ISSN: 2456-8090 (online)
DOI: https://doi.org/10.26440/IHRJ/0508.11478

REVIEW

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Preterm Labor and Treatment Efficacy-Safety

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ABSTRACT

With medical sciences on the verge of advancement, preterm labor still remains a bothersome issue in modern obstetrics. A few therapeutic agents that suppress uterine contractile activity have gained success up to some extent. Tocolytics are medications used to suppress premature labor. These drugs can decrease the strength and frequency of uterine contractions and help in delay the onset of labor but are not able to prolong pregnancy to full-term. Presently, the choice of a best tocolytic drug remains debatable. This review discusses efficacy and safety of various useful agents which have been used so far. Further clinical trials are required to select an effective, and most importantly, safe therapy for the threatened preterm labor.

KEYWORDS: Tocolytics, Calcium Channel Blockers, Preterm Labor

INTRODUCTION

Preterm labor is defined as delivery occurring between 22 and 36+6 weeks of gestation, with gestational age determined based on the 1st day of the last menstrual period and fetal scanning performed in the 1st trimester.[1] About 15 million babies are born prematurely each year, and this number steadily increases. Complications of preterm labor are the leading cause of death in infants under 5 years of age. According to the WHO, the rates of preterm labor range from 5 to 18% of the number of the newborns in 184 countries.[2] Clinical symptoms that determine the true onset of labor are the same regardless of gestational age and are manifested as structural changes in the cervix and the onset of regular labor activity. Cervical changes include dilatation of internal orifice, shortening, softening, and centralization of the cervix. Cervical changes in the started PL occur within several hours, which distinguishes them from the cervical ripening process, which occurs over days or even weeks.[1]

The criteria for diagnosing the threatened preterm labor are manifested as irregular pain in the lower abdomen and lumbar region. Uterine hypertonus, shortening of the cervix, and opening of the external orifice are objectively detected. The started preterm labor is accompanied by lower abdominal pain, recorded regular uterine activity, central position of the shortened, softened, and often dilated cervix, mucosal or mucosal-serous secretions from the genital tracts suggestive of cervical ripening. Amniotic fluid may discharge prematurely. In a few countries, nifedipine and atosiban are recommended as first-line tocolytic therapy.[1] Nifedipine and atosiban have comparable efficacy in prolonging pregnancy for up to 7 days. Compared with β-agonists, nifedipine is associated with improved neonatal outcome, but long-term data are not available to date. A meta-analysis showed no significant differences between atosiban and nifedipine in prolonging pregnancy. However, atosiban was associated with fewer maternal side effects than nifedipine.[3] The use of nifedipine and atosiban within 48 hours in pregnant women at risk of preterm labor is associated with similar perinatal outcomes.[4] A study showed showed that infants born before 32 weeks of gestation after tocolytics use had a high incidence of craniocerebral injury. No significant differences were found in the organic brain lesion between neonates whose mothers received nifedipine and neonates who received atosiban.[5] Compared with β-adrenergic agonists the use of atosiban was associated with a significantly lower incidence of adverse events such as tachycardia, palpitations, vomiting, headache, hyperglycemia, tremor, dyspnea, chest pain,

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Submitted on: 16-Oct-2021; **Accepted on:** 23-Nov-2021

hypokalemia, and fetal tachycardia.[6] In another study, atosiban was found to be a more effective tocolytic than hexoprenaline in the treatment of threatened preterm labor. A study showed that atosiban prolonged pregnancy by 48 hours or more in 71.9% of pregnant women.[7] In another study, the comparison of nifedipine and fenoterol showed the same latent period in both groups. More side effects were reported in the fenoterol group. The economic evaluation did not reveal a significant difference in cost savings between the groups receiving either drug. Neither clinical nor economic superiority of either of the two drugs was demonstrated in the study.[8] A randomized study showed a difference between oral and sublingual use of nifedipine. The time required for tocolysis was significantly shorter with sublingual nifedipine. Sublingual nifedipine was also more effective than oral nifedipine in stopping preterm labor within 90 minutes.[9] Other randomized study demonstrated the efficacy of nifedipine in combination with sildenafil citrate with fewer deliveries within 7 days of hospitalization and fewer admissions in neonatal intensive care units, fewer early preterm deliveries, and increased birth weights.[10] Comparison of nifedipine with terbutaline in other study showed a similar tocolytic effect of the drugs. However, nifedipine was associated with fewer side effects.[11]

Atosiban is also preferred over β-adrenergic agonists and drugs with similar effects. The prolongation of pregnancy by 48 hours was significantly higher in the atosiban group than in the ritodrine group, while the prolongation of pregnancy by 7 days was similar in both groups. The incidence of side effects in pregnant women was higher in the ritodrine group than in the atosiban group, but the prevalence of abnormal fetal heart rhythm was not statistically significantly different. Both perinatal mortality and prevalence of neonatal asphyxia were significantly lower in the atosiban group. Perinatal mortality and prevalence of neonatal pneumonia were also lower in the atosiban group when using the drug at gestational age less than 28 weeks. Regardless of the drug initiation time, there were no significant differences between the atosiban and ritodrine groups in the cases of neonatal asphyxia, acute respiratory distress syndrome, neonatal craniocerebral injury, or neonatal sepsis.[12] A randomized, controlled study compared the efficacy of the nicorandil, a potassium channel blocker, and nifedipine, a calcium channel blocker, for tocolysis in preterm labor. Nicorandil was comparable to nifedipine in terms of pregnancy prolongation by 48 hours, 7 days and up to 37 weeks of gestation. Nausea and vomiting, maternal tachycardia, and fetal tachycardia were significantly more common in women treated with nicorandil. Headaches were significantly more common in women treated with nifedipine. There was no difference in neonatal outcome between the two groups.[13] To date, indomethacin remains a second line tocolytic, but studies have shown a low safety profile. A meta-analysis showed the probability of pregnancy prolongation by 48 hours was highest in prostaglandin inhibitors versus placebo, followed by magnesium sulfate, calcium channel blockers, β-adrenergic agonists, and atosiban. Compared to placebo, the side effects requiring drug switching were significantly higher for β-adrenergic agonists, magnesium sulfate, and calcium channel.[14] Studies of progesterone use in successful tocolysis are controversial and require further investigation. Maintenance vaginal progesterone tocolysis is associated with significant prolongation of pregnancy and lower neonatal sepsis.[15] Another study also showed benefits of vaginal progesterone in pregnancy prolongation after successful tocolysis with atosiban.[16] A systematic review by showed that women treated with 17-alpha hydroxyprogesterone caproate had significantly later gestational age at delivery and higher neonatal weights compared to controls. Other secondary outcomes, including neonatal mortality, neonatal intensive care unit admission rate, neonatal respiratory distress syndrome, bronchopulmonary dysplasia, intraventricular hemorrhage, necrotizing enterocolitis, and neonatal sepsis, were similar in both groups.[17] In contrast, other study showed that injections of 17-alpha-hydroxyprogesterone caproate did not significantly prolong pregnancy in women with preterm labor after tocolysis.[18] Two studies demonstrated the efficacy of prolonged progesterone tocolysis compared to nifedipine with better neonatal outcomes and fewer side effects.[19,20] A study conducted in India showed that oral micronized progesterone significantly prolonged pregnancy.[21] A systematic review including 16 randomized controlled trials showed that the preterm labor rate at less than 37 weeks of gestation decreased and gestational age increased when women received progestogens compared to placebo or no treatment.[22] Another study showed that progesterone was ineffective in the prevention of PL after successful tocolysis.[23] Both the development of new drugs for tocolysis and the study of

combinations of the available tocolytics are promising. It is not clear whether a combination of tocolytic drugs in preterm labor is more effective in women and/or neonates because of the lack of large studies of combination tocolytic regimens. Further trials are needed before specific conclusions can be drawn about the use of combination tocolytic therapy in preterm labor.

CONCLUSION

The analysis of available literature showed that preterm labor is the leading cause of neonatal morbidity, mortality, and long-term consequences. Prevention and treatment of preterm labor remain a challenge in modern obstetrics. The accumulated domestic and foreign experience suggests that despite the increasing range of tocolytic agents, there are currently no more effective agents to suppress the contractility of the uterus than oxytocin receptor agonists and calcium channel blockers. As for neonatal outcomes, it is difficult to select the preferred drug because all tocolytics have a similar spectrum of outcomes for the fetus and newborn. Many studies suggest that clinicians should use a tocolytic that has produced the best results with the least adverse effects for the mother/newborn. It is necessary to continue clinical trials in order to select an effective, and most importantly safe, therapy for threatened preterm labor.

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Source of support: Nil, **Conflict of interest:** None declared

Cite this article as:
Gurung P, Thakur S, Pradhan D. Preterm Labor and Treatment Efficacy-Safety. Int Healthc Res J. 2021;5(8):RV9-RV12. https://doi.org/10.26440/IHRJ/0508.11478

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