Magnesium Sulfate Versus Ritodrine Hydrochloride for Preterm Labor Management

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OBJECTIVE: To compare the tocolytic effectiveness and side effects of $MgSO_4$ and Ritodrine Hydrochloride for preterm labor treatment.
STUDY DESIGN: Randomly selected 150 cases of singleton pregnant women hospitalized because of preterm labor in 1 year period were evaluated prospectively.
RESULTS: In cases whose cervical dilatations were ≤2 cm, and cervical effecements ≤50%, both tocolytic agent postponed delivery effectively for ≥48hrs and ≥7days. In cases whose cervical dilatations were >3-4 cm, and cervical effecements >50%, tocolytic effectiveness was not different between $MgSO_4$ and Ritodrin groups; and, rates of success of both agents for postponing delivery for ≥7days were observed to be lower. Rates of delivery after 36th weeks of pregnancy, gestational week at delivery and gained time by tocolysis were same in two groups.
CONCLUSION: There is no difference between $MgSO_4$ and Ritodrin in the effectiveness of tocolytic treatment. Because of the lower side effects, we thought $MgSO_4$ may be first line agent for tocolysis.
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Key Words: Magnesium sulfate ($MgSO_4$), Ritodrin, Tocolysis, Preterm labor

Preterm labor and delivery are most important causes of perinatal morbidity and mortality.[1] The efficacy and safety of the most commonly used tocolytic agents-beta adrenergic agonists and intravenous magnesium sulfate- have been questioned.[2] Their failure to significantly decrease the incidence of preterm delivery may be caused primarily by failure to detect preterm labor early enough as patients are candidates for treatment.[3]

Materials and Methods

This study is performed prospectively on randomly selected 150 chorioamniotic membranes intact singleton pregnant women hospitalized because of preterm labor between 01.04.2000 and 01.04.2001 in Zeynep Kamil Women and Children's Education and Research Hospital. During this time period, 1700 pregnant women with preterm labor were hospitalized. Women whose gestational age were between 20 to 36 gestational weeks basing on last menstrual period and first trimestr crown rump length measurement were included in the study. Preterm labor was diagnosed by the existence of at least 1 regular uterine contraction confirmed by cardiotocography in a 10 minute period lasting at least 30 seconds and associated with cervical effecement and dilatation.

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Patients with cervical dilatation higher than 4 cm, unknown last menstrual period or without first trimester ultrasonographic examination and with additional high risk factors (multiple gestation, preeclampsia, PROM, fetal distress, chorioamnionitis, ablatio placenta, fetal anomaly, intraauterine growth restriction etc.) were excluded. Randomly selected 70 and 80 cases of 150 were treated with magnesium sulfate ($MgSO_4$) and ritodrine hydrochloride (HCl), respectively. Patients admitted to hospital in single days of the month were recruited in $MgSO_4$ group and others in ritodrine HCl.

All cases were observed in delivery room during their treatment and then in high risk pregnancy section. All cases were examined vaginally to determine cervical effecement and dilatation. Uterine contractions were evaluated by uterine palpation (every four hour) and by external electronic fetal monitor (two times a day). Bed rest in lateral decubitus position was advised. Fetal anatomy and biometrical measurements, amniotic fluid, placental localisation were obtained by ultrasonographic examination. Complet urine analysis and urine culture, complet blood count, serum electrolites, glucose, urea and electrocardiogram were obtained. Cases with urinary infection were treated by ampicilline 1 g, q.i.d.

After 6 g loading dose of $MgSO_4$ (1 ampule= 10 ml= 1.5 g) in 150 ml of dextrose 5% was administered over 20 minutes, continuous intravenous infusion of 2 g/h in 100 ml of Ringer lactate was began by infusion pump. Dose was increased 0.5 g/h every 30 minutes until cessation of uterine contractions or serious side effects occurred. If contractions persisted after 1 hour, the infusion was increased to 3 g/hr. After a 12 hour period without uterine contraction, infusion was stopped.

Two ampules of ritodrine HCl (1 ampule=50 mg) was added to 500 cc of dextrose 5% and infused at 50mg/min

and increased every 15-20 minutes by 50mg/min until contractions were inhibited or serious side effects occured (ie., chest pain, shortness of breath, hypotension, or extreme tachycardia). Maximum dose was 350 mg/min. After a 12 hour period without uterine contraction, infusion was stopped.

During treatment blood pressure, heart rate, respiration were evaluated hourly in both groups. Urine output and reflexes were evaluated hourly in $MgSO_4$ group. Successfully treated cases were sent home and called once a week to evaluate. Information for signs of preterm labor were given to all cases. Great amount of water consumption, bed rest, restriction of physical activity and coitus were advised. Oral maintenance therapy was not administered to any case.

Cessation of uterine contraction for at least 48 hours and 7 days or longer, delivery after 36 weeks of gestation were accepted as 'short-term success of tocolytic therapy' and 'long-term success of tocolytic therapy', respectively.

Betamethasone (12 mg intramuscularly in two doses 24 hours apart), was administered to accelerate fetal lung maturation in all cases.

Treatment was accepted as unsuccessful if amniorrhexis and/or serious side effects of therapy was observed or uterine contractions continued, cervical effecement and dilatation increased. Tocolytic therapy was stopped when cervical dilatation greater than 4 cm and effecement greater than 80% was examined. Success rates, effects on fetus and mother of both therapy were evaluated.

Statistical analysis of the study was performed by SPSS 9.0 (Statistical Package for Social Sciences) software program. Student t test, Mann Whitney U test, Chi-square, Fisher's exact test were used in the statistical analyses of the data.

Results

$MgSO_4$ and ritodrine HCl groups were found to be similar for maternal characteristics (Table 1). In both groups, preterm delivery was postponed successfully greater or equal to 48 hours in 59 cases (84.3%) and 64 cases (80.0%), ($p< 0.05$); and ≥7 days in 49 cases (70.0%) and 54 cases (67.5%) ($p<0.05$), respectively. Longer periods gained by tocolysis by $MgSO_4$ and ritodrine HCl were 77 and 70 days, respectively.

Table 2 shows success of therapy in both groups. In cases whose cervical dilatations were ≤2cm, gained time ≥48 hours and for ≥7 days were not different between $MgSO_4$ and ritodrine HCl groups. In cases whose cervical dilatations were >3-4 cm, gained time ≥48 hours and for ≥7 days were not different between $MgSO_4$ and ritodrine HCl groups too.

Pretreatment serum magnesium level was 1.98±0.77 mg/dl. During treatment, serum magnesium levels were 4.97 ±0.77 mg/dl and 5.10±1.05 mg/dl in cases treated with 2 g/h and 3 g/h magnesium, respectively. Treatment failure was seen in 8 cases in both groups. The mean pre and during treatment basal fetal heart rates in $MgSO_4$ and ritodrine HCl groups were 141.6±8.1 beats/min vs 140.7±8.7 beats/min, p=0.83 and 143.5±14.1 beats/min vs 147.9±8.1 beats/min, p=0.001, respectively.

Maternal mean pre and during treatment heart rates in MgSO4 and ritodrine HCl groups were 91.1±11.0 beats/min vs 89.4±11.6 beats/min, p=0.014 and 91.3±10.4 beats/min vs 111.8±11.1 beats/min, p=0.001, respectively. Maternal mean pre and during treatment sistolic blood pressures in MgSO4 and ritodrine HCl groups were 113.7±16.9 mmHg vs 112.4± 14.2 mmHg, p=0.4 and 106.0±11.5 mmHg vs 105.9±8.8 mmHg, p=0.9, respectively.

Maternal mean pre and during treatment diastolic blood pressures in $MgSO_4$ and ritodrine HCl groups were 69.1± 12.0 mmHg vs 68.6±9.7 mmHg, p=0.6 and 66.2±13.1 mmHg vs 63.3±7.2 mmHg, p=0.017, respectively.

Increased maternal heart rate was treated by decreasing infusion rate in ritodrine HCl group.

Table 3 shows side effects observed during therapy in two groups. In both groups, no serious side effect of therapy was seen. Minor side effects were seen in 27 (8.57%) and 50 (62.5%) cases in magnesium and ritodrine HCl groups, respectively.

Table 4 shows neonatal outcomes. There was no intrauterine fetal exitus in both groups.

Discussion

Early diagnosis of preterm labor is difficult. In the controlled studies detecting the effectiveness of the tocolytic agents, different success rates with placebo (from 44% to 73%) is probably due to false diagnosis of preterm labor.[2,4-8]

In our study, tocolytic therapy was accepted successful in short term when gained time by tocolysis was equal or higher than 48 hrs. It is necessary to delay delivery at least 48 hrs to obtain maximum benefit from corticosteroid for accelerating fetal lung maturity.

In our study, all over success rates of $MgSO_4$ and ritodrine HCl for gaining time ≥48 h were 84.3% and 70.0%, respectively; and for gaining time ≥7 days were 81.0% and 68.4 %. We could not find any statistical difference between $MgSO_4$ and ritodrine HCl in the success rates for postponing delivery ≥48 hrs and ≥7 days. This finding correlates with the results of other studies.[9-11] In accordance with the conclusions of Martin et al[12] and Ricci et al,[13] we also found that the rates of delivery after 36 weeks of gestation, gestational week at delivery, and gained time (days) were not different between $MgSO_4$ and ritodrine HCl groups.

Table 1. Maternal characteristics in both groups

	$MgSO_4$ (n=70)	Ritodrine HCl (n=80)	p
Mean age (years) ± SD	25.25±6.04 (17-43)	24.18±4.63 (18-41)	0.085
Mean parity ±SD	0.92±1.23	0.68±0.90	0.392
Mean Gestational age (weeks) ±SD	31.75±2.29 (25-35)	31.78±2.50 (26-35)	0.939
Mean cervical dilatation (cm)±SD	1.47±1.05	1.76±1.20	0.162
Cervical dilatation (n,%)			
≤ 2 cm	56 (80.0%)	59 (73.7%)	0.09
>3-4 cm	14 (20.0%)	21 (26.3%)	
Cervical effecement (n, %)			
≥50%	24 (34.3%)	28 (35.0%)	0.927
< 50%	46 (65.7%)	52 (65.0%)	
Delivery>36 gestational week (n,%)	33 (47.1%)	28 (35.0%)	NS
Mean gestational age at delivery±SD	34.90± 2.66	34.33 ± 3.04	NS
Mean gained time (days) ±SD	24.00±17.19	19.36 ± 16.36	NS

Table 2. Gained times according to cervical dilatation and effecement.

	CD ≤2 cm		CD> >3-4 cm		CE ≥%50		CE<%50	
	MgSO4 n=56	Ritodrine n=59	MgSO4 n=14	Ritodrine n=21	MgSO4 n=24	Ritodrine n=28	MgSO4 n=46	Ritodrine n=52
Gained time								
≥48hrs (n,%)	54 (96.4%)	50 (84.7%)	5 (35.7%)	14 (66.7%)	15 (62.5%)	17 (60.7%)	44 (95.6%)	47 (90.4%)
≥7days(n,%)	44 (78.6%)	44 (74.6%)	5 (35.7%)	10 (47.6%)	10 (41.7%)	13 (46.4%)	39 (84.8%)	41 (78.8%)

Table 3. Side effects.

	$MgSO_4$ (n=70)	Ritodrine HCl (n=80)	p
Vomitus (n, %)	8 (11.4%)	16 (20.0%)	0.15
Nausea (n, %)	6 (8.6%)	10 (12.5%)	0.43
Head ache (n, %)	4 (5.7%)	10 (12.5%)	0.0001
Chilling (n, %)	0	15 (18.7%)	0.15
Tachicardia (n, %)	1 (1.4%)	24 (30.0%)	0.00001
Palpitation (n, %)	1 (1.4%)	36 (45.0%)	0.0001
Vertigo (n, %)	3 (4.3%)	1 (1.2%)	0.34
Hot flushing (n, %)	30 (%42.9)	2 (2.5%)	0.0001
Weakness (n, %)	6 (%8.6)	3 (%3.75)	0.037
Burning in eyes (n, %)	4 (5.7%)	1 (1.2%)	0.18
Accelerated ventilation (n, %)	0	6 (7.5%)	0.021
Dose decreament (n, %)	0	20 (25.0%)	0.0001
Stopping the treatment (n, %)	0	2 (2.5%)	0.50

Table 4. Neonatal outcomes.

	Ritodrine HCl	MgSO4	p
Mean neonatal weight (g) ± SD	2702.4±654.3	2566.8±637.1	0.205
Mean Apgar (1min.) ± SD	7.3±1.4	7.4±1.4	0.68
Mean Apgar (5 min.) ± SD	8.6±1.2	8.7±1.1	0.76
Perinatal mortality (n, %)	2 (2.8%)	3 (3.7%)	>0.05
Intrauterine fetal loss (n, %)	0	0	

Because of tachyphylaxis, the effectiveness of ritodrine is limited for inhibition of myometrial contractions whereas, magnesium sulfate reduces the frequency of spontaneous contractions without affecting the amplitude.[14]

Elliot et al[15] treated 355 amniotic membrane intact pregnant women at preterm labor with $MgSO_4$ and delayed delivery for 48 hrs in 76% of cases; in cases whose cervical dilatation were ≤2cm and >3-4 cm, this rate was 87% and 64%, respectively. Delivery was delayed for ≥7 days in 51% of cases; in cases whose cervical dilatation were ≤2cm and >3-4 cm, this rate was 64% and 56%, respectively. Authors concluded that $MgSO_4$ is effective tocolytic agent and the dose may be increased to 3g/h if necessary.

Dudley et al[16] reported the rate of tocolytic success of $MgSO_4$ for 72 hrs as 56% and concluded that the success of therapy was lower in cases with increased cervical dilatation. This authors defined maximum dose of $MgSO_4$ as 4g/h.

Spisso et al[17] found the success rates of $MgSO_4$ to delay delivery for 48 hrs and, ≥7 days as 70.6% and 45.4%, respectively. These rates were 84.3% and 36.9%, respectively for cases with cervical dilatation of ≤2cm and >3-5 cm. Authors defined maximum dose as 2.4 g/h and concluded that $MgSO_4$ was an effective tocolytic agent provided it is started in the early latent phase of labor.

Madden et al[18] evaluated the success of tocolysis due to cervical dilatation in 83 patients treated by $MgSO_4$ and reported the rates of success for 48 hrs in cases whose cervical dilatations were ≤2cm and >3-4 cm as 88.0% and 47.7%, respectively. Success rates in these groups for 7 days were 68.0% and 32.0%, respectively. These authors defined maximum dose of $MgSO_4$ as 3 g/h.

Hollander et al[10] compared the succes rates of $MgSO_4$ and ritodrine HCl on 72 cases, and found these rates as 88.0 % vs 79.7% for 72 hrs, as 75.0% vs 72.0% for ≥7 days, respectively. Authors concluded that $MgSO_4$ might be used as first line tocolytic agent whereas, Cox et al[5] concluded that $MgSO_4$ is not an effective tocolytic agent, basing on a controlled study performed on 56 cases. Authors found the succes rates for 48 hrs in $MgSO_4$ group and control group as 70.0% and 73.0%, respectively, and for ≥7 days as 52.0% and 64.0%, respectively. These authors defined maximum dose of $MgSO_4$ as 3 g/h. Statistical power may be lower in these two studies due to small study group

Spellacy,[6] basing on a controlled study performed on 39 cases, reported the success rates for 48 hrs in ritodrine HCl and placebo groups as 43.0% and 27.0%, respectively.

Leveno et al,[2] in their controlled study, found the success rates for 24 hrs were 72.0% and 52.0%, and for ≥7 days 55.0 % and 39.0%, in ritodrine HCl and control groups, respectively and concluded that ritodrine HCl was an effective agent for short-term but not for long-term.

Beall et al,[9] in their study comparing the effectiveness of ritodrine HCl, terbutaline and $MgSO_4$ for postponing preterm delivery for 48 hrs, found these rates as 69.0%, 47.0%, 70.0%, respectively, and concluded that there was no difference in the effectiveness of these agents.

Wilkins et al,[11] in a controlled study comparing the effectiveness of $MgSO_4$ and ritodrine HCl on 128 cases, found the tocolytic effectiveness of both agents were same. Success rates for both agents for 48 hrs and ≥7 days were 92.3% vs 96.3% and 80.3% vs 83.3%, respectively.

Macones et al[19] didn't find any differences between tocolytic effectiveness of magnesium sulfate and ritodrine. They found a significant difference between two drugs in the frequency of medication discontinuation because of side effects, but not in the frequency of major adverse drug events.

We postponed preterm delivery succesfully for ≥48 hrs in both groups. We didn't administer neither ritodrine HCl nor $MgSO_4$ for oral maintenence therapy. During effective tocolytic treatment by ritodrine HCl and $MgSO_4$ infusion, blood levels of these agents were found to be 91-123 ng/ml and 4-8mg/dl, whereas, during oral maintenence, these levels were found to be 3.2-30.5 ng/ml and 1.8-2.1 mg/dl, respectively. So, effectivenesses of oral administration of both agents were debatable.[12] Other controlled studies concluded with the same idea.[2,13,20,21]

We found blood $MgSO_4$ levels in cases administered doses of 2 g/h and 3 g/h as 4.97±0.77 mg/dl and 5.10±1.05 mg/dl, respectively. These values are in accordance with literature finding.[10]

Side effects of therapy were seen 38.5% and 62.5% in $MgSO_4$ and ritodrine HCl groups. Tachicardia was not observed in $MgSO_4$ group, whereas it was observed in 45.0% of ritodrine HCl group. Rate of infusion was decreased because of severe tachycardia in 25.0% of ritodrine HCl group.

Side effects of tocolysis by $MgSO_4$ include hot flushing, weakness, nausea, vertigo, eye burning, deficits in attention and working memory, deficits in information-processing ability[5,10,11,15,22] ritodrine HCl frequently causes nausea, vomiting, vertigo, chilling, palpitation, tachycardia, increased rate of ventilation.[4,9-11,21,23,24] Breast engorgement and galactorrhea occasionally occur during tocolysis with ritodrine and Magnesium sulfate.[25]

Pezzati et al[26] suggested that maternal antenatal administration of magnesium sulphate compared to ritodrine, does not induce any significant differences either in cerebral blood flow velocity or in cerebral vascular resistance of preterm infants in the first hours of life, whereas, Rantonen et al[27] found that maternal $MgSO_4$ treatment was associated with lowered cerebral perfusion in preterm infants on the first day of life.

Early vascular stabilizing effect of antenatal $MgSO_4$ exposure may contribute to a lowered risk of cerebral vascular catastrophes, in the vulnerable areas of the brain, among the preterm infants with respiratory distress syndrome.[28] On the other hand, ritodrine did not appear to affect the incidence of neonatal IVH.[29]

The rate of side effect necessitating to stop treatment of $MgSO_4$ and ritodrin were reported as 2.0% and 30.0%, respectively,[11] and we concluded that the side effect frequency of tocolysis with $MgSO_4$ was lower than ritodrine HCl. Wil-

kins et al[11] also reported side effect frequency to be insignificantly higher in cases treated with ritodrine HCl than $MgSO_4$ (20% vs 14%). On the other hand, Hollander et al[10] reported higher side effect frequency of two agents without giving a percent, and stressed that the side effects might be serious by $MgSO_4$.

Ritodrine infusion may alter placental and cerebral blood flow and may have a selective effect on the left side of the heart.[30] In pregnant women with threatened preterm labour intravenous administration of ritodrine decreases vagal cardiac baroreflex sensitivity and vagal modulation of heart rate, and increases sympathetically mediated blood pressure variability. Decreased baroreflex sensitivity and heart rate variability are known to be associated with a poor prognosis in some patient groups, so the effects of ritodrine tocolysis may be unfavourable in women with impaired circulatory homeostasis.[31] Wilkins et al[11] reported that both ritodrine HCl and $MgSO_4$ didn't have any effect on neither systolic (SBP) nor diastolic blood pressure (DBP), whereas Thiagarojah[32] reported that tocolysis by $MgSO_4$ lowered systolic blood pressure but not have any effect on diastolic blood pressure. We could not found any difference in SBP, DBP and maternal heart rate between pre and during tocolysis by $MgSO_4$. Fetal heart rate was not changed. Ritodrine HCl increased maternal heart and fetal heart rates significantly but not had any effect on SBP, DBP, and variability of FHR. Thiagarojah[32] and Brar[33] also could not found any change in variability of FHR due to ritodrine HCl.

In accordance with the results of other studies,[5,13,34] we observed that either $MgSO_4$ nor ritodrin HCl had effect on Apgar scores, birth weight and perinatal mortality. There was no intrauterine fetal loss. Rates of neonatal loss in $MgSO_4$ and ritodrin were 3.75% and 2.85%, respectively.

Conclusion

There is no difference between $MgSO_4$ and ritodrin in the effectiveness of tocolytic treatment.

In cases whose cervical dilatations were ≤2 cm, and cervical effecements ≤50%, both tocolytic agent postponed delivery effectively for ≥48hrs and ≥7days.

In cases whose cervical dilatations were >3-4 cm, and cervical effecements >50%, tocolytic effectiveness was not different between $MgSO_4$ and ritodrin groups. In these cases, rates of success of both agent for postponing delivery ≥7 days were observed to be lower.

Rates of delivery after 36th weeks of pregnancy, gestational week at delivery, gained time by tocolysis were same in two groups.

Because of the lower side effects, we thought MgSO4 must be first line agent for tocolysis.

Preterm Travayın Yönetiminde Magnesyum Sülfat ile Ritodrin Hidroklorid'in Karşılaştırılması

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Preterm travayın tedavisinde $MgSO_4$ ve Ritodrin Hidroklorid'in tokolitik etkinliklerinin ve yan etkilerini karşılaştırmak amacıyla bu çalışma planlandı. Bir yıllık bir dönemde preterm travay nedeni ile hastaneye yatırılan tekiz gebelikli olgular arasında rasgele olarak seçilen 150 olgu ileri dönük olarak değerlendirildi. Servikal dilatasyonları ≤2 cm ve servikal efasmanları ≤50% olan olgularda doğum hem 48 saatten uzun hem de 7 günden uzun süreyle her iki ajanla etkili bir şekilde ertelendi. Servikal dilatasyonu >3-4 cm ve servikal efasmanı >50% olan olgularda iki grup arasında tokolitik etkinlik bakımından fark yoktu; her iki ajanın doğumu 7 günden uzun süreyle ertelemedeki başarısı düşük olarak gözlendi. 36. cı haftadan sonra doğum, doğumdaki gebelik haftası ve tokoliz ile kazanılan süre iki grupta aynı idi. $MgSO_4$ ve Ritodrin in tokolitik etkinlikleri arasında farklılık yoktur. Yan etkilerinin az olması nedeni ile $MgSO_4$ ilk seçilecek tokolitik ajan olabilir.

Anahtar Kelimeler: Magnezyum sülfat ($MgSO_4$), Ritodrin, Tokoliz, Preterm eylem

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