Nifedipine versus placebo or no treatment. CI = confidence interval; IV = inverse variance; SD = standard deviation.

arrested preterm labor. Compared to Suhag's study, our study evaluated the efficacy of maintenance tocolysis with vaginal progesterone and nifedipine. Another review [21] evaluated the efficacy of maintenance tocolysis with 17-alpha-hydroxyprogesterone caproate, which suggested that 17-alpha-hydroxyprogesterone caproate for maintenance tocolysis is associated with a significant prolongation of pregnancy, and significantly higher birth weight. Further study could evaluate the relative efficacy of maintenance tocolysis with progesterone versus 17-alpha-hydroxyprogesterone caproate.

Nifedipine, a slow-release calcium channel blocker, is an alternative tocolytic agent. Maintenance nifedipine tocolysis is a common practice in the United States. In a survey to which 46% of Society for Maternal–Fetal Medicine members responded, 29% of members reported that they would recommend maintenance tocolysis, and of these, 79% reported that nifedipine was their first-line maintenance tocolytic [19]. One included trial [20] demonstrated that oral maintenance tocolysis with nifedipine could significantly prolong gestational age. However, other included trials did not observe the same results [10,13–15], and the pooled results

found that maintenance nifedipine tocolysis did not provide any benefit for pregnancy prolongation or the outcomes of the neonates. Our present study found that maintenance tocolysis with progesterone was effective for prolonging pregnancy and improving the birth weight of neonates for patients who had an episode of threatened preterm labor successfully treated with acute tocolytic therapy, whereas maintenance tocolysis therapy with nifedipine did not have the expected efficacy of pregnancy prolongation.

Conflicts of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

This work was supported by grant from the National Key Clinical Department Funding of China (201101ckZD) and the National Natural Science Foundation of China (Chongqing, China. no. 81170585).

References

[1] Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of preterm birth. Lancet 2008;371:75–84.
[2] Simmons LE, Rubens CE, Darmstadt GL, Gravett MG. Preventing preterm birth and neonatal mortality: exploring the epidemiology, causes, and interventions. Semin Perinatol 2010;34:408–15.
[3] Bolisetty S, Bajuk B, Abdel-Latif ME, Vincent T, Sutton L, Lui K. Preterm outcome table (POT): a simple tool to aid counselling parents of very preterm infants. Aust N Z J Obstet Gynaecol 2006;46:189–92.
[4] Soloff MS, Jeng YJ, Copland JA, Strakova Z, Hoare S. Signal pathways mediating oxytocin stimulation of prostaglandin synthesis in select target cells. Exp Physiol 2000;85 Spec No:51S–8S.
[5] Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration. 2011. Available from:, www.cochrane-handbook.org [accessed 03.04.16].
[6] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[7] Areia A, Fonseca E, Moura P. Progesterone use after successful treatment of threatened pre-term delivery. J Obstet Gynaecol 2013;33:678–81.
[8] Arikan I, Barut A, Harma M, Harma IM. Effect of progesterone as a tocolytic and in maintenance therapy during preterm labor. Gynecol Obstet Invest 2011;72:269–73.
[9] Borna S, Sahabi N. Progesterone for maintenance tocolytic therapy after threatened preterm labour: a randomised controlled trial. Aust N Z J Obstet Gynaecol 2008;48:58–63.
[10] Carr DB, Clark AL, Kernek K, Spinnato JA. Maintenance oral nifedipine for preterm labor: a randomized clinical trial. Am J Obstet Gynecol 1999;181:822–7.
[11] Choudhary M, Suneja A, Vaid NB, Guleria K, Faridi MM. Maintenance tocolysis with oral micronized progesterone for prevention of preterm birth after arrested preterm labor. Int J Gynaecol Obstet 2014;126:60–3.
[12] Kamat S, Veena P, Rani R. Comparison of nifedipine and progesterone for maintenance tocolysis after arrested preterm labour. J Obstet Gynaecol 2014;34:322–5.
[13] Lyell DJ, Pullen KM, Mannan J, Chitkara U, Druzin ML, Caughey AB, et al. Maintenance nifedipine tocolysis compared with placebo: a randomized controlled trial. Obstet Gynecol 2008;112:1221–6.
[14] Parry E, Roos C, Stone P, Hayward L, Mol BW, McCowan L. The NIFTY study: a multicentre randomised double-blind placebo-controlled trial of nifedipine maintenance tocolysis in fetal fibronectin-positive women in threatened preterm labour. Aust N Z J Obstet Gynaecol 2014;54:231–6.
[15] Roos C, Spaanderman ME, Schuit E, Bloemenkamp KW, Bolte AC, Cornette J, et al. APOSTEL-II Study Group. Effect of maintenance tocolysis with nifedipine in threatened preterm labor on perinatal outcomes: a randomized controlled trial. JAMA 2013;309:41–7.
[16] Cenk Sayin N, Varol Fusun G, Balkanli-Kaplan Petek, Sayin Muge. Oral nifedipine maintenance therapy after acute intravenous tocolysis in preterm labor. J Perinat Med 2004;32:220–4.
[17] DeFranco EA, O'Brien JM, Adair CD, Lewis DF, Hall DR, Fusey S, et al. Vaginal progesterone is associated with a decrease in risk for early preterm birth and improved neonatal outcome in women with a short cervix: a secondary analysis from a randomized, double-blind, placebo-controlled trial. Ultrasound Obstet Gynecol 2007;30:697–705.
[18] Fonseca EB, Celik E, Parra M, Singh M, Nicolaides KH, Fetal Medicine Foundation Second Trimester Screening Group. Progesterone and the risk of preterm birth among women with a short cervix. N Engl J Med 2007;357:462–9.
[19] Haas DM, Caldwell DM, Kirkpatrick P, McIntosh JJ, Welton NJ. Tocolytic therapy for preterm delivery: systematic review and network meta-analysis. BMJ 2012;345:e6226.
[20] Suhag A, Saccone G, Berghella V. Vaginal progesterone for maintenance tocolysis: a systematic review and metaanalysis of randomized trials. Am J Obstet Gynecol 2015;213:479–87. pii: S0002-9378(15)00261-6.
[21] Saccone G, Suhag A, Berghella V. 17-alpha-hydroxyprogesterone caproate for maintenance tocolysis: a systematic review and metaanalysis of randomized trials. Am J Obstet Gynecol 2015;213:16–22.