TOCOLYSIS WITH RITODRINE: A COMPARATIVE STUDY IN PRETERM LABOUR
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ABSTRACT:
Objective: Preterm delivery is an important cause of perinatal morbidity and mortality. This study was conducted with an objective to assess the effect of ritodrine on perinatal mortality as compared to isoxsuprine and the effect of ritodrine on maternal morbidity and neonatal morbidity in comparison to isoxsuprine with the extent to which delivery was delayed.

Design: A randomized study with 25 patients with ritodrine treatment (Group-1) and 25 patients to isoxsuprine treatment (Group-2) were studied.

Setting: Rajah Muthiah Medical College and Hospital, Annamalai University, India

Results: Tocolysis was reported to be successful for more than 72 hours in 96% in ritodrine group and 84% in isoxsuprine group. Ritodrine was found superior because of lesser incidences of side effects (56%) with ritodrine and (64%) with isoxsuprine. In terms of effectiveness of tocolysis number of patients failed cases were 16% with isoxsuprine when compared to 4% with ritodrine. The mean birth weight of neonate was 3115.38 gm ± 642.3 in ritodrine groups and 2786.53 gm ± 673.43 is isoxsuprine group.

Conclusion: Ritodrine is more efficacious in delaying delivery and increasing fetal maturity as compared to isoxsuprine.

KEY WORDS: Ritodrine, Isoxsuprine, Tocolysis, Preterm Birth.

INTRODUCTION
Preterm delivery is an important cause of perinatal morbidity and mortality. Preterm labour is defined as one where the labour starts before the 36th completed week (<259 days), counting from the first day of the last menstrual period. Spontaneous preterm labour is the leading cause of preterm delivery. The incidence of preterm delivery varies between 5% and 10% of pregnancies but 70-80% of perinatal deaths occur in preterm infants. Many a time, patients are erroneously diagnosed as having preterm labour and are given treatment, which has potential maternal and foetal side effects. Past and current approaches to the prevention of preterm death have focused on the early diagnosis of Pre-Term Labour (PTL) with intact membranes and based on clinical markers such as cervical change detected manually or by ultrasound, increasing contraction frequency, vaginal bleeding and foetal behavioral states affected by labour. Aggressive tocolytic therapy with ritodrine in preterm labour allows prolongation of pregnancy by several days and even weeks. These drugs act by stimulating α-adrenergic receptors in the uterus and other organs. Ritodrine is the most widely used tocolytic, which is approved by the U.S. Food and Drug Administration for treating premature labour.¹⁻³
Risk factor for preterm labour: Women with a history of previous preterm delivery carry the highest risk of recurrence, estimated to be between 17 to 37 percent. Risk factors for preterm labour are given as follows: previous preterm delivery, Low socioeconomic status, Maternal age <18 years or >40 years, Preterm premature rupture of the membranes, Multiple gestation, Maternal history of one or more spontaneous second trimester abortions, Maternal complications (maternal or obstetric), Maternal behaviors like smoking, illicit drug use or alcohol use, Lack of prenatal care, Uterine causes like – myomata (particularly sub mucosal or sub placental), uterine septum, bicornuate uterus or cervical incompetence, Exposure to Di-Ethyl-Stilbestrol (DES), infectious causes – chorioamnionitis, bacterial vaginitis, asymptomatic bacteruria, acute pyelonephritis, cervical / vaginal colonization, fetal causes - intrauterine fetal death, intrauterine growth retardation, Congenital anomalies or abnormal placentation and presence of a retained intrauterine device.4-11

Causes of Pre Term Birth:12,13 Preterm labour is the final common pathway after several potential insults to the uterus or fetus. The preterm labour syndrome may be precipitated by several different pathophysiologic events, including intrauterine infection, uterine ischemia, uterine over distension, hormonal disturbances and other problems. Intrauterine infections are associated with increased amniotic fluid concentrations of pro inflammatory cytokines and gestational tissues and the fetus is the potential sources of these cytokines.

Since the immunology and endocrinology system regulate each other extensively, there is potential for corticotrophin-releasing hormone to regulate inflammatory responses (cytokine interleukin-1) and vice-versa. Because maternal stress is associated with preterm birth, abnormalities in the regulation of corticotrophin-releasing hormone and the production of inflammatory cytokines may be a mechanism that could form the pathophysiologic basis for the association. Preterm birth is a heterogeneous condition, which is affected by many factors such as faulty placentation & immune response, cervical incompetence, trauma and foetal anomalies. The etiology of preterm birth is multifactorial, being associated with (a) Chorioamnionitis (infection of the amniotic fluid) (b) Uterine over distension- twin pregnancy, hydramnios (excessive accumulation of amniotic fluid) (c) Uterine problems / infections outside uterus. e.g. Urinary Tract Infection (d) Maternal problems- pulmonary / systemic hypertension, renal disease, heart disease, severe anemia, malnutrition or obesity, diarrhea (dehydration may cause intra uterine fetal death/ pre term labour) (e) Surgical disorders / trauma (f) Placental abnormalities (g) Fetal anomalies (h) Pre-term rupture of membrane (PROM) (i) Cervical incompetence (j) Idiopathic (unknown reason).14-17

Rationale Use of Beta Mimetic: Uterine smooth muscle contraction and onset of labour is influenced by ã1, ã2 and ã2 adrenergic receptors in uterine wall. Stimulation of ã2 receptors is responsible for relaxation of uterus. ã2 receptors can be stimulated by nor adrenaline or by beta mimetics. However, some of these drugs also have pronounced effects on ã receptors in the heart and sometimes on ã-receptors, producing a relatively high incidence of cardiovascular and other side effects, which limit their usefulness. Hence, a beta mimetic specific to the uterine receptors is required. Ritodrine hydrochloride meets the need for the specific uterine relaxant. Ritodrine is a specific beta – mimetic for the uterus, developed specifically for obstetric use.

Unique Features of Ritodrine:3,5,18,19
* First US FDA approved tocolytic agent for preterm labour.
* Reduced incidence of neonatal death and Respiratory Distress Syndrome (RDS).
* Promotes maturation of foetal lungs.
* Low replace rate by effective treatment with I.V. infusion followed by oral administration.
* Loading dose of ritodrine infusion postponed delivery for more than 48 hrs. and beyond 37 weeks of gestation.
* Produces more rapid suppression of uterine activity and significantly improves the num
ber of days gained by the foetus in utero.

* Prolongs gestation period. In a large scale British study gestation was prolonged for 28-55 days in 50% women.

* Ritodrine is well tolerated by mother.

**METHODOLOGY**

This study was conducted in the labour ward of Rajah Muthiah Medical College and Hospital, Annamalai University, India for a period of 8 months. Our objectives of the study was to assess the effect of ritodrine on perinatal mortality as compared to isoxsuprine, evaluate the extent to which delivery was delayed with ritodrine as compared to isoxsuprine, evaluate the effect of ritodrine on maternal morbidity and neonatal morbidity in comparison to isoxsuprine and study the incidence of common side effects of ritodrine and isoxsuprine and compare them in this aspect.

All the patients presented with preterm labour were scrutinized to select the patients for tocolysis; those who fulfilled the selection criteria for tocolysis were divided into two groups with one group being administered ritodrine (Group-1) and the other isoxsuprine (Group-2). The patients receiving these two drugs were matched for age, previous risk factors, gestational age and cervical changes. In this randomized, controlled trial we studied the use of ritodrine versus isoxsuprine under ordinary clinical conditions. Patients with preterm labour that occurred between 28 to 36 completed weeks of gestation were included in this study.

**Exclusion criteria:** Patients complaining any of the following conditions were excluded from the study; suspected chorioamnionitis, foetal distress, serious vaginal bleeding, severe pre eclampsia, any condition necessitating immediate delivery, suspicion that the fetus was lethally malformed or dead, or any contraindication to the use of beta-agonist drug in the mother, such as hypovolemia, cardiovascular disease (including pulmonary hypertension and arrhythmia’s)’s hyperthyroidism, uncontrolled diabetes mellitus and asthma.20,21

The treatment was started with 2 ampoules (100mg) of ritodrine in 500ml of 5% dextrose (with 4 drops / min (0.05mg/min) via continuous infusion). Increased by 2 drops / min every 15 minutes up to 12 drops / min (0.15 mg/min) until contraction stops or maternal heart rate reaches above 140 beats / min. followed by an oral 10mg tablet before end of infusion. Tablet was continued till contraction stopped.

The second groups of patients who were treated with Isoxsuprine started initially by I.V. infusion a solution containing 100mg in 500ml of glucose injection (5%) is infused at the rate of 1 to 1.5 ml per minute (200 to 300mcg per min.) increased according to the patients response, to 2.5ml per min. with regular monitoring of blood pressure and maternal and fetal heart rate and continued until control is established. Subsequent treatment consists of I.M. injection of 10 mg every 3 hrs. for a further 48 hrs. and then 10 – 20mg by mouth 3-4 times daily. The outcome parameter is evaluated with the successful tocolysis effect of ritodrine and isoxsuprine by assessing safety and efficacy on maternal morbidity and neonatal morbidity.

**RESULT**

During the period of study fifty patients were enrolled in the study; 25 were randomized to ritodrine treatment (Group-1) and 25 to isoxsuprine (Group-2). Treatment was initiated with IV therapy followed by oral tablet.

The age variations among the two groups were found to be similar. The maximum of 40% patients was in the age group of 26-30 in the ritodrine group whereas in isoxsuprine group it was 36%. The gestational age between the two groups was also taken in to consideration. The gestational age between 34-36 weeks was 11 (44%) in ritodrine group whereas in isoxsuprine group it was 16 (64%). The details of age variations are given in Table-I.

The groups were similar with respect to maternal age, gestational age, parity and dilatation of the cervix. Details of the characteristics of the two groups are given in the Table-II. There were no significant differences in maternal age, parity, gestational age, cervical
dilatation or effacement. Previous abortions have been observed with both groups. In ritodrine group 7 (n=25) patients and in isoxsuprine group with 10 (n=25) patients. Tocolysis effectiveness was studied in these groups. Tocolysis failed in 1 (4%) and 4 (16%) patients in both groups respectively. It was successful in 24 (96%) and 21 (84%) patients with ritodrine and isoxsuprine therapy respectively. There were 14 (56%) and 8 (32%) term deliveries in both groups respectively and difference between the two treatment groups is statistically significant. Data is presented in Table-III.

Analysis demonstrated differences between the two groups. The percentage of women who delivered in 72 hrs is 4 % with ritodrine & 8 % with isoxsuprine. Full term delivery was observed in 56 % of women on ritodrine therapy whereas it was 32 % in the isoxsuprine group. Tocolysis was reported to be successful for more than 72 hours in 96% in ritodrine group and 84% in isoxsuprine group. Data given in Table-IV.

Table-I: Age variations among the two groups

<table>
<thead>
<tr>
<th>Age in Year</th>
<th>Ritodrine</th>
<th>Isoxsuprine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=25</td>
<td>n=25</td>
</tr>
<tr>
<td>15-20</td>
<td>4 (16)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>21-25</td>
<td>8 (32)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>26-30</td>
<td>10 (40)</td>
<td>9 (36)</td>
</tr>
<tr>
<td>31-35</td>
<td>2 (8)</td>
<td>3 (12)</td>
</tr>
<tr>
<td>36-40</td>
<td>1 (4)</td>
<td>1 (4)</td>
</tr>
</tbody>
</table>

Table-II: Clinical characteristics of two groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Ritodrine</th>
<th>Isoxsuprine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (in year)</td>
<td>25.84±4.52</td>
<td>26.65±6.02</td>
</tr>
<tr>
<td>Parity</td>
<td>1.74±0.79</td>
<td>1.52±0.62</td>
</tr>
<tr>
<td>Gestational age (week)</td>
<td>32.65±1.91</td>
<td>33.23±2.67</td>
</tr>
<tr>
<td>Previous abortion</td>
<td>7/25</td>
<td>10/25</td>
</tr>
<tr>
<td>Cervical dilatation (cm)</td>
<td>1.56±0.45</td>
<td>1.67±0.53</td>
</tr>
<tr>
<td>Cervical effacement (%)</td>
<td>47.39±21.15</td>
<td>48.26±17.74</td>
</tr>
</tbody>
</table>

Data presented as mean ± S.D.

Data presented as n (%)
Where n = No. of patients in the study group

dilatation or effacement. Previous abortions have been observed with both groups. In ritodrine group 7 (n=25) patients and in isoxsuprine group with 10 (n=25) patients.

Tocolysis effectiveness was studied in these groups. Tocolysis failed in 1 (4%) and 4 (16%) patients in both groups respectively. It was successful in 24 (96%) and 21 (84%) patients with ritodrine and isoxsuprine therapy respectively. There were 14 (56%) and 8 (32%) term deliveries in both groups respectively and difference between the two treatment groups is statistically significant. Data is presented in Table-III.

The mean gestational age achieved at delivery was 36.15 weeks ±1.18 and 35.5 weeks ±1.83 in the two groups respectively. There were significant differences at 5% level where P<0.05, when inter group comparisons were performed on outcome parameters. One perinatal death was reported in the isoxsuprine group. The reason was unknown. The Apgar scale was taken at the time of neonatal birth and found that both the groups were similar. The mean birth weight of neonate was 3115.38 gm ± 642.3 in ritodrine groups and 2786.53 gm ± 673.43 is isoxsuprine group. The differences were P<0.05 at 5% level that is significant

Table-V: Perinatal outcome for fetuses exposed to Ritodrine and Isoxsuprine

<table>
<thead>
<tr>
<th>Ritodrine* (n=25)</th>
<th>Isoxsuprine* (n=25)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age achievement* (Wk)</td>
<td>36.15±1.18</td>
<td>35.5±1.83</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 15</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>Female 10</td>
<td>12</td>
</tr>
<tr>
<td>Birth Weight* (gm)</td>
<td>3115.38±642.30</td>
<td>2786.53±673.43</td>
</tr>
<tr>
<td>Admission to NICU</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Apgar Score &lt;7</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1 min. 9</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>5 min. 2</td>
<td>2</td>
</tr>
<tr>
<td>Death (neonatal)</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Delivery *</td>
<td>Normal 18 (72)</td>
<td>15 (60)</td>
</tr>
<tr>
<td></td>
<td>Caesarian (LSCS) 7 (28)</td>
<td>10 (40)</td>
</tr>
</tbody>
</table>

*Data are presented as Mean ± S.D., + n (%)

It was found that 44% of women were in primi pregnancy in ritodrine group as compared to 36% women in isoxsuprine group. Pharmacoeconomics of the two drug treatments was has also studied. The duration of treatment with ritodrine ranged from 2 to 5 days whereas treatment duration with isoxsuprine ranged from 4 to 14 days. The cost involved in treatment with ritodrine ranged from Rs.207.00 - 315.00 when compared to isoxsuprine treatment of Rs. 74.90 - 101.60. It has been observed that the cost involved in isoxsuprine treatment as compared to ritodrine treatment is in 1:3 ratios. Treatment cost doesn’t include patient bed charges and other expenses. The average cost of therapy per patient with ritodrine is Rs.229.68 when compared to isoxsuprine treatment Rs.82.29.

**DISCUSSION**

Our study demonstrated that isoxsuprine is a comparable but not superior tocolytic agent when compared with ritodrine hydrochloride. Preterm labour is probably a syndrome of disorders with different causes and associated perturbations of the mechanisms responsible for regulating uterine contractility.

Although the regulation of uterine contractility is complex and incompletely understood, it is believed that â-adrenergic agents act through a different cellular mechanism to achieve uterine quiescence. On both drug
comparisons results showed that mean prolongation of 23.46 days ± 15.26 with ritodrine and 15.30 days ± 13.44 with isoxsuprine. It was also observed that the achievement of gestational age in both the groups was 36.15 weeks ±1.18 and 35.50 weeks ±1.83 respectively. Compared to ritodrine, the outcome with isoxsuprine treatment group had more number of patients complaining of side effects. The percentage of caesarian cases was 28% with ritodrine & 40% with isoxsuprine.

CONCLUSION

This study shows that ritodrine is more efficacious in delaying delivery and increasing fetal maturity as compared to isoxsuprine.

Ritodrine therapy is three times more sensitive than the isoxsuprine therapy. As regards benefit and cost effectiveness, ritodrine is superior because of lesser incidences of side effects (56%) with ritodrine and (64%) with isoxsuprine. In terms of effectiveness of tocolysis number of patients failed cases were 16% with isoxsuprine when compared to 4% with ritodrine. Ritodrine was effective with term birth’s in 56% as compared to 32% of isoxsuprine treatment. Comparisons of both the drugs showed mean prolongation of 23.46 days ± 15.26 with ritodrine and 15.30 days ± 13.44 with isoxsuprine and in term of foetus outcome ritodrine showed a better outcome with a mean birth weight of 3115.38 gm. ± 642.30 when compared to isoxsuprine 2786.53 gm. ± 673.43.

REFERENCES