Maintenance Tocolytic Therapy

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Abstract

Several drugs have been developed to reduce the likelihood of preterm delivery even though its efficacy lasts <48 h. Each tocolytic agent has side effects and evidence of limited efficacy, therefore is not suitable for long-term usage. Maintenance therapy with nifedipine, ritodrine, terbutaline, or magnesium sulfate has been assessed, resulting in neither improved perinatal outcome nor pregnancy prolongation. It is conceivable that it may be beneficial to use maintenance therapy in selected cases of very preterm birth, where fetal compromise and intrauterine infection have been ruled out.

Keywords

Preterm delivery · Maintenance tocolytic therapy · Prolongation pregnancy Perinatal outcome

12.1 Introduction

Preterm birth is the leading cause of neonatal mortality and morbidity in developed countries. In this regard, several drugs have been developed to reduce the likelihood of preterm delivery <48 h, although effectiveness beyond this period has not been established. Short-term prolongation of pregnancy (<48 h) allows the complete a course of antenatal corticosteroids and magnesium sulfate for neuroprotection, as well as maternal transfer to a tertiary facility, which are very beneficial both to fetus and mother. After acute inhibition of preterm labor, maintenance tocolytic therapy

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has been conducted with nifedipine, terbutaline, or magnesium sulfate and assessed in systematic reviews of randomized trials [1–4].

12.2 Magnesium Sulfate

One Cochrane review which was updated in 2013 included four randomized controlled trials involving a total of 422 women [1]. In this review, the trials did not show any differences between magnesium maintenance therapy and placebo or other treatments (ritodrine or terbutaline) in the reduction of preterm birth or perinatal deaths. Magnesium sulfate has fewer side effects compared to betamimetics such as particularly palpitations or tachycardia, although diarrhea is more common. These trials were too small to exclude either essential benefits or harms, whereas none of them looked at the infant's long-term development. In 2013, Food and Drug Administration (FDA) had warned against long-term use of magnesium sulfate exposed for more than 5–7 days, which may lead to low calcium levels and bone problems in the developing baby or fetus, including osteopenia and fractures [5]. The shortest duration of treatment that can result in harm to the baby is also not known. Based on these findings, it is inappropriate to use magnesium sulfate beyond 48 h as a tocolytic agent, and it should use if needed clearly.

12.3 Betamimetics

Of betamimetics, terbutaline is commonly used in the USA, whereas ritodrine is commercially available and still used in Japan as a tocolytic agent. Conversely, ritodrine was withdrawn from the US market in 2003. In randomized studies, intravenous ritodrine has been shown to delay the delivery from 24 to up to 48 h [6]. Long-term usage of ritodrine for tocolysis will not be authorized in the standpoint of its multiple adverse effects unless close monitoring is paid to both fetus and mother in the case of unavoidable circumstances.

Terbutaline is taken orally, though, it does not seem to prevent returning contractions. In Cochrane review, oral betamimetics for maintenance therapy after threatened preterm labor do not reduce the incidence of preterm labor, based on 13 randomized controlled trials with a total of 1551 women [2]. The betamimetics ritodrine and terbutaline did not reduce the rate of preterm birth or prevent problems with neonates that required admission to the neonatal intensive care unit when compared with placebo, no treatment, or other tocolytic drugs. Another option of terbutaline is to use a small portable pump that feeds a continuous dose under the skin. Such low-dose terbutaline maintenance therapy with subcutaneous pump can be administered long term, which has been evaluated by a Cochrane review last updated in 2014 [3]. They found no evidence that terbutaline pump maintenance therapy decreased adverse neonatal outcomes. In 2011, the Food and Drug Administration (FDA) issued warnings specifically cautioning against the use of maintenance oral terbutaline during pregnancy because of reports of serious side effects [7]. Physicians

should be aware that death and serious adverse reactions could occur, including increased heart rate, transient hyperglycemia, hypokalemia, cardiac arrhythmias, pulmonary edema, and myocardial ischemia. These side effects were usually confirmed after prolonged administration both in oral or subcutaneous use. American College of Obstetrics and Gynecology (ACOG) recommends only short-term usage as a tocolytic or as acute therapy of uterine tachysystole with subcutaneous dosages of 0.25 mg [8]. Of note, oral terbutaline is ineffective to treat preterm labor and if injectable terbutaline is needed, it should not be used in the outpatient or home setting. The FDA recommends treatment with terbutaline administered by injection or by continuous infusion pump has to be used no longer than 48–72 h [7].

In Japan, it is commonly used ritodrine and/or magnesium sulfate as long-term tocolytic agents. Thus we performed a retrospective study to determine the efficacy of long-term tocolytic therapy (for more than 4 days) [8]. Between 1998 and 2005, 48 singleton pregnant women with uncomplicated preterm labor and intact membranes were enrolled. They are treated with long-term tocolytic therapy with intravenous magnesium sulfate and/or ritodrine for more than 4 days until 35 weeks of gestation (tocolysis off group). Controls were uncomplicated singleton pregnancies ($n = 419$) and enrolled at 35 weeks gestation. We determined the incidence of preterm delivery after cessation of agents, which was compared with the controls. Preterm birth occurred significantly more often in tocolysis off group compared with controls (58% versus 4%, $P < 0.01$). The odds ratio of preterm birth was 40 (95% confidence intervals: 16–98). These results suggest that long-term tocolysis is beneficial to prolong pregnancy in at least 58% of treated patients.

We evaluated the efficacy of magnesium sulfate as a second-line tocolysis for 48 h [9]. A multi-institutional, simple 2-arm randomized controlled trial was performed. Forty-five women at 22–34 weeks of gestation were eligible, whose ritodrine did not sufficiently inhibit uterine contractions. After excluding 12 women who failed to meet the inclusion criteria of preterm labor, 33 were randomly assigned to either magnesium alone or combination of ritodrine and magnesium. The treatment was determined as effective if the frequency of uterine contraction was reduced by 30% at 48 h of the treatment. After magnesium sulfate infusion, 90% prolonged their pregnancy for >48 h. Combination therapy was effective in 95% (18/19), which was significantly higher than 50% (7/14) for magnesium alone. Our randomized trial revealed that combination therapy significantly reduced uterine contractions, suggesting that adjuvant magnesium with ritodrine is recommended, rather than changing into magnesium alone, when uterine contractions are intractable with ritodrine alone.

12.4 Oxytocin Receptor Antagonists

The only tocolytic that has been shown to prolong gestation as maintenance therapy is oxytocin receptor antagonists, atosiban [10]. Atosiban is not available in the USA and also in Japan. Romero and coworkers reported that treatment for preterm labor with atosiban resulted in prolongation of pregnancy for up to 7 days for those at a gestational age at or more than 28 weeks, occurring with less maternal-fetal adverse

effects [10]. While in a Cochrane review of oxytocin receptor antagonists (largely atosiban) as a tocolytic agent did not demonstrate the superiority of oxytocin receptor antagonists compared with placebo, betamimetics, or calcium channel blocker (largely nifedipine) [11]. Concern to maintenance therapy with atosiban, Valenzuela and colleagues performed a multicenter, double-blind, placebo-controlled trial [12] which was also reviewed in Cochrane review [13]. This trial compared atosiban with placebo, both administered by a subcutaneous infusion pump to women in whom preterm labor had ceased following treatment with atosiban. In both groups, atosiban or matching placebo was given as subcutaneous infusion continuously. Atosiban infused of 6 mL/h (30 μg/min) to the end of 36 weeks' gestation. Compared with placebo, the use of atosiban as maintenance therapy for prevention of recurrent preterm labor did not reduce the incidence of preterm birth. While the median interval from the start of maintenance therapy to the first recurrence of labor was prolonged (32.6 days versus 27.6 days), as was the time to recurrence of preterm labor (36.2 versus 28.2 days).

12.5 Calcium-Channel Blockers

Calcium-channel blockers, especially nifedipine is safer and more effective as a tocolytic agent than betamimetics, but only sometimes more effective than other types of tocolytics [14]. However, maintenance therapy with nifedipine does not show a reduction in preterm birth or improvement in neonatal outcomes. van Vliet and colleagues performed a meta-analysis, compared maintenance nifedipine tocolysis with placebo or no treatment [4]. Six randomized controlled trials were enrolled, encompassing data from 787 patients. There was no difference between these two groups for the incidence of perinatal death, neonatal mobility, and prolongation of pregnancy.

12.6 Conclusions

Tocolytic agents are usually used up to 48 h to prolong pregnancy to afford time for maternal transfer, infusion of magnesium sulfate for neuroprotection, and fetal maturation after administration of an antenatal corticosteroid. After the acute inhibition of preterm labor, maintenance therapy with tocolytic agents is not recommended. Because systematic reviews of randomized trials have consistently found ineffective evidence in both for preventing preterm birth and improving neonatal outcome. Additionally, maintenance therapy just for pregnancy prolonging could be harmful both to the mother and the fetus due to their severe adverse effects. It is conceivable that it might be beneficial to use maintenance therapy in selected cases of very preterm birth, at least where fetal compromise intrauterine infection has been ruled out and in the unavoidable circumstances.

References

1. Han S, Crowther CA, Moore V. Magnesium maintenance therapy for preventing preterm birth after threatened preterm labour. Cochrane Database Syst Rev. 2013;(5):CD000940. https://doi.org/10.1002/14651858.CD000940.pub3.
2. Dodd JM, Crowther CA, Middleton P. Oral betamimetics for maintenance therapy after threatened preterm labour oral betamimetics for maintenance therapy after threatened preterm labour. Cochrane Database Syst Rev. 2012;(12):CD003927. https://doi.org/10.1002/14651858.CD003927.pub3.
3. Chawanpaiboon S, Laopaiboon M, Lumbiganon P, Sangkomkamhang US, Dowswell T. Terbutaline pump maintenance therapy after threatened preterm labour for reducing adverse neonatal outcomes. Cochrane Database Syst Rev. 2014;(3):CD010800. https://doi.org/10.1002/14651858.CD010800.pub2.
4. van Vliet E, Dijkema GH, Schuit E, Heida KY, Roos C, van der Post J, et al. Nifedipine maintenance tocolysis and perinatal outcome: an individual participant data meta-analysis. BJOG. 2016;123:1753.
5. U.S. Food and Drug Administration. FDA drug safety communication: FDA recommends against prolonged use of magnesium sulfate to stop pre-term labor due to bone changes in exposed babies. 2013 May 30. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-recommends-against-prolonged-use-magnesium-sulfate-stop-pre-term. Accessed 2 May 2019.
6. Neilson JP, West HM, Dowswell T. Betamimetics for inhibiting preterm labour (review). Cochrane Database Syst Rev. 2014;(2):CD004352. https://doi.org/10.1002/14651858.CD004352.pub3.
7. U.S. Food and Drug Administration. FDA drug safety communication: new warnings against use of terbutaline to treat preterm labor. https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-new-warnings-against-use-terbutaline-treat-preterm-labor. Accessed 2 May 2019.
8. Kawagoe Y, Sameshima H, Ikenoue T. Evaluation of the efficacy of long-term tocolysis for prolongation of pregnancy. J Jpn Soc Perin Neon Med. 2009;45(4):1048–50.
9. Kawagoe Y, Sameshima H, Ikenoue T, Yasuhi I, Kawarabayashi T. Magnesium sulfate as a second-line tocolytic agent for preterm labor: a randomized controlled trial in Kyushu Island. J Pregnancy. 2011;2011:965060. https://doi.org/10.1155/2011/965060.
10. Romero R, Sibai BM, Sanchez-Ramos L, Valenzuela GJ, Veille JC, Tabor B, et al. An oxytocin receptor antagonist (atosiban) in the treatment of preterm labor: a randomized, double-blind, placebo-controlled trial with tocolytic rescue. Am J Obstet Gynecol. 2000;182(5):1173–83.
11. Flenady V, Reinebrant HE, Liley HG, Tambimuttu EG, Papatsonis DN. Oxytocin receptor antagonists for inhibiting preterm labour. Cochrane Database Syst Rev. 2014;(6):CD004452. https://doi.org/10.1002/14651858.CD004452.pub3.
12. Valenzuela G, Sanchez-Ramos L, Romero R, Silver HM, Koltun WD, Millar L, et al. Maintenance treatment of preterm labor with the oxytocin antagonist atosiban. The atosiban PTL-098 Study Group. Am J Obstet Gynecol. 2000;182:1184–90.
13. Papatsonis DNM, Flenady V, Liley HG. Maintenance therapy with oxytocin antagonists for inhibiting preterm birth after threatened preterm labour. Cochrane Database Syst Rev. 2013;(10):CD005938. https://doi.org/10.1002/14651858.CD005938.pub3.
14. Flenady V, Wojcieszek AM, Papatsonis DN, Stock OM, Murray L, Jardine LA, et al. Calcium channel blockers for inhibiting preterm labour and birth. Cochrane Database Syst Rev. 2014;(6):CD002255. https://doi.org/10.1002/14651858.CD002255.pub2.