

## A Comparison between Magnesium Sulphate and Ritodrine on Delaying The Active Phase of Labor in Women with Premature Rupture of Membranes with Preterm Labor

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### ABSTRACT

**Background:** Preterm premature rupture of membranes (PPROM) refers to PROM before 37 weeks of gestation. It is responsible for, or associated with, approximately one-third of preterm births and the single most common identifiable factor associated with preterm labor (PTL). This is the leading cause of perinatal morbidity and mortality. Management of preterm labor includes bed rest, adequate hydration, prophylactic cervical cerclage and use of tocolytic drugs. Administrations of tocolytic drugs including magnesium sulphate (MgSO<sub>4</sub>) and ritodrine have considerable influences on pregnancy outcomes.

**Objective:** The present study aimed at comparing between the effects of magnesium sulphate administration and ritodrine on delaying the active phase of labor in women with premature rupture of membrane (PROM) and preterm labor, and determining the best drug with best results and fewest side effects.

**Patients and Methods:** The present study was conducted on 80 patients, with established PROM, whose gestational ages ranged between 28 and 34 weeks, admitted to the hospital with PROM with PTL. In the current study, patients were allocated into two equal groups: group A (MgSO<sub>4</sub>), and group B (Ritodrine).

**Results:** Both drugs (MgSO<sub>4</sub> and ritodrine) were effective on prolonging the gestational age of the studied women in both groups, and there was no significant difference between both groups. MgSO<sub>4</sub> had fewer side effects than ritodrine, and there was significant difference between both groups.

**Conclusion:** Both magnesium sulphate and ritodrine increase delay in reaching the active phase of labor in women with PROM with preterm labor.

**Keywords:** PROM, PTL, Tocolytics, Delay, Labor, Magnesium Sulphate and Ritodrine.

### INTRODUCTION

Premature rupture of membranes (PROM) is the rupture of the fetal membranes before the onset of labor. In most cases, this occurs near term. However, when membrane rupture occurs before 37 weeks' gestation, it is known as preterm PROM (PPROM). PPRM is one of the clinical subtypes of preterm birth, and occurs in ~3% of pregnancies, resulting in one-third of preterm births. It remains the leading cause of preterm deliveries and neonatal mortality and morbidity<sup>(1)</sup>.

Preterm labor is a leading cause of perinatal morbidity and mortality. In spite of the improvement in survival rates of preterm neonates, they are at increased risk of long term neurodevelopmental disabilities, respiratory and gastrointestinal complications. More than three-quarters of premature babies can be saved with feasible, cost effective care, e.g. essential care during child birth and in the postnatal period for every mother and baby, antenatal steroid injections given to pregnant women at risk of preterm labor<sup>(2)</sup>.

Management of preterm labor includes bed rest, adequate hydration, prophylactic cervical cerclage and use of tocolytic drugs. Various tocolytic agents include  $\beta$  mimetics (Ritodrine), MgSO<sub>4</sub>, prostaglandin inhibitors (Indomethacin), calcium

channel blockers (Nifedipine), nitrate (Nitroglycerine) and oxytocin receptor blockers (Atosiban)<sup>(3)</sup>.

Tocolytics are used to ensure the administration of corticosteroids and transportation to a center with neonatal intensive care unit facilities, tocolytic therapy can be administered for 48 hours. Throughout the years several types of tocolytic drugs have been used, all with different mechanisms of action<sup>(4)</sup>.

The aim of this study was to compare between the effects of magnesium sulphate administration and ritodrine on delaying the active phase of labor in women with premature rupture of membrane (PROM) and preterm labor, and determining the best drug with best results and fewest side effects.

### SUBJECTS AND METHODS

This study was a comparative study which was conducted at the Department of Obstetrics and Gynecology, Al- Hussein University Hospital from July, 2017 to Mars, 2018 on pregnant women with gestational age from 28 to 34 weeks, who were hospitalized for PPRM. The study was approved by the Ethics Board of Al-Azhar University.

Patients were allocated into two equal groups: group A (Magnesium sulphate- treated) included 40

pregnant women and group B (Ritodrine-treated) included 40 pregnant women.

They all received a corticosteroid in the form of 4 doses of dexamethasone (6 mg 12 h apart) and ampicillin (2 g intravenously every 6 hours for 48 hours), followed by amoxicillin (500 mg orally 3 times daily) for an additional 5 days.

**Group A** received 4 g of MgSO<sub>4</sub> dissolved in 100 mL of normal saline solution for 20 minutes to reach loading dose. Then, they received 2 g of MgSO<sub>4</sub> dissolved in 100 mL of normal saline by infusion every hour. Infusion was continued until 24 hours after complete cessation of uterine contractions.

During therapy, strict monitoring of the respiratory rate, knee jerk and urine output were observed. MgSO<sub>4</sub> was stopped if respiratory rate was less than 12/min, loss of knee jerk, or urine output less than 100 ml/4 hours. Total IV fluids in 24 hours did not exceed 3000 ml. Magnesium therapy was continued for 24 hours with the lowest effective dose to keep the patient away from having contraction.

**Group B** received the β-adrenergic receptor agonist ritodrine (Yutopar®). In a dose of 50 µgm/min by intravenous infusion. It increased by a rate of 50 µgm/min every 15 minutes if needed till a maximum dose of 350 µgm/min according to the situation. The infusion was stopped after cessation of contractions by 24 hours.

Strict monitoring of pulse and blood pressure every 15 minutes was done, and the drug was stopped if heart rate exceeded 130 beats per minute or blood pressure decreased below 90/60. Chest pain or dyspnea warranted stoppage of the drug and cardiological assessment.

The study was approved at Al-Azhar University ethical committee. All persons enrolled to the study signed informed consents. The study was conducted at level of declaration of Helsinki.

### **Statistical analysis**

Data were statistically described in terms of range, mean±standard deviation (± SD), frequencies (number of cases), and relative frequencies (percentages) when appropriate. For comparing categorical data, Chi square (x<sup>2</sup>) test was performed.

A probability value (p value) less than 0.05 was considered statistically significant.

### **RESULTS**

Comparison between the baseline characteristics was presented followed by comparison between the results of management among the two groups.

Concerning the baseline characteristics, several items were compared; this included socio demographic criteria including (maternal age, parity, gestational age at presentation and history of preterm labor), frequency of contractions, and Bishop Score.

Concerning the results of treatment, several items were compared; this included frequency of contractions, Bishop Score after treatment, prolongation of pregnancy in days, mode of delivery and drug complications.

Concerning neonatal outcome, Apgar scores at 1 and 5 minutes, neonatal birth weight and the percentage of admission to the incubator were compared among the two groups.

Patients were allocated into two equal groups: group A (Magnesium sulfate) and group B (Ritodrine).

Table (1) represented demographic data (maternal age, parity, gestational age at presentation and history of preterm labor). 60% of group A were at the age group 25-35 years, while, in group B, 45% of the studied women were in the age group 15-25 years, and 45% were in the age group 25-35 years. Mean age of both groups was 27.4 ± 5.7 years with no significant difference between both groups. 57.5% of the studied women in group A, and 47.5% of women in group B were para 1-2.

Mean number of parity was 1.6 ± 1.2; there was no significant difference between both groups. 62.5% of group A, and 70% of group B, were 30-34 weeks of gestation. Mean of gestational age of both groups was 31.9 ± 2.4 weeks, with no significant difference. 47.5% of group A had no history of PTL, and 42.5% had history for PTL for single time. In group B, 42.5% had no history of PTL, with mean 0.73± 0.78; there was no significant difference between both groups regarding history of PTL.

**Table (1): Comparison between the two groups according to demographic criteria**

Groups Variables	Group A (MgSO <sub>4</sub> )		Group B (Ritodrine)		X <sup>2</sup> P value
	No.	%	No.	%	
<b>Age (years)</b>					
15<25	13	32.5	18	40.5	X <sup>2</sup> = 1.806 P= 0.405
25<35	24	60.0	18	45.0	
35-45	3	7.5	4	10.0	
Min-Max	18-38				
Mean± SD	27.4 ± 5.7				
<b>Parity</b>					
0	7	17.5	10	25.0	X <sup>2</sup> = 1.910 P=0.591
1-2	23	57.5	19	47.5	
3-4	10	25.0	10	24.0	
>4	0	0.0	1	2.5	
Min-Max	0-5				
Mean± SD	1.6 ± 1.2				
<b>Gestational age (Weeks)</b>					
25<30	15	37.5	12	30.0	X <sup>2</sup> = 0.503 P=0.478
30-35	25	62.5	28	70.0	
Min-Max	26-34				
Mean± SD	31.9 ± 2.4				
<b>History of pre-term labor</b>					
None	19	47.5	17	42.5	X <sup>2</sup> = 3.56 P=0.312
Once	17	42.5	13	32.5	
Twice	4	10.0	9	22.5	
Three times	0	0.0	1	2.5	
Min-Max	0-3				
Mean± SD	0.73± 0.78				

Table (2) showed (frequency of contractions in 20 minutes and Bishop Score) before and after treatment. Before treatment, there were 4 contractions in most patients of group A, whereas 60% of patients in group B had 4 contractions in 20 minutes. Mean of frequency of contractions of both groups was  $4.2 \pm 0.43$ , there was significant difference between both groups. Regarding Bishop Score, 52.5% of the studied women in group A and 45% of women in group B had 6 in that score. Mean score was  $5.08 \pm 1.02$  with no significant difference between both groups.

After treatment, frequency of contractions was 3-4 in about 33% of women in group A, while 40% of women in group B had 5-6 contractions. Mean of frequency of contractions in 20 minutes was  $2.8 \pm 1.9$  with no significant difference between both groups. Bishop Score was 5-7 in 52.5% of the studied women in group A, while in group B, that score was 2-4 in 42.5% in the studied women and 5-7 in 40% of women of the same group. Mean was  $6.08 \pm 2.5$ , with no significant difference between both groups.

**Table (2): Comparison between the two groups according to frequency of contractions/20 minutes and Bishop Score**

Groups Variables	Group A (MgSO <sub>4</sub> )		Group B (Ritodrine)		X <sup>2</sup> P value
	No.	%	No.	%	
<b>Frequency of contractions/20minutes before treatment</b>					
Four	36	90.0	24	60.0	X <sup>2</sup> = 9.6 P= 0.002*
Five	4	10.0	16	40.0	
Min-Max	4-5				
Mean± SD	4.2 ± 0.43				
<b>Bishop score before treatment</b>					
Four	18	45.0	17	42.5	X <sup>2</sup> = 3.06 P= 0.383
Five	1	2.5	4	10.0	
Six	21	52.5	18	45.0	
Eight	0	0.0	1	2.5	
Min-Max	4-8				
Mean± SD	5.08 ± 1.02				
<b>Frequency of contractions/20minutes after treatment</b>					
None	9	22.5	9	22.5	X <sup>2</sup> = 7.05 P= 0.07
1-2	12	30.0	7	17.5	
3-4	13	32.5	8	20.0	
5-6	6	15.0	16	40.0	
Min-Max	0-5				
Mean± SD	2.8 ± 1.9				
<b>Bishop score after treatment</b>					
2-4	14	35.0	17	42.5	X <sup>2</sup> = 1.48 P= 0.915
5-7	21	52.5	16	40.0	
8-10	5	12.5	7	17.5	
Min-Max	4-10				
Mean± SD	6.08 ± 2.5				

\*: Statistically significant at  $p \leq 0.05$

Table (3) represented results of treatment, including prolongation of pregnancy, gestational age at delivery, number of cases reached 37 weeks and mode of delivery.

In group A, 32.5% of the studied women had prolongation of pregnancy for 1-5 days, while 30% of patients of the same group had 6-10 days. In group B, 40% of women had prolongation for 1-5 days. Mean was  $6.9 \pm 8.05$  days with no significant difference between both groups. In group A, 50% of the studied women delivered at a gestational age 31-35 weeks, also 50% of women in group B delivered

at 31-35 weeks. Mean gestational age at delivery was  $32.8 \pm 2.9$ . There was no significant difference between both groups.

In group A, 15% of the studied women reached 37 weeks at delivery, while only 7.5% of women in group B reached 37 weeks. There was no significant difference between both groups. 62.5% of the studied women in group A delivered vaginally, while 60% in group B, delivered via cesarean section. So there was no significant difference between both groups.

**Table (3): Comparison between the two groups according to prolongation of pregnancy, gestational age at delivery, reaching 37 weeks and mode of delivery**

Groups Variables	Group A (MgSO <sub>4</sub> )		Group B (Ritodrine)		X <sup>2</sup> P value
	No.	%	No.	%	
<b>Prolongation of pregnancy in days</b>					
No prolongation	7	17.5	9	22.5	X <sup>2</sup> = 4.90 P= 0.556
1-5	13	32.5	16	40.0	
6-10	12	30.0	6	15.0	
11-15	4	10.0	3	7.5	
16-20	0	0.0	0	0.0	
21-25	1	2.5	3	7.5	
26-30	2	5.0	3	7.5	
31-35	1	2.5	0	0.0	
Min-Max	0-32				
Mean± SD	6.9 ± 8.05				
<b>Gestational age at delivery (weeks)</b>					
26-30	13	32.5	14	27.5	X <sup>2</sup> = 0.417 P= 0.812
31-35	20	50.0	20	50.0	
36-40	7	17.5	9	22.5	
Min-Max	28-37				
Mean± SD	32.8 ± 2.9				
<b>Reaching 37 weeks at delivery</b>					
Yes	6	15.0	3	7.5	X <sup>2</sup> = 1.12 P= 0.481
No	34	85.0	37	92.5	
<b>Mode of delivery</b>					
Caesarian section	15	37.5	16	40.0	X <sup>2</sup> = 0.53 P= 0.500
Vaginal delivery	25	62.5	24	60.0	

Table (4) showed neonatal outcome, including, Apgar score at 1 and 5 minutes, neonatal birth weight and the need for incubation. 65% of delivered neonates for women in group A had score 5 at Apgar score at 1 minute. On the other hand, 35% of delivered neonates for women in group B had score 4 at Apgar score. Mean score was  $4.5 \pm 0.81$ , so there was significant difference between both groups. In group A, 35% of delivered neonates had score 6 at Apgar score at 5 minutes, while 30% had score 10. In group B, 37.5% had score 6, while 27.5% had score 5. Mean score was  $7.2 \pm 1.9$ . There was no significant difference between both groups. Neonatal birth weight at the time of delivery was 1000-1500 gram in 42.5% of both groups. Mean birth weight was  $1705.25 \pm 526.76$  gram, with no significant difference between both groups. 65.5% of delivered neonates for studied women in group A were indicated for NICU admission, while 72.5% of neonates in group B were indicated for admission. There was no significant difference between both groups.

**Table (4): comparison between the two groups according to Apgar score at 1 and 5 minutes, neonatal birth weight and neonatal need for incubation.**

Groups Variables	Group A (MgSO <sub>4</sub> )		Group B (Ritodrine)		X <sup>2</sup> P value
	No.	%	No.	%	
<b>Apgar score at one minute</b>					
Three	1	2.5	9	22.5	X <sup>2</sup> = 14.4 P= 0.002*
Four	12	30.0	14	35.0	
Five	26	65.0	12	30.0	
Six	1	2.5	5	12.5	
Min-Max	3-6				
Mean± SD	4.5 ± 0.81				
<b>Apgar score at five minutes</b>					
Five	5	12.5	11	27.5	X <sup>2</sup> = 3.86 P= 0.227
Six	14	35.0	15	37.5	
Eight	9	22.5	5	12.5	
Ten	12	30.0	9	22.5	
Min-Max	5-10				
Mean± SD	7.2 ± 1.9				
<b>Birth weight (gram)</b>					
1000-1500	17	42.5	17	42.5	X <sup>2</sup> = 0.177 P= 0.981
1500-2000	15	37.5	14	35.0	
2000-2500	5	12.5	5	12.5	
2500-3000	3	7.5	4	10.0	
Min-Max	1000-3000				
Mean± SD	1705.25 ± 526.76				
<b>Need for incubation</b>					
Yes	26	65.0	29	72.5	X <sup>2</sup> = 0.524 P= 0.469
No	14	35.0	11	27.5	

\*: Statistically significant at  $p \leq 0.05$

Table (5) showed the complications resulting from MgSO<sub>4</sub> and ritodrine administration; 85% of the studied women in group A had no complications, while 42.5% of the studied women in group B developed tachycardia. There was a significant difference between both groups.

**Table (5): Comparison between the two groups according to the complications.**

Groups Variables	Group A (MgSO <sub>4</sub> )		Group B (Ritodrine)		X <sup>2</sup> P value
	No.	%	No.	%	
None	34	85.0	12	30	X <sup>2</sup> = 20.009 P<0.001*
Flushing	2	5.0	2	5.0	
Headache	2	5.0	3	7.5	
Hypotension	1	2.5	1	2.5	
Tachycardia	1	2.5	17	42.5	
Dyspnea	0	0	5	12.5	

\*: Statistically significant at  $p \leq 0.05$

## DISCUSSION

Preterm birth represents the single largest cause of mortality and morbidity for newborns and a major cause of morbidity for pregnant women. Tocolytic agents include a wide range of drugs that can inhibit labor to prolong pregnancy. This may gain time to allow the fetus to mature further before being born, permit antenatal corticosteroid administration for lung maturation, and allow time for intrauterine transfer to a hospital with neonatal intensive care facilities<sup>(5)</sup>.

Several medications have been used in preterm labor; ritodrine and magnesium sulphate are the most frequently used tocolytics<sup>(6)</sup>. Magnesium sulphate is commonly used to treat pregnancy-induced hypertension and though unlicensed, is widely used for tocolysis in the USA. It can decrease uterine activity, but the basis for this tocolytic action is unknown<sup>(7)</sup>.

In the present study, group A received MgSO<sub>4</sub> in the form of 4 g as a loading dose over 30 minutes followed by a maintenance dose of 1.0-2.0 g/hr. It was similar to a study of **Kawagoe *et al.***<sup>(8)</sup>, as they started MgSO<sub>4</sub> with a loading dose of 4 g over 30 minutes followed by a maintenance dose of 1.0-2.0 g/hr. (magnesium alone), which was titrated as uterine contractions changed. Similar to **Han *et al.***<sup>(9)</sup>, group B received ritodrine in a dose of 50 µg/min by intravenous infusion. It increased by a rate of 50 µg/min every 15 minutes if needed till a maximum dose of 350 µg/min according to the situation.

Results of the current study showed that there was no statistically significant difference between both studied groups as regard prolongation of pregnancy.

It was similar to **Kim *et al.***<sup>(10)</sup>; who found that the efficacy of MgSO<sub>4</sub> was analyzed in relation to ritodrine hydrochloride. A total number of 201 patients were enrolled including 177 cases in ritodrine group and 24 cases in magnesium sulfate group. The efficacy of both tocolytics (preterm delivery within 48 hours, 7 days, or 37 weeks of gestation and need for 2<sup>nd</sup> line therapy) was not different between the 2 groups of cases.

Also, **Elliot *et al.***<sup>(11)</sup> concluded that MgSO<sub>4</sub> does work as well as other parenteral drugs to stop the contractions associated with acute PTL, when appropriate dosages are used. Tocolysis for acute PTL should start with a 6-g bolus with MgSO<sub>4</sub> followed by 3–5-g/h. continuous infusion which can be adjusted based on the clinical response.

Comparison of magnesium sulphate and ritodrine in control of preterm labor in the current study,

showed no statistically significant difference between both groups.

Similar to the present study, **Kam and Lamont**<sup>(12)</sup>, **Van *et al.***<sup>(13)</sup> and **Vogel *et al.***<sup>(5)</sup> randomized control studies concerning the effects of ritodrine in the control of preterm labor compared with MgSO<sub>4</sub>.

In the current study several complications were noted with ritodrine, namely tachycardia, hypotension, flushing, dyspnea and headache. It was similar to the study of **Han *et al.***<sup>(9)</sup>; as side effects were most frequently found in beta-agonists, including maternal tachycardia, chest discomfort, dyspnea, tremor, pleural effusion, pulmonary edema, dizziness, uncontrolled blood glucose, tingling sensation in extremities, and elevated liver enzymes.

Complications were not frequent with magnesium sulphate, such as tachycardia, headache, hypotension and flushing.

Also similar to **Kim *et al.***<sup>(10)</sup>, who compared the safety and efficacy of magnesium sulfate, as an alternative tocolytics, with that of ritodrine. As a result of specific mechanism of action of both tocolytics, side effects related with vital signs such as palpitations, hand tremor, tachycardia, chest discomfort, and tachypnea were significantly more frequent in ritodrine group whereas facial flushing, lethargy, and dizziness were much significantly occurred in magnesium sulfate group.

**Conclusion:** The effect of ritodrine in prolonging the gestational age of preterm labor is definite but limited to only two days. Although two days are enough for further maturity of fetal lung by hormones, such as dexamethasone, ritodrine cannot prolong pregnancy effectively to term. Moreover, ritodrine can cause more side effects if it is given for a long period. Ritodrine had no significant superiority over magnesium sulphate in the treatment of preterm labor. On the other hand, MgSO<sub>4</sub> had fewer side effects than ritodrine. As, ritodrine belongs to β<sub>2</sub> adrenergic agonist, it can cause several complications including maternal and fetal tachycardia, hypotension, and hyperglycemia. Thus, ritodrine decreased the compliance of the patients because of relatively more side effects.

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