The Use of Tocolytic Therapy in the Prevention of Preterm Labour

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Introduction

In Hong Kong, the incidences of preterm delivery (<37 completed weeks) and early preterm delivery (<33 weeks) were 6.7% and 1.2% respectively in 2004[1]. Preterm delivery has been shown to account for 80% of foetal morbidities and mortalities.[2] Although a proportion of the preterm deliveries are iatrogenic because of maternal and foetal indication, spontaneous preterm labour still accounts for 45% of preterm births.[3]

The role of tocolytic therapy in the prevention of preterm labour is still controversial. Tocolysis is not associated with any clear effects on perinatal death or on any measure of neonatal morbidity, such as respiratory distress syndrome or intraventricular haemorrhage.[4] Tocolysis should be considered to prolong the pregnancy for 48 hours for completing a course of corticosteroids which has been shown to reduce the risk of respiratory distress syndrome by at least 50%[5] or in utero transfer.

When the Patient has Preterm Labour, Should We Start Tocolytic Therapy?

With the improvement of neonatal care, tocolytic therapy is usually necessary for those patients with gestational age less than 34 weeks. We still need to exclude some conditions such as intrauterine infection, placental abruption or foetal distress, which may affect foetal well being if it is still maintained in utero.

Before starting tocolytic therapy, it is important to identify women with false labour as 30% of preterm labours would resolve spontaneously.[6] Foetal fibronectin (FFN) is an extracellular matrix glycoprotein localised at the maternal-foetal interface of the amniotic membranes, between chorion and decidua. FFN is found at very low levels in cervico-vaginal secretions. Foetal Fibronectin level of 50ng/ml or more can predict only 20 to 50% preterm delivery.[7] Transvaginal ultrasound scan measurement of cervical length 1.5cm or less has a positive predictive value of 65%.8 However both of them are not good predictors for true labour. On the other hand, a negative FFN (less than 50ng/ml) test result can identify 99.5% of patients who are unlikely to deliver within 7 to 10 days.[7] Cervical length of 2.5 to 3.0 cm or above has a negative predictive value of 99 to 100%.[8,9] A combination of these two modalities have been shown to be useful in detection of false labour.[10] It can decrease the chance of over diagnosis and subsequently reduces the side effects of medication, cost of hospitalisation, and the social isolation.

If We Want to Start Tocolytic Therapy, What are the Drugs We Can Choose?

The commonly used tocolytic agents include nifedipine, atosiban, ritrodrine and indomethacin or sulindac. The regime, contraindications and side effects of these drugs are summariesed in Table1. Magnesium sulphate is not mentioned here as recent literature had shown that this drug was no more efficacious than placebo, but associated with increased risk of foetal and paediatric death (Relative Risk(RR) 2.82 with Confident Interval(CI) 1.2 to 6.62).[11] It is time to quit this drug as a tocolytic agent.[12]

Nifedipine:

It is a calcium channel blocker which inhibits the influx of calcium ions into myometrial and other cells and thereby reduces muscle contractility.[13]

Although there is no placebo controlled study, King JF et al have reviewed 12 randomised controlled trials involving 1209 women and showed that nifedipine was associated with a reduction in the number of delayed delivery for 7 days (RR 0.76 ; 95% CI, 0.60 to 0.97) and before 34 weeks of gestation (RR 0.83; 95% CI, 0.69 to 0.99). It appeared to reduce the frequency of respiratory distress syndrome, necrotising enterocolitis, intraventricular haemorrhage and neonatal jaundice and fewer maternal adverse effects than beta-mimetics.[14]

Dyspnoea, pulmonary oedema, myocardial infarction, severe hypotension, hypoxia and elevated liver enzymes had been associated with nifedipine tocolysis.[15] One local study had shown that only 2% had severe maternal hypotension and all returned to normal thereafter.[16]

Atosiban

It is a competitive antagonist for oxytocin receptors. It binds to receptors in the myometrium and decidua, thus preventing the increase in intracellular free calcium that occurs with receptor binding.[17]

Atosiban has been shown to have similar efficacy in preventing preterm labour when compared to beta-mimetics but with reduced maternal side effects in a multiple centre, double-blind, placebo controlled trial.[18] A recent Cochrane review six trials in 2005 [19] showed

that atosiban did not reduce the incidence of preterm delivery or improve the neonatal outcome as compared with placebo in 2 trials. In one trial, it has been associated with an increase in infant deaths with a relative risk of 6.15 (95% CI 1.39 -27.22).[20] Please note that this trial randomised significantly more women to atosiban before 26 weeks of gestation which can account for the excess in deaths. This phenomenon was not observed in other studies. There was no difference in the effects on delayed delivery when atosiban was compared with betamimetics. Atosiban increased the number of infants born under 1.5kg but had fewer maternal drug reactions.

Atosiban is licensed in the United Kingdom for the treatment of threatened preterm labour.[4] However the Food and Drug Administration of the United States has not approved the use of this drug because of the study of apparent increased risk of foetal and infant deaths.[21]

Beta-mimetics: Ritrodrine

Ritodrine is one of the widely used tocolytic agents. This drug binds to the β-2 receptors on the surface of the myocytes and mediates myometrial relaxation by stimulating cyclic AMP. However, it also has a stimulatory effect on the β-1 in the heart, liver, pancreas, and kidney which account for the side effects. Prolonged use of this drug would induce down-regulation of the β-2 receptors and more drug (i.e. more side effects) is necessary to maintain the effect.[22]

A meta-analysis of all randomised controlled trials on intravenous ritrodrine hydrochloride when compared to placebo had lower risk of preterm delivery for tocolysis in preterm labour. The relative risks (RR) related to placebo for delivery within 48 hours or 7 days for intravenous ritodrine hydrochloride were 0.74 (95% CI 0.56-0.97) and 0.85 (95% CI: 0.74 - 0.97) respectively.[23] However maternal adverse effects included chest pain, dyspnoea, tachycardia, palpitations, tremor, headache, hypokalaemia, hyperglycaemia, nausea and vomiting, and nasal stuffiness were reported. The RR for cessation of treatment because of adverse events was 11.3 (95 percent CI, 3.8 to 33.5). There was no difference in the rate of perinatal and neonatal deaths. Treatment had no effect on neonatal morbidity such as respiratory distress syndrome, cerebral palsy, and necrotising enterocolitis.[24]

Non-steroidal Anti-inflammatory Agents (NSAID): Indomethacin / Sulindac

Prostaglandins are important intermediates of the many pathways leading to spontaneous preterm labour. The efficacy of NSAID lies in their ability to interrupt the actions of prostaglandins at multiple sites in preterm labour cascade.[25]

Indomethacin is currently the most common non-steroidal anti-inflammatory drug (NSAID) used in the treatment of preterm labour. King J reviewed 13 trials and showed that the use of indomethacin had lower preterm delivery when compared to placebo and other tocolytics mainly the betamimetics and magnesium sulphate. However due to the smaller number of cases, there was insufficient information on which to base decisions about its role for women in preterm labour.[26]

Furthermore, concern has been raised about the safety of the drug for the foetus and newborn. Premature closure of the ductus arteriosus occurs in 10 to 50% of foetuses exposed to indomethacin. It is more prevalent in later gestations (>32 weeks).[27] A meta-analysis had shown antenatal indomethacin was associated with an increased risk of periventricular leukomalacia (RR 2.0; 95% CI 1.3 -3.1) and necrotising enterocolitis (RR 2.2; 95% CI 1.1 - 4.2).[28]

Sulindac, a more selective cyclo-oxygnease 2 inhibitor had been shown to have similar effect as indomethacin but with lesser effects on amniotic fluid volume or foetal ductus in a small study.[29] A bigger study is necessary to delineate the efficacy and safety of this drug.

Among All the Tocolyitc Agents, Which One Should We Choose First?

The Royal College of Obstetricians and Gynaecologists' Green Top Guidelines in 2002 stated that when a tocolytic is required, nifedipine or atosiban (an oxytocin receptor antagonist) should be used as the preferred first line tocolytic agent, in preference to beta-mimetics.[4] Afterwards, there have been increasing debates into which drug is the first choice. Without direct comparison between the two drugs, Coomarasamy et al pooled analysis of the odds indirectly. It was shown that nifedipine tocolysis was associated with a significant reduction in respiratory distress syndrome compared with atosiban (RR 0.55, 95% CI 0.32-0.97). It also increased the number of women whose delivery was delayed by 48 hours (RR 1.20, 95% CI 0.73-1.95), although this result was not statistically significant.[30] Before further evidence is available, nifedipine would be the preferred first line tocolytic agent when there is no contra-indication.

Should We Use Tocolytic Agents to Maintain a Pregnancy?

Sanchez-Ramos et al in 1999 reviewed 12 trials on 855 receiving maintenance tocolysis and 735 receiving placebo or no treatment. There were no significant differences in preterm delivery and recurrent preterm labour.[31] Dodd JM et al in a recent review did not found evidence to support the use of oral betamimetics for maintenance therapy after threatened preterm labour.[32]

Which Agent If the First Line Tocolytics Failed?

If the first line tocolytic failed even on maximum dosage, it is important to review the whole case again. Cervical assessment may help to find out whether the patient is in true preterm labour. The possible underlying infection or abruptio placenta needs to be considered.

If nifedipine is the first line treatment, the cardiovascular effects of nifedipine preclude its use in combination with betamimetics.[15] Therefore, the choice of second line agents would be either atosiban or sulindac. Given the

potential foetal side effects of sulindac, atosiban can used as the second line of treatment.

Should We Give Tocolytics in Preterm Premature Rupture of Membranes?

The value of tocolytic therapy after PPROM remains controversial. The main concern is that PPROM is commonly associated with subclinical intra-uterine infection and that contractions could be a marker for overt infection. Tocolysis might prolong pregnancy and thus expose the mother and foetus to undue risk from intra-uterine infection. Weiner CP et al showed that tocolytic therapy might have a longer latency when compared to bed rest alone (105.2 vs 62.1hrs).[33] However, Decavalas et al showed that prolonged tocolytic therapy might increase the risk of chorioamnionitis (RR: 2.47; 95% CI: 1.42-4.66) and postpartum endomyometritis (RR: 1.74; 95% CI: 1.10-2.75) when compared to limited tocolytic therapy to 48 horus.[34] Recently Combs et al showed that limited tocolysis to 48 hours did not have more frequent maternal or neonatal infection.[35] Therefore tocolysis in patients with PPROM should be limited to 48 hours for the effects of corticosteroid or in-utero transfer.

Is There Any Tocolytic Therapy in Preventing Preterm Labour in Asymptomatic Patients?

There is no evidence to support that prophylactic oral betamimetics can prevent birth in high risk pregnancy with previous preterm delivery or twin pregnancy.[36,37]

Progesterone, on the other hand, has been widely investigated in preventing preterm labour. A large randomised placebo controlled trial had shown weekly intramuscular injections of 17α\-hydroxyprogeterone caproate (not commercially available yet) in high risk population (previous spontaneous preterm delivery less than 37 weeks) can significantly reduce preterm labour (36.3% versus 54.9%).[38] Furthermore, in patients found to have short cervix (<15mm) detected between 20 and 25 weeks, daily vaginal progesterone (200mg micronised progesterone capsules) significantly reduces the rate of spontaneous preterm birth less than 34 weeks of gestation (19.2% versus 34.5%).[39] Unfortunately, progesterone has not been shown to be useful in twin pregnancy.[40] The American College of Obstetricians and Gynecolgists has recommended progesterone supplementation for prevention of recurrent preterm birth should be offered to women with a singleton pregnancy and a prior spontaneous preterm birth due to spontaneous preterm labour or premature rupture of membranes. Current evidence does not support the routine use of progesterone in women with multiple pregnancies. It may be considered in patients with short cervical length (< 15mm).[41]

Conclusion:

Progesterone may be used for the prevention of spontaneous preterm labour in high risk singleton pregnancy. When a patient has preterm labour, foetal fibronectin and cervical length assessment may help in identify those cases with false labour. When tocolytic therapy is indicated, nifedipine is the first drug of choice. Atosiban can be used as the second line drug if nifedipine is contraindicated or fails.

Declaration

The author declares no conflicts of interest.

Table 1. Commonly used tocolytic agents: regime, side effects and contraindications

Agent	Regime	Side effects		Contraindications
		Maternal	Fetal	
Nifedipine	Initial dosage :- sublingual 10mg, repeat every 15 minutes until contractions cease total maximum dosage 40mg - Maintenance dosage: Oral 20mg start 6 hrs after the initial sublingual dose q8h for 2 days Titrate against response and side-effects Can increase dosage, firstly to 20mg q6h then up to 40 mg q6h on the first day	- Flushing or headache - Significant hypotension, maternal tachycardia,	Foetal tachycardia	Hypotension Preload-dependent cardiac lesions (e.g. aortic insufficiency)
Atosiban	Loading dose: - 6.75mg ivi over 1 minute - Then start high dose loading infusion: 75mg in 100ml. Infusion rate 24ml/hour (18mg/hour or 300mcg/min) for 3 hours - Then start low dose Maintenance infusion: (75mg/100ml) Infusion rate to 8ml/hour (6mg/hour or 100mcg/min) for 21 hours (Maximum duration: 45 hours)	- Nausea and vomiting - Dizziness and hot flushes - Tachycardia and hypotension - Hyperglycaemia - Injection site reaction		Allergy to Atosiban
Indomethacin	50 to 100mg rectal suppository Then 15mg 4-6 hrs for 48 hours	GI upset (Nausea, heartburn) Drug rash, bleeding disorders	Transient constriction foetal ductus arteriosus, oligohydramnios	Asthma Drug allergy Renal, cardiac, hepatic impairment Peptic ulcer Thrombocytopenia
Sulindac	200mg po Q12H for 4 doses			
Ritodrine	Start IV infusion using syringe pump (150mg in 50ml 5%-dextrose) with 50ug/min or 1ml/hr Increment at 15 minute-interval by 50ug/min until uterine contractions are suppressed, or maximum dosage attained (350ug/min), or complications arise Maintain infusion rate for at least 6 hours after contractions have ceased, and up to 24 hours for steroid to work	Tachycardia and hypotension Palpitation Shortness of breath chest discomfort Hypokalaemia Hyperglycaemia ECG changes (ST depression, prolonged QT interval), pulmonary edema	Foetal tachycardia Increased intraventricular haemorrhage	- Severe cardiac diseases and arrhythmia - Poorly controlled hyperthyroidism or taking beta-blocker for control of tachycardia - Poorly controlled diabetes mellitus

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