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Role of Tocolytics in Preterm

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Tocolytics are the drugs that are used to prolong the time of child birth, for a short period - up to 2 days. If the labour starts too early during pregnancy also termed as preterm birth, which is supposed to be one of the major cause of neonatal mortality and morbidity, all over the world. Administration of tocolytic agents can help in preterm labour to delay the preterm labour by 48 hours. Tocolytics temporarily slow the contractions and hence it is possible to transport the patient to a hospital, where specialized care can be provided to premature baby and also corticosteroids can be administered, which help mature the baby's lungs. Different class of drugs are studied as tocolytics. Beta-Adrenergic receptor agonists like Terbutaline, Ritodrine, Fenoterol, Metaproterenol, Hexoprenaline, Albuterol, Orciprenaline, Nylidrin. Calcium channel blockers like Nicardipine and Nifedipine. Magnesium Sulfate. Nonsteroidal anti-inflammatories or prostaglandin inhibitors like Indomethacin, and Oxytocin inhibitors like Atosiban were found effective in different studies with some side effects, are discussed here briefly. Some Nitrates, alcohol, Progesterone have also been tried with not much significant effect. Calcium channel blocker specially Nifedipine is most studied and found to be safer and effective for tocolysis. Individual uterine relaxant therapy should take into account individual differences in metabolism and response to drugs.. Short term use of tocolytics has been proven more effective and safer than longer use of it for pre-term labour.

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1. INTRODUCTION

Preterm birth is still a major problem faced by Gynaecologists and obstetricians all over the world. Preterm is defined as babies born alive before the completion of 37 weeks of gestation or less than 259 days of gestation by World Health Organization (WHO) [1]. The reason for preterm labour is still not clear. It could be because of premature activation of the contraction of uterine muscles due to physiological or pathological factors. Uterine distension is due to multiple pregnancies, placental ischemia, cervicitis, immune and allergic phenomena, placental abruption or residual bleeding, intrauterine infections, and other complications. Inflammatory process may be the cause of preterm labour [2].

According to the WHO report, it is estimated that every year around the world there are about 15 million premature births. This number can be counted as more than 1 in 10 live births. About 1 million babies die due to complications arising from premature birth, every year [2]. In India, a total of 27 million preterm births take place every year, out of which 3.5 million are born preterm or may qualify as preterm labor [3]. Premature birth is supposed to be one of the major causes of infant mortality and morbidity.

Tocolytics are the drugs that are used to prolong the time of child birth for a short period - up to 2 days [4]. Tocolytics temporarily slow the contractions and hence it is possible to transport the patient to a hospital, where specialized care can be provided to premature baby and also corticosteroids or antibiotics can be administered [5].

Recommended treatments for preterm labour can help stop or delay the contractions at the time of labour and prevent the future health problems for both mother and baby. By reducing the uterine contractions, placental blood flow can be improved thereby the oxygen supply to the foetus can be improved. Prenatal corticosteroid has clearly showed that it is useful in reducing infant multiple morbidity and mortality [6]. Antenatal corticosteroids like betamethasone and dexamethasone can be administered to speed up the development of baby's lung. The chances of having major health problems after birth like, problems of respiratory system - respiratory distress syndrome, intraventricular haemorrhage, necrotizing enterocolitis and various bacterial infections can are reduced only if preterm is delayed.

The purpose of this review is to take a look on currently used tocolytic drugs and putting forward the evidence showing their effectiveness in prolonging pregnancy by short period of time of at least 2 days.

2. MECHANISMS OF TOCOLYSIS

The average gestational age of women starting labour is 40 weeks. In case of preterm labour, uterine contractions start due to change in the equilibrium of proinflammatory and anti-inflammatory cytokines [7]. Tocolysis focuses on delaying uterine contractions and making them weak. The myometrium, the smooth muscles in the uterus are responsible for the contractions of uterus. Contraction of myometrium can be explained as a process, which is complex and based on the functions of myocytes, the special muscle cells. It is associated with the hormonal receptors, intercellular gap junctions, ions channels. The regulatory increase in the intracellular calcium concentration is an important factor for the smooth muscle contraction of the uterus [8,9]. The initiation of the contractions is not a result of any hormonal stimulus or any kind of nerve input. The contractions begin with a impulsive depolarization of the cells, which in turn opens the calcium channels [10].

The smooth muscle cells or uterine myocytes , which contain many dense bodies, dense bands and myofilaments. The actin filaments of dense bodies attach to each other, thereby forcibly making the uterine contractions along the lengthwise direction of the cell. The contractile apparatus containing actin filaments connect to the cytoskeleton to form the dense bands. The result is the transmission of force from the contractile muscles to the plasma membrane resulting in condensing of the muscles of cytoskeleton [11]. Beta-adrenergic receptor agonists, nitric oxide donors, magnesium sulfate, and ca channel blockers interfere with the intracellular messenger responsible for the effects of uterine muscle contraction and relaxation proteins. In addition, the oxytocin receptor antagonist, Atosiban and prostaglandin synthetase inhibitors interfere with endogenous stimulants in the uterus to inhibit the synthesis of

contractile factors. They are the most commonly used antipyretics today.

3. TYPES OF TOCOLYTIC TREATMENT

[1] Beta-Adrenergic receptor agonists

The most common Beta-Adrenergic receptor agonists are terbutaline, ritodrine, albuterol, fenoterol, hexoprenaline, metaproterenol, nylidrin, and orciprenaline [11]. All of these are selective beta 2 agonists. Ritodrine and salbutamol were used regularly for preterm labour in 1980.

During acute phase, they are administered by IV infusion. For prophylactic therapy, they are given orally. A scientist divided the adrenergic receptors into alpha- and beta-adrenergic receptors which are placed on the cell membrane. All adrenergic receptors are coupled with G-protein receptors which help in regulating the production of intracellular second messengers.

Betamimetics exert a stimulant effect on beta-2 receptors. When cyclic AMP is increased cyclically, the intracellular ca levels are depleted, reducing the contractility of the uterine muscles. As per many studies, beta-2 adrenergic receptor agonists are known for causing adverse effects in mother. They are dyspnoea, tachycardia, chest pain, hyperglycaemia and hypokalaemia [12].

Tremor is due to stimulation of beta 2 receptors of skeletal muscle. Tolerance develops to this effect on continued administration. Tachycardia and palpitation are due to stimulation of beta 1 receptors of heart. Hyperglycaemia may occur in diabetic following parenteral administration of beta 2 agonists. Hypokalaemia is due to shift of k+ not cells. So, though they are efficient, the wellbeing of mother and child is one of the real troubles which is responsible for discontinuation of therapy.

[2] Ca channel blockers

They work on T-type ca channels and the entry of calcium into the smooth muscle of uterus is inhibited [13]. Dihydropyridine ca channel blockers, for example nicardipine and nifedipine, act on L-type ca channels and inhibit the ca inflow into myocytes of uterus. The decreased intracellular ca concentration arrest the renovation of the myosin chain kinase, and thus uterine muscle contraction is prevented or impaired.

The most studied ca channel blocker is nifedipine and many analysis are in support of its effectiveness as far as acute tocolysis is concerned. A recent study, which included 26 studies and involved 2,179 women, found that there is no major difference between the tocolytic, nifedipine and other tocolytics in delaying delivery by up to 2 days [14]. The study stated, nifedipine showed to have fewer maternal adverse effects than other analgesics. A recent network analysis and another decision study showed that ca channel blockers would be the best choice antipyretic as far as preterm labour is concerned [15]. It is given orally.

[3] Magnesium sulphate

It is supposed to be the safest tocolytic therapy since 1971 [16]. Calcium antagonism present in the motor terminal layer, arrest the release of acetylcholine and the transfer of stimuli. Ca interference at the membrane of plasma arrests its intracellular flow and the myosin kinase chain required for uterine muscle contraction is activated. It has a depressant effect on the uterine smooth muscle, central nervous system and myocardium. It is used to control convulsions and BP in toxaemia of pregnancy. It is useful when beta 2 agonists are contraindicated.

Magnesium sulfate is supposed to be given IV to achieve normal levels. Initially a heavy dose of 4-6 g in 10-20% solution over half an hour is given, followed by dose of 2 g every hour [17]. The adverse effects of magnesium sulfate treatment on maternal health can be like, flushing and somnolence to major symptoms like, cardiac arrhythmias and respiratory depression.

[4] Oxytocin receptor blockers

A selective oxytocin or vasopressin, Atosiban receptor antagonist, works by reducing intracellular calcium and thereby inhibiting uterine contractions [18]. This is done by blocking oxytocin receptors and the preventing the transformation of phosphatidylinositol to inositol triphosphate. Ca is released in the protoplasm, in this process.

An intravenous agent, Atosiban is given 6.75 mg bolus over one minute, IV followed by a continuous infusion at 18 mg/hour for continuous 3 hours, then 6 mg/hour for up to 45 hours [19].

Atosiban showed rare and non-life threatening adverse effects on maternal health and the only reactions were hypersensitivity.

A Cochrane review of 6 trials involving 1695 patients studied with Atosiban did not show superiority in terms of efficacy as far as lipolysis or neonatal outcomes is concerned [20].

[5] Prostaglandin inhibitors

Indomethacin is a prostaglandin inhibitor widely used to delay preterm labor [21]. Prostaglandins are endocrine hormones acting and influencing the contraction of the uterine muscles and forming the junctions of uterine muscle gap. They are responsible for the free intracellular ca concentration and activate of the myosin chain kinase.

Usually, indomethacin is given orally as a heavy dose of 50 mg, followed by 25 to 50 mg orally every four times a day for up to2 days. Due to the adverse effects, its use is limited in pre mature labour with normal amniotic fluid levels and normal kidney function [22].

A recent study showed that prostaglandin inhibitors were more effective inprolonging delivery for 2 days. In addition, prostaglandin inhibitors showed more benefit than any other antipyretic and had a 95% chance of being ranked in first 3 useful known antipyretics, used [23].

[6] Nitrates and other drugs

Alcohol was used as tocolytic agentin1970. But the bad effect on maternal health and infant were more as compared to any benefits [22].

Nitric Oxide is a powerful vasodilator. It is synthesized in an oxidation of amino acids. It is present in the cells of the uterine muscle and there is a connection between the production of nitric oxide and relaxation of uterus.

The transdermal nitro-glycerine was used in preterm labour, but the absence of large randomized studies has made its use limited. Nitrate drugs have been used based on animal studies confirming that activity correlates with work. But studies in humans show opposite results. A recent network study determined that nitrates had only a 5% chance of being the best agent for delaying labour by 2 days and a 11% chance of being the good agent for reducing maternal adverse events [23].

[7] Progesterone

Progesterone is described as a steroid hormone, which is secreted after the completion of 8 weeks of pregnancy, by the corpus luteum and placenta. It shows effects on the intracellular ca concentration and the synthesis of prostaglandins. The Progesterone therapy is used commonly as a preventive strategy. It is found helpful in reducing pre mature births in certain high-risk populations [24]. However, not many trials have suggested that the use of progesterone for acute tocolysis, is useful. These studies showed several problems, including their use with other tocolytics. Studies also often don't report delivery times of 48 hours. Therefore, the Cochrane review of the topic did not find sufficient evidence to support pregnancy-inducing agents as tocogenic agents [25].

[8] Antibiotics

Bacterial infection is one of the causes of pre mature labour but usually before 30 weeks. The antibiotics used to prevent the pre mature labour have been studied and it is generally not recommended because of only small evidence of benefit [26]. But in cases of premature rupture of membranes, a analysis of 22 studies, which was conducted on approximately 6000 patients, showed a significant reduction in the number of premature births and reduction in complications in infants in the treated group [27]. Tocolytic tests typically utilize drug from above mentioned drugs. Beside this, study on other drugs is limited in the field of tocolysis. Ifenprodil, when used in a small trial in France, it was not found to be as effective as ritodrine.

[9] Other drugs

Halothane, a fluorinated inhalational anaesthetic, has a potent tocolytic effect. Some studies state that it is still not clear about its use in pregnancy. Whether its use will cause any harm to the foetus is the question and hence it is very rarely used as tocolytic.

4. DISCUSSION

Many interventions are possible in treating the problems or in delaying the pre mature delivery. As mentioned above not all the drugs are proved efficient. Though some drugs showed proven

efficacy on the contraction of the uterus, there is no confirmation on the improvement in neonatal outcome. Single drug is used in some cases and combined therapy is observed in many cases. The data is still not sufficient to decide, which drug should be given and at what stage [28-30].

In a pregnant woman with history of multiple pregnancies, atosiban showed better results as compared to drugs like ca channel blocker or magnesium sulphate. Also in the cases of anaemia, again atosiban showed better results as compared to beta adrenergic receptor agonists. Atosiban showed less adverse effects than other tocolytics. Beta adrenergic receptor can cause foetal tachycardia. Indomethacin can be held responsible for renal dysfunction. The foetal right ventricular function is seen depressed due to magnesium sulphate. The reason for all above adverse effects can be stated as these drugs traverse the placenta quickly but their excretion is slower by the kidneys of the foetus as compared to the kidneys of the mother [31-33].

Hence, it is very important during the premature delivery, to choose a tocolytic drug which is safe as well as effective and at the same time, it should be patient specific.

General considerations while using tocolytic or any other drugs in pregnancy (pharmacological):

When choosing a tocolytic or any other drug, the characteristics of the patient should be taken into account. Individualized lipolysis is essential, and metabolism differences in different pregnant women and response for the drug in individual patients should be taken into consideration. Pregnancy is also known to change the disposal of medicine. In a pregnant woman who is otherwise healthy, the clearance of creatinine is seen increased by 1.5-fold times [29]. This in turn will increase the clearance of many drugs like magnesium. Comorbidities should also be taken into consideration, while choosing tocolytic therapy. For example, in pregnant women with impaired kidney function, magnesium and indomethacin should not be used.

Tocolytic medications should not be used in women when the following complications are observed in pregnant women:

- Eclampsia – increase in blood pressure beyond the normal limits, during pregnancy or
- Severe preeclampsia
- Hemorrhage or severe bleeding
- Chorioamnionitis or any kind of womb infection
- Also if there is some kind of abnormality detected in the foetus that could lead to the death of baby after the delivery or if the foetus is not live.

But, tocolytic medications are advised by the doctors in the following conditions as the benefits will definitely exceed the risks for both the mother and child.

- Dilated cervix – More than 4 centimetres
- Mild preeclampsia
- Stable and mild bleeding during the third trimester

Also when, the baby shows an abnormal heart rate on the foetal heart monitor.

5. CONCLUSION

Using Tocolytics for a Short period is common procedure to prolong pregnancy, so as it allows transportation of the mother to the hospital nearby or the tertiary care centre and to start therapies for growth and well-being of the foetus. Tocolytics were used in some trials for long periods, but they failed to demonstrate major benefits. Various types of tocolytics were used in different studies. Although the choice of which agent should be used first is not clear, it is clear that short-term tocolytic is an effective and useful therapy for women with pre mature labour. These could give us insight into the future of obstetric therapy and further personalize drug treatment during pregnancy.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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