Evaluation of Tocolysis with Ritodrine: The Wadia Experience

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Summary: Ritodrine is the only drug approved by FDA for tocolysis. A trial was conducted at Nowrosjee Wadia Maternity Hospital to see the efficacy of parenteral ritodrine for management of preterm labour and its efficacy, when used prophylactically as in cases of os tightening. Solvays regimen was used for therapy.

A total of 65 patients were enrolled who fulfilled the inclusion and exclusion criteria. Of these in 15 patients ritodrine was used prophylactically and in 50 patients for management of preterm labour.

In properly selected cases tocolysis was achieved in 92.9% of patients for > 48 hrs. when gestation age at presentation was > 28 weeks.

Success to tocolysis at > 28 weeks was 92.9% while at < 28 weeks it is 38 – 39%.

Gestational age is prolonged by 1 – 4 weeks in 78% patients.
Solvay's recommendation decreased the incidence of complication of pulmonary edema.

Even in the high tech world of today, nothing supersedes the best incubator "THE UTERUS" In spite of improvement in antenatal care, preterm labour remains an important obstetric problem and poses the greatest risk to the newborn (Barden TP 1974). It has been reported that infants of < 750gm. at birth have a 20% survival rate in ontrast to 80% in infants weighing between 1000-1500gm. The time difference between these two weight classes is only about 4 weeks (Martin 1982). Other studies have shown that postponing delivery until 33 weeks of gestation causes a reduction in mortality rate (Rush et al 1978, Check 1980). A very small increase in the period of gestation can have significant improvement in the survival rate of the neonate.

Earlier the diagnosis, better is the prevention. The clinical sign that help in diagnosing preterm labour are: -

a. Cervical changes
b. Uterine activity – Objectively measured by HUAM (Home Uterine Activity Monitoring)
c. Papernick risk scoring system.
d. Decreased fetal breathing due to increase in prostaglandins.

Biochemical markers are theoretically important.
The etiopathogenesis of preterm labour: -

a. Infection.
b. Inflammation.
c. Stress.

All of which cause increase in WBC and interleukins, which in turn increase the prostaglandin (PG's) and oxytocin level and receptor concentration, thereby causing uterine contraction and cervical changes (Lamont, 1993).

A brief consideration of various tocolytic agents from isoxuprine hydrochloride to oxytocin antagonist Atosiban the latest drug in treatment of preterm labour.

A. Indomethacin: Zuckerman in 1974 used indomethacin for the first time for prevention of preterm labour. (Zuckerman et al 1984).

Comparing it's efficacy with ritodrine it has been shown that they both have the same therapeutic effect. Dual therapy with both is more effective than ritodrine alone. (Katz et al 1983)

The maternal side effect with indomethacin includes profound acute changes in maternal bleeding time but no effect on PT or PPT (Lunt et al, 1994). Pulmonary edema is seen in patients with abnormal renal functions.
Contraindications to use of indomethacin:

a. Uncontrolled hypertension.
b. Bleeding disorder.
c. Renal Disease.
d. Hypothyroidism.

B. Magnesium Sulphate: Not approved by FDA for tocolysis.

Specific indication for use are: -

a. Heart disease.
b. Diabetes mellitus.
c. Hypothyroidism.

C. Beta – Agonists: **Ritodrine** is the only drug approved by FDA for tocolysis. Terbutaline though a effective tocolytic is not a drug of choice because in doses exceeding 20 ug./ml, it shows maximum side effects like tachycardia and carbohydrate intolerance.

A brief consideration of Ritodrine Hydrochloride:

It is a beta-2 sympathomimetic agent specifically developed for uncomplicated preterm labour, being effective orally and parenterally.

Aim:

The aim of our study in N.W.M.H. was: -

a. To see clinical efficacy of ritodrine when used prophylactically in patient with high risk for preterm labour for e.g. patients in whom prophylactic os tigntening was done.
b. To see its efficacy in controlling preterm labour in patients falling within the selection criteria for the same.

Material and Methods

Prophylactic ritodrine was used IV or IM in patients who had undergone the surgery of cervical cercelage prophylactically.

Selection criteria for enrolling the patients for treatment of preterm labour were as follows:

a. Preterm uterine contraction.
b. Cervical dilatation < 4 cm.
c. Effacement < 80%.
d. No evidence of infection.
e. Intact membranes.

Exclusion criteria were as follows:

a. Antepartum haemorrhage
b. Pre-ecclampsia.
c. Hyperthyroidism.
d. Cardiac disease
e. Concurrent treatment with other beta-mimetics or beta-blockers.
f. Any condition where prolongation of pregnancy is contraindicated.

Dosage Schedule:

The dosage schedule by Solvay is by adding 2 ampoules of 50 mgm. ritodrine in 500 ml. of dextrose – 5% starting at 50ug./min. and titrating every 10 min. by 50 ug. The dose should never exceed 350 ug/min. and the fluid should not exceed 2 litres over 24 hours, to prevent maternal complication like pulmonary edema. When changing over from IV to oral therapy it is important to have an overlap of ½ hour. Treatment with anxiolytic agents further helps to prevent tachycardia.

IV dosage time schedule

Time	Dose
First 10 min.	50 ug./min.
Next 10 min.	100 ug/min.
Next 10 min.	150 ug/min.

Suggested Method of administration

Add 2 x 5 ml. amp. of ritodrine in 500 ml. of 5% w/v Dextrose

Rate (Drops / mins.)

Drip set (1ml. = 20 drops)	Paediatric set (1ml = 60 drops)
5	15
10	30
15	45

Continue effective dose (dose at which uterine contractions have ceased) for minimum 1 hour. Then reduce the dose to 100 ug./min. (if effective dose is > 100 ug./min.) and continue for 12 to 48 hours.

Monitor maternal and fetal heart rate while on infusion therapy. Initiate oral therapy minimum 30 min. before terminating IV therapy.

Administer 1 tablet (10 mg.) every 2 hours for minimum 24 hours. In the present trial patients were given 1 tablet (10 mg.) every 4 to 6 hourly and effective tocolysis was sustained.

Failure of tocolysis was considered if one could not achieve cessation of uterine contraction within the therapeutic dosage limit or presence of maternal tachycardia. In both the condition discontinuation of therapy was advocated.

Results:

The patients were analysed as per their parity, gestational age at presentation, achievement of tocolysis with particular attention given for achieving atleast 48 hours of tocolysis and pregnancy outcome in form of delivery or abortion. A study of complication was also undertaken.

Table 1

Total no. of patients analysed	Prophylactic	Therapeutic
65	15 (23%)	50 (77%)

Table II

Prophylactic patients	IM	IV
15	9	6
	(60%)	(40%)

Prophylactically used ritodrine failure was considered if parenteral treatment was required after administration of oral therapy. The failures were nil when ritodrine was used prophylactically.

Table III
Gestational Age Distribution

Total patients	<28 weeks	28-31 weeks	32-34 weeks
50	8	29	13
	(16%)	(58%)	(26%)

Hence preterm labour was most preventable between 28-31 weeks.

Table IV
Parity Distribution

Total Patients	Parity		
50	1	2-3	>3
	31	15	4
	(62%)	(30%)	(8%)

Maximum patients were primigravidas.

Table V
Achievement of Tocolysis

Total Patients	< 48 hrs.	48-72 hrs.	1-4 weeks	> 4 weeks
50	50	44	39	25
	(100%)	(88%)	(78%)	(50%)

100% tocolysis was achieved for < 24 hrs. and 88% tocolysis achieved for 48-72 hrs. In 78% of the patients tocolysis was effective for 1-4 weeks, while pregnancy could be prolonged for > 4 weeks in 50%.

Table VI
Effective tocolysis against gestational age.

Tocolysis	< 28 weeks	> 28 weeks
< 48 hrs	8 pts.	42 pts.
	(100%)	(100%)
> 48 hrs.	3 pts.	39 pts.
	(37-38%)	(92.9%)

38% tocolysis was achieved for > 48 hrs. when patients presented at < 28 weeks of gestation and tocolysis was achieved in 92.9% of patients of > 28 weeks for > 48 hrs.

Table VII
Patients delivered or aborted with gestation age.

< 28 week.	> 28 week.
6 pts.	24 pts.

Of the 6 patients in < 28 weeks group – 5 aborted, 1 delivered at 33 weeks of gestation and 2 are ongoing pregnancies. The 5 cases of < 28 weeks were nonviable.

Of the 24 patients in > 28 weeks group majority delivered at 33 weeks with an average birth weight of 1320 gm.

Complication

1 patient had severe tachycardia (144/min.) for which therapy was discontinued.
None had postpartum haemorrhage.
There was no change in blood pressure, chest pain or palpitation.
No patient had pulmonary edema.

Conclusion

Ritodrine has definite beneficial role when used prophylactically in post os-tightening patients. In properly

selected cases we have been successful in achieving tocolysis in 92.9% patients for > 48 hrs., when the gestational age at presentation is > 28 weeks, which allows enough time for the dexamethasone to act and subsequently decrease the incidence of RDS.

Prolongation of gestation by 1-4 weeks was achieved in 78% of patients which allowed a gain in birth weight.

Other inference drawn were, a success rate of tocolysis at > 28 weeks is 92.9% while at < 28 weeks of gestation it is 37-38%.

If the method of administration and monitoring is proper the complications are minimal or nil. By simultaneous administration of an anxioytic agent e.g. Alprazolam the incidence of tachycardia is further reduced. If Solvay's recommendations regarding fluid input < 2 lit./24 hrs. and using dextrose - 5% as a diluent were religiously followed the incidence of pulmonary edema was nil.

Our study clearly demonstrates that uterine relaxation can be sustained effectively by titrating the drip to 20 drops/min. and then down regulating the drip to a maintenance of 10 to 15 drops/min. The maintenance of tocolysis is sustained by further treating the patient with oral Tab. Ritodrine 10 mg. given 4-6 hourly.

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