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Review Article

Recent Update on Tocolytics for the Management of Preterm Labour

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Abstract

Tocolysis is the relaxation of the pregnant uterus to postpone delivery. Tocolytics are a wide variety of agents used to suppress uterine contraction given when delivery would result in preterm birth. Preterm birth the most important single determinant of adverse outcome in terms of both survival and quality of life of baby. Although preterm birth is defined as being before 37 completed weeks most mortality and morbidity is experienced by babies born before 34 weeks. Prevention and treatment of preterm birth is important though it is not possible when labour is too advanced, cervix is dilated for more than 4 cm and prolongation of pregnancy is hazardous because of intrauterine infection, placental abruption, IUGR, lethal congenital anomaly, severe PIH, eclampsia, active vaginal bleeding or cardiac disease [1,2].

The aim of this paper is to review available data about the tocolytics. The tocolytic therapy also helpful for getting time for the administration of dexamethasone/betamethasone, a glucocorticoid drug which greatly accelerates fetal lung maturity. There is no clear first line tocolytic agent [3,4]. Various types of drugs are used, with varying success rates and side effects that includes calcium-channel blockers, β adrenergic receptor agonists, magnesium sulphate, prostaglandin-synthetase inhibitors, oxytocin receptor antagonists. Their specific effects on myometrial contractility, their safety, their efficiency, doses, route of entry, and side effects profile for the mother and the fetus are presented. The main question which tocolytic should be administrated is discussed.

Introduction

Tocolytics (also called anti-contraction medications or labor repressants) are medications used to suppress uterine contraction (from the Greek *tokos*, childbirth, and *lytic*, capable of dissolving)[5]. Preterm birth is a major contributor to perinatal mortality and morbidity and affects approximately six to seven per cent of births in developed countries. Preterm labor is defined as regular uterine contractions causing cervical dilation. The increase of intracellular calcium concentration is essential for the uterine smooth muscle contraction [6].

The suppression of contractions is often only partial and tocolytics can only be relied on to delay birth for several days which allows maximum effect for parenteral steroid administration and transfer in utero[5]. Tocolytics are promising drugs as they suppress the uterine contraction, but still tocolytics are not shown to be very effective in PTL management. Tocolysis aims not only to inhibit uterine contractions but also to allow a safe transfer of the pregnant patient to a tertiary care centre. It gives the opportunity to administrate corticosteroids for preventing neonatal risks associated with prematurity [7-9].

Preterm labour (PTL) is responsible for approximately 75% of neonatal death and 50% of childhood neurological morbidities and demands huge expenditure. This perinatal morbidities and mortalities depend upon not only on gestations but also on steroid administration and care in tertiary centre and it is linked with respiratory immaturity, intracranial haemorrhage and infection[10].

Every year around 130 million PTL occurs all over the world[11]. The incidence of PTL has been steadily rising, it has become public health concern and calls for preventive measures[7]. Among with other preventive measures tocolytic is one of the important issue. Even with prediction by proper history, toco-dynamometry, measurement of cervical length,

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genetic marker, assessment of biochemical markers have not lowered the rate of PTL[12]. A wide range of tocolytics have been utilized for the management of PTL already mentioned. Debate is going on which tocolytic is the best? There is little reliable information about current clinical practice but it is likely that ritodrine hydrochloride, a beta-agonist, remains the most widely used tocolytic . Magnesium sulphate is popular for tocolysis in the USA and some other parts of the world, but is rarely used for this indication in the UK[13]. There is growing interest in calcium channel blockers as a potentially effective and well tolerated form of tocolysis[14].

Types of Tocolytic

Calcium channel blockers (CCB) - These agents interfere with the calcium ions transfer through the myometrial cell membrane. They decrease intracellular free calcium concentration and induce myometrial relaxation [15-17]. When tocolysis is indicated for women in preterm labour, calcium channel blockers are preferable to other tocolytic agents compared, mainly beta-agonists[18]. Nifedipine is used most commonly and is very popular to the obstetrician. Numerous RCTs have shown them to be effective as Beta- agonist and Magnesium sulphate and Atosiban. A comperative study showed that CCB have fewer maternal side effects than other tocolytics and have no adverse effects on foetal outcome[15]. In general patients may complain of headache, dizziness, tachycardia, palpitations, flushing, and nausea. Continuous monitoring of the fetal heart rate is recommended as transient hypotension may occur but it is reversible. In 2002 meta analysis of 12 RCT n==1029, concluded that nifedipine is more effective than B agonist and clearly proved to be superior. The investigators found a reduced risk of delivery within 7 days and at less than 34 weeks' gestation. Cessation of treatment due to adverse reaction occurred in 1 of 419 patients, vs 29 of 414 with other tocolytics[16]. The nifedipine- treated neonates also had decreased risk of respiratory distress syndrome, necrotizing enterocolitis, and intraventricular hemorrhage[17].

The recommended protocol consists of 20 mg orally stat, followed by 20 mg orally after 30 minutes if contractions persist, followed by 20 mg orally every 3-8 hours for 48-72 hours as indicated. The maximum dose is 160 mg/day. After 72 hours, if maintenance is required, patients can be changed to long-acting nifedipine 30-60 mg daily. Contraindications include allergy to nifedipine, hypotension, hepatic dysfunction, concurrent use of beta-agonists, transdermal nitrates, or other antihypertensive medication[18]. Hypotension can occur with concurrent use of nifedipine and magnesium. Hypotension is a side effect; however, it is minimal in normotensive patients[19]. Continuous monitoring of the fetal heart rate is recommended as long as the patient has contractions, and the patient's pulse and blood pressure should be monitored every 30 minutes for the first hour, then hourly for the first 24 hours, then every 4 hours[20].

Beta agonists- Selective β 2 agonists such as ritodrine and salbutamol with predominantly β 2-receptor effects that relaxes muscle in the uterus have been used in clinical practice for preterm labour since the 1980s[21]. A wide variety of agents have been advocated as suppressing uterine contractions. Currently the most widely used is ritodrine hydrochloride, a beta-agonist activates the enzyme, adenyl cyclase. This in turn leads to the activation of the secondary messenger cyclic adenosine monophosphate and induces myometrial relaxation[22]. The maximum recommended dose is 350g/min. The dose should be kept to the minimum required to inhibit uterine contractions and should be increased at 15 minute intervals until uterine contractions are inhibited, or maternal pulse rate exceeds 140/min, or other side effects become excessive[23]. The recommended infusion rates are given in the table.

Syringe pump Add 3×5ml ampoules ritodrine to 35ml 5% dextrose		Controlled infusion device Add 3×5ml ampoules ritodrine to 500ml 5% dextrose	
Dose	Rate	Dose	Rate
50 g/min	1 ml/hour	50 g/min	10 ml/hour
100 g/min	2 ml/hour	100 g/min	20 ml/hour
150 g/min	3 ml/hour	150 g/min	30 ml/hour
200 g/min	4 ml/hour	200 g/min	40 ml/hour
250 g/min	5 ml/hour	250 g/min	50 ml/hour
300 g/min	6 ml/hour	300 g/min	60 ml/hour
350 g/min	7 ml/hour	350 g/min	70 ml/hour

Recently an alternative regimen, which uses a 200µg/min loading dose until tocolysis is reached followed by a reducing dosage infusion, has been suggested[21].

But these drugs are widely crticised for unpleasant and even fatal maternal side effects. The maternal adverse effects are tachycardia, arrythmia, dyspnoea, hypokalemia, hyperglycemia, and chest pain, hypotension, pulmonary oedema and rarely death. The ritodrine is also associated with hallucination and antidiuresis[24-26]. Therefore obstetrician need to be very careful about - β agonists while treating PTL . Twin Pregnancy or pregnancy with diabetes and arrythmia are contraindicated for these tocolytics . Specially concomitant use of steroid and beta agonists need extreme caution as pulmonary oedema may kill the patient. Although they have been shown to delay delivery, beta agonists have not been shown to improve perinatal outcome. Though the efficacy of β -agonists in postponement of PTL is similar to the other tocolytics and placebo but they are no longer seem the best choice and gradually its popularity is declining. Several RCT trials showed that ritodrine or β agonists should not be the 1st line of tocolytic[27].

The beta-3 adrenoreceptor agonist BRL 37344 induced relaxation of human myometrial contractions with similar potency to that of the most commonly used tocolytic agent ritodrine. This raises the possibility that the novel beta-3 adrenoreceptor agonists may have potential as therapeutic agents for human preterm labour. In view of their reported reduced cardiovascular side effects their potential clinical use requires further evaluation[14].

Magnesium sulfate **-** The relaxant effect of Magnesium sulphate in vitro and in vivo on human uterine contractility has been widely reported. As magnesium is a calcium antagonist, it decreases calcium intracellular concentration and inhibits contraction process[28]. It is an important tocolytic act by inhibiting myocin light chain and thereby suppressing the uterine contraction. Magnesium sulfate is also commonly used, better tolerated, but the patient must be monitored for toxic effects, such as respiratory depression or even cardiac arrest, which can occur at super therapeutic levels. Common maternal side effects include flushing, nausea, headache, drowsiness, and blurred vision. Magnesium crosses the placenta and can cause respiratory and motor depression of the neonate. Magnesium sulfate is usually given through a vein (intravenously) until contractions have slowed and the mother's cervix has stopped thinning (effacing) or opening (dilating)[28]. The usual dose is 4-8 gm iv slowly. Numerous RCT have shown that it is effective as other tocolytics as β-agonists, CCB, and atosiban. But again the safety profile is argued everywhere. The most disadvantage is it needs intravenous adminstration and it produces hot flushes, lethargy, headache, diplopia, dry mouth, and rarely cardio respiratory arrest.

Oxytocin Receptor Antagonists **-** These agents are in competition with the myometrial and decidual oxytocin receptors. The only drug used in clinical practice is Atosiban. It blocks in a reversive manner the intracytoplasmic calcium release associated with contractions and down regulates prostaglandin synthesis. This drug is FDA approved and when compared to the other tocolytics and placebo it is proved to be very effective tocolytic. Atosiban is given 7.5 mg/ml solution for injection, immediately followed by a continuous high dose infusion (loading infusion 300 micrograms/min) of Atosiban 7.5 mg/ml concentrate for solution for infusion during three hours, followed by a lower dose of Atosiban 7.5 mg/ml concentrate for solution for infusion (subsequent infusion 100 micrograms/min) up to 45 hours. The duration of the treatment should not exceed 48 hours. The total dose given during a full course of therapy should preferably not exceed 330 mg of the active substance[24].

Prostaglandin-Synthetase Inhibitors **-** Prostaglandin-synthetase or cyclooxygenase (COX) isoforms COX-1 and -2 are essential enzymes for converting arachidonic acid to prostaglandins. Prostaglandins are well-known uterine contraction inducer by enhancing myometrial gap junction and increasing intracellular calcium concentration[7,14]. Indomethacin a nonspecific COX-2 inhibitor, has been reported in studies and in a recent meta-analysis to be an efficient tocolytic drug compared to placebo, significantly delaying preterm delivery[29]. It can be administrated rectally or orally. Its use should be restricted in duration and limited to pregnancies below 32 weeks because of fetal ductus arteriosus closure risk and decreased urine production responsible for oligohydramnios[29]. These treatments also have maternal side effects including gastric ulcer or asthma recurrence (NASAID- indomethacin has also been

shown to have efficacy similar to that of ritodrine). It is associated with infrequent maternal side effects, but it readily crosses the placenta and can cause oligohydramnios if used for more than 48 hours. Usually the amniotic fluid reaccumulates, but persistent fetal anuria, renal microcystic lesions, and neonatal death have been reported.

Discussion

The short term goal of tocolysis is to continue pregnancy for 48 hours and long term goal to continue pregnancy beyond 34-37 weeks at which point tocolysis can be discontinued for diminished chance of fetal morbidity and mortality. Since none of the existing treatments truly arrest the process for more than a few days, and on the assumption that they are similar in severity and frequency of side-effects, the most important outcome measure can be argued to be admission rates to the neonatal intensive-care unit. As a proxy for serious morbidity, as well as for cost, admissions to the intensive-care unit represent a straightforward measure of the value of a tocolytic agent. In this study, the nifedipine-treated group had significantly fewer admissions than did the ritodrine-treated group.

Although Nifedipine can cross the placenta, most of the RCT trials and Cochrane systemic review showed that CCB are effective, cheap, easily adminstrable with fewer side effects. On the other hand Atosiban though not available in our country has better maternal safety but not devoid of foetal adverse outcome even it is been associated with perinatal death[30]. Moreover it is very expensive. Recent study by ABRAHAM et al proved that Nifedipine could be a reasonable 1st choice as tocolytic because it does not carry any foetal risks unlike indomethacin or β agonists[30]. Depending on the tocolytic used the mother or fetus may require monitoring, as for instance blood pressure monitoring when nifedipine is used as it reduces blood pressure. In any case the risk of preterm labor alone justifies hospitalization.

Therefore till date Nifedipine (CCB) could be the best option as 1st line tocolytic for the management of preterm labour. Osmay et al commented that CCB are better in achieving tocolysis and their safety profile are better than other tocolytics[14]. The Cochrane data base 2003 showed CCB reduced the no, of women giving birth with in 7 days compared with other tocolytics.[RR 0;76 ; 95% CI 0.60 TO 0.97][17].Cochrane database 2005 – commented nifedipine is better drug than others and have better neonatal outcome[26]. A huge RCT (n=3263) showed that nifedipine is very effective in delaying PTL and improve maternal and neonatal outcome[19]. Coomassasay et al had RCT which proved CCB is more effective than Atosiban and less expensive[31]. In 2009 the big study again showed that CCB reduce RDS, IVH, and have very few maternal side effects and their tocolytic effect is same as β-agonists and Atosiban[25].

Efficacy in delaying delivery for 24-48 hours has been shown with beta-adrenergic agents, such as ritodrine; however, they cause unpleasant maternal side effects, such as palpitations. Virtually no one is the best but they can be compared for the better option. Other Beta agonists, like salbutamol, terbutalin, are widely used tocolytics [FDA approved]. Randomized Controlled Trial have shown these are very effective in delaying PTL and their efficacy are not less than other tocolytics. In compare to nifedipine and atosiban, the B- agonists produce neonatal tachycardia, hypoglycemia, hypokalemia, hyperbilirubinaemia, hypo or hypertension and rarely intraventricular haemorrhage[11]. So neonatologist must aware of the tocolytics used for PTL and they should apprehend the situation.

Moreover $Mgso_4$ needs extensive monitoring specially serum magnesium which is not always available. $Magso_4$ has adverse fetal effect like respiratory depression, hypotonia, deminarilasion[15]. So intravenous route, maternal and foetal adverse effects and necessity of strict monitoring for MgSO4 make it unpopular. Calcium-channel blockers and an oxytocin antagonist can delay delivery by 2–7 days[13]. Otherwise, tocolysis is rarely successful beyond 24–48 hours because current medication do not alter the fundamentals of labor activation[14]. However, just gaining 48 hours is sufficient to allow the pregnant women to be transferred to a center specialized for management of preterm deliveries and give administered corticosteroids the possibility to reduce neonatal organ immaturity.

RCT trial of atosiban with B- agonists showed that both of them are equally effective as tocolytics and there is no significant difference in neonatal morbidities and mortalities. Unlike β-agonists Atosiban has less maternal side effects and appeared superior to β- agonists & $Mgso_4$.

The consensus is Atosiban & nifedipine appear preferable than any other tocolytics as they have

fewer side effects, but 3RCT trials showed that Atosiban has no better efficacy than β-agonists and CCB rather Atosiban is associated with few perinatal death[4]. Indomethacin, is often used as tocoyltic but they are associeted with severe neonatal side effects particularly anuria, oliguria, necrotising colitis and closure of ductus arteriosus. Therefore again they are not being used as primary tocolytic.

Conclusion:

Ideal tocolytics should not do harm to foetus and to mother & should be very easily adminstrable. They should be very cheap and their efficacy should be almost 100 % but unfortunately none of the tocolytics fulfill these criterias . Nevertheless upto now Nifedipine is found to be preferable for our country.

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