The Efficacy of Terbutaline and Magnesium Sulfate in the Management of Preterm Labor

PRAYONG SURICHAMORN, M.D.*

Abstract

Ninety-six patients with preterm labor at 28 weeks to 35 weeks gestation were randomized to terbutaline or magnesium sulfate untill 36 weeks gestation, 25 patients were excluded from the study. Of the remaining 71 patients, 35 patients received terbutaline and 36 patients received magnesium sulfate. The result of the study showed that, there were no significant differences ($P > 0.05$) regarding time to stop, mean gestational age at delivery, time gained, failure rate, time to recurrent labor and readmission for recurrent labor, birth weight, apgar score and fetal survival. Serious maternal side effects were not observed with terbutaline or magnesium sulfate, although the majority of women also received dexamethasone. Neither drug caused serious adverse neonatal effects.

Key word : Terbutaline, Magnesium Sulfate, Preterm Labor

SURICHAMORN P
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Prematurity continues to be the major cause of neonatal morbidity and mortality. Strategies to prevent premature labor and subsequent preterm delivery are of major importance. In an attempt to prevent the sequelae of premature delivery attention has logically centered on efforts to find safe and effective tocolytic drugs. The drugs most commonly used in this country[1,2] for the suppression of preterm labor are the β-sympathomimetic agents terbutaline and magnesium sulfate. Both agents have been associated with the occurrence of severe side effects such as pulmonary edema or respiratory depression[3-7]. Preliminary reports have also indicated that the use of concurrent two-agent therapy is associated with an even greater incidence of side effects[8]. Some data

* Department of Obstetrics and Gynaecology, Sing Buri Hospital, Sing Buri 16000, Thailand.

exist, however, to suggest that sequential therapy may be less hazardous and more effective[1,2,9,10]. Because terbutaline[1,2,11,12] has replaced magnesium sulfate in many obstetric centers as the first-line agent in the treatment of preterm labor, the efficacy and safety of terbutaline must be assessed in comparison with magnesium sulfate. The present study compared terbutaline and magnesium sulfate in a prospective, randomized trial to determine the relative efficacy and safety of these agents in women with preterm labor.

MATERIAL AND METHOD

The study was carried out in the obstetric service, Sing Buri Hospital from January 1995 to December 1998. Patients in the study included those who met all of the following criteria: (1) Duration of gestation 28 to 35 weeks. (2) Regular, painful contractions, occurring at intervals of less than 10 minutes, observed for at least 30 minutes. (3) The cervix effaced or almost effaced and dilatation not more than 3 cm. (4) Singleton pregnancy. Patients meeting these criteria were excluded from the study if there was fever, placenta praevia, abruptio placentae, fetal abnormality, hydramnios, incompetent cervix, premature rupture of membranes, maternal arrhythmias, hypertension, hyperthyroidism, diabetes mellitus, received prior tocolytic agent or absolute contraindication to terbutaline or magnesium sulfate. Eligible patients, after signing informed consent were randomized to receive terbutaline or magnesium sulfate by means of sealed envelopes.

Each patient underwent a complete medical history, physical examination, and laboratory test. Maternal blood pressure was recorded every 15 minutes during the first 2 hours of treatment and every 2 to 4 hours thereafter. Fetal heart rate and uterine activity were monitored continuously during the study. A sample was obtained for urine culture. A sonogram was obtained on the day of admission to assess amniotic fluid volume, to screen for lethal congenital anomalies, and to confirm gestational age. The tocolytic agents were administered according to the following schedules.

Magnesium sulfate therapy consisted of a loading dose of 4 g given intravenously over 20 minutes. This was followed by an infusion of 2 g/h, increasing to a maximum rate of 4 g/h as needed to arrest labor for 24 hours. Deep tendon reflexes were elicited every 2 hours. Additionally, the recording of hourly fluid balance was strictly maintained. After contractions had been arrested for 24 hours, the patients was weaned at the rate of 0.5 g every 4 to 6 hours. Then oral terbutaline treatment was given, 10 mg/day (2.5 mg every 6 hours) until 36 weeks of pregnancy.

Terbutaline therapy consisted of an initial intravenous bolus infusion of 0.25 mg terbutaline, followed by an intravenous infusion at an initial rate of 10 microgram/min, and increased by 5 microgram/min every 10 minutes up to a maximum of 25 microgram/min, or until uterine contractions ceased. During the intravenous infusion vital signs were recorded at 15 minute intervals. Once contractions stopped, the infusion was maintained at the same rate for 2 hours. This was followed by subcutaneous injections of terbutaline 0.25 mg every 4 hours for 24 hours. Then oral terbutaline treatment was given, 10 mg/day (2.5 mg every 6 hours) until 36 weeks of pregnancy.

On completion of parenteral administration, patients were allowed to ambulate, and were discharged within 24 to 48 hours of the initiation of oral maintenance. They were then seen as outpatients in the high-risk clinic every week until delivery. At each clinic visit there was a repeat cervical examination. Additionally, at each clinic visit blood pressure, maternal heart rate, and fetal heart rate were recorded. Patients who resumed uterine contractions while on either subcutaneous or oral therapy were restarted on intravenous terbutaline or magnesium sulfate.

Intramuscular dexamethasone (12 mg) was given at the initiation of therapy, 24 hours later and every week until completion of 32 weeks of gestation. A paediatrician attended the delivery of most patients and assessed the infants.

All data were analyzed for statistical significance by means of analysis of variance, Student *t*, X^2 or Fisher exact tests where appropriate. A P value < 0.05 was considered significant.

RESULTS

During the study period, the 96 patients enrolled in the study were randomized into two study groups. 49 patients received magnesium sulfate, and 47 patients received terbutaline. There were no significant differences in the entry

Table 1. Entry variables of study groups.

Entry variables	Magnesium Sulfate (n = 36)	Terbutaline (n = 35)	Significance
Age (yr, mean ± SD)	21.92 ± 4.87	23.18 ± 4.12	NS
Primigravid (No.)	16 (44.44%)	15 (42.86%)	NS
Previous preterm (No.)	5 (13.89%)	4 (11.43%)	NS
Urine culture (No.)	3 (8.33%)	3 (8.57%)	NS
Cervical examination (Mean ± SD)			
Dilatation (cm)	2.27 ± 0.82	2.38 ± 0.89	NS
Effacement (%)	42.68 ± 7.12	43.02 ± 7.93	NS
Station	-3.13 ± 0.64	-3.11 ± 0.68	NS
Contraction frequency (min, mean ± SD)	4.51 ± 1.01	4.49 ± 1.12	NS

NS = not significant

Table 2. Effectiveness of tocolytic agents.

Effectiveness	Magnesium Sulfate (n = 36)	Terbutaline (n = 35)	Significance
Time to stop (h, mean ± SD)	4.43 ± 1.72	4.15 ± 1.83	NS
Gestational age (wk, mean ± SD)			
Admission	30.82 ± 3.02	31.26 ± 2.95	NS
Delivery	36.21 ± 2.76	36.01 ± 2.81	NS
Time gained (No.)			
≥ 2 days	34 (94.44%)	32 (91.43%)	NS
≥ 3 days	31 (86.11%)	29 (82.86%)	NS
≥ 7 days	26 (72.22%)	24 (68.57%)	NS
≥ 37 wks	15 (41.67%)	15 (42.86%)	NS
Failure (No.)	6 (16.67%)	7 (20.00%)	NS
Labor	1	2	
Rupture of membranes	4	5	
Side effects	1	-	
Time to recurrent labor (days)	21.82	21.95	NS
Readmission for recurrent labor (No.)	9 (25.00%)	9 (25.71%)	NS

NS = not significant

characteristics variables between the two groups. Twenty five patients were excluded from the study. Among patients enrolled in the magnesium sulfate groups, 13 patients were excluded : 11 patients had received prior tocolytic therapy, one patient had hydramnios, and one patient had rupture of the membranes. 12 patients assigned to the terbutaline group were excluded : 11 patients because of prior tocolytic therapy, and one patient because of rupture of the membranes. Of the remaining 71 patients, 36 patients received magnesium sulfate and 35 patients received terbutaline. A comparison of the study groups, summarized in Table 1, indicates the groups to be similar in terms of the number of entry variables. Both groups were similar in terms of age, previous preterm, urine culture, contraction frequency and cervical dilation at enrollment into the study. The tocolytic efficacy of each tocolytic agent is summarized in Table 2. There was no significant difference in the time required for each agent to achieve cessation of contractions, in the proportion of patients in whom delivery was delayed at least 2 days, 3 days on 7 days or in the proportion of patients who achieved at least 37 weeks of gestation. There were no differences in the number

Table 3. Maternal side effects.

Maternal side effects	Magnesium Sulfate (n = 36)	Terbutaline (n = 35)
Chest pain	6 (1*)	3
Nausea or vomiting	4	3
Headache	1	2
Dizziness	-	1
Transient hypotension	1	2
Total	12 (33.33%)	11 (31.43%)

* Neccessitating decrease of dosage

of patients failing tocolysis with the primary tocolytic agent, 16.87 per cent *versus* 20 per cent for the magnesium sulfate and terbutaline groups, respectively. Thus, no significant difference was noted in the relative efficacy of the two tocolytic regimens. There were no differences in the proportion of patients admitted with recurrent labor or in the time elapsed to readmission with recurrent labor, suggesting no difference between terbutaline and magnesium sulfate in preventing recurrent labor.

Maternal side effects were experienced in 12 patients (33.33%) treated with magnesium sulfate, resulting in drug neccessitating decrease of dosage in one patient (2.78%) as some with side effects in 11patients (31.43%) in the terbutaline group, none of whom required drug discontinuation (Table 3). However, after the first dose, one patient in the magnesium sulfate group and two patients in the terbutaline group experienced transient hypotension, defined as a decrease in the systolic and diastolic blood pressure of 15 and 10 mm Hg, respectively, associated with a transient increase in maternal heart rate of at least 10 beats/min. However, these hemodynamic changes lasted < 10 minutes and resolved spontaneously without evidence of prolonged maternal or fetal symptoms.

Neonatal outcome is summarized in Table 4, with no differences observed between the groups in terms of mean birth weight, Apgar scores, and proportion of survival. There were no stillbirths and only three neonatal deaths from prematurity, birth weights of 1,590, 1,600 and 1,670 g and gestational age less than 30 weeks, one in the magnesium group and two the terbutaline group.

DISCUSSION

Preterm labor remains a major cause of preterm birth[1,2,6-10]. Neonatal morbidity and mortality associated with preterm delivery remain important problems. The use of a parenteral tocolytic agents to arrest premature labor and an additional oral tocolytic agents to prevent recurrence has support from previous studies [1,2,6-11], which demonstrated and increased success in prolonging pregnancy with magnesium sulfate[6-9,12-16] and terbutaline[1,2,10,17-23]. Clinical studies of the efficacy of magnesium sulfate are abundant,[6,7,12-16] and were able to demonstrate an improvement in successful preterm labor. They reported an 80 per cent success rate in patients receiving continuous intravenous infusion of magnesium sulfate and were able to delay delivery 24 hours in 80-84 per cent of the patients[6,7]. There were fewer side effects[6,7]. The adverse effects of hypermagnesemia[14] include impaired deep tendon reflexes, decreased muscle tone, decreased respiration, cardiac arrythmias, and possible respiratory and cardiac arrest. Adverse effects may be minimized by monitoring urinary output and clinical parameters.

Table 4. Neonatal outcome.

Neonatal outcome	Magnesium Sulfate (n = 36)	Terbutaline (n = 35)	Significance
Weight (g, mean ± SD)	2587 ± 584	2534 ± 602	NS
Apgar score (mean ± SD)			
1 min	7.31 ± 1.72	7.12 ± 1.64	NS
5 min	8.29 ± 1.69	8.32 ± 1.66	NS
Survival	35 (97.22%)	33 (94.29%)	NS

NS = not significant

It should be stated that significant lethargy due to the action of ionized magnesium on the neuromuscular junction and striated muscle is frequent. Nausea, emesis, chest tightness, and pulmonary edema have also been reported. Hypocalcemia has been the only metabolic change noted, and cardiovascular changes including transient hypotension, peripheral vasodilatation, and increased stroke volume have been reported.

Terbutaline is a "selective" β_2-receptor stimulator and inhibits uterine activity at term, even during the second stage[13]. Previous studies, [1,2,17-23] showed that terbutaline is significantly effective in treating preterm labor, and fetal or neonatal outcome was not adversely effected. Infusion of terbutaline caused maternal tachycardia and reduction in diastolic blood pressure[24] or any serious side effects, such as pulmonary edema [3,4]. More recent studies[6,7,12-14,23] have also established the clinical efficacy of this salt while studies directly comparing magnesium to β-adrenergic receptor agonists have shown no difference in efficacy. The use of tocolytic agent to delay delivery as long as possible, either to allows the corticosteroids to have an effect or gives time for the natural process of lung maturation to occur[2], while maternal glucocorticoid administration can accelerate fetal pulmonary maturation[25-27].

In this prospective study comparing these two drugs, terbutaline was found to be as efficacious as magnesium sulfate in arresting labor with no fetal or neonatal side effects and with fewer maternal side effects requiring drug decrease of dosage. The use of oral terbutaline maintenance prevents the recurrence of preterm labor with no maternal complaints.

In conclusion, these results indicate that terbutaline is as effective as magnesium sulfate in treating preterm labor. No serious complication occurred from the use of terbutaline and magnesium sulfate, either in the mothers or their infants.

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ประสิทธิผลของยาเทอร์บูทาลีนกับแมกนีเซียมซัลเฟตในการรักษาภาวะเจ็บครรภ์ก่อนกำหนด

*ประยงค์ สุริย์จามร, พ.บ.**

สตรีเจ็บครรภ์ก่อนกำหนดที่มีอายุครรภ์ตั้งแต่ 28 ถึง 35 สัปดาห์ จำนวน 96 ราย ทำการแบ่งโดยการสุ่มออกเป็น 2 กลุ่ม ได้แก่ กลุ่มได้รับยาเทอร์บูทาลีน และกลุ่มได้รับยาแมกนีเซียมซัลเฟต จนตั้งครรภ์ครบ 36 สัปดาห์ พบว่ามีจำนวน 25 ราย ที่ถูกคัดออกจากการศึกษา เหลือผู้ป่วยจำนวน 71 รายที่สามารถทำการศึกษาจนครบและนำมาวิเคราะห์ได้ โดยแบ่งเป็นกลุ่มได้รับยาเทอร์บูทาลีน จำนวน 35 ราย และได้รับยาแมกนีเซียมซัลเฟต จำนวน 36 ราย ผลการศึกษาพบว่า ไม่มีความแตกต่างอย่างมีนัยสำคัญที่ระดับ 0.05 ในด้านระยะเวลาในการหยุดการเจ็บครรภ์ก่อนกำหนด อายุครรภ์ในขณะคลอด ระยะเวลาที่ประสบความสำเร็จ อัตราความล้มเหลว ระยะเวลาของการเจ็บครรภ์ก่อนกำหนดซ้ำ อัตราการรับเข้าอยู่โรงพยาบาลใหม่เนื่องจากการเจ็บครรภ์คลอดก่อนกำหนดซ้ำ น้ำหนักทารกแรกคลอด คะแนนแอปการ์ และทารกที่รอดชีวิต ไม่พบภาวะแทรกซ้อนต่อมารดาที่รุนแรงของยาเทอร์บูทาลีนหรือแมกนีเซียมซัลเฟต ถึงแม้ว่าผู้ป่วยส่วนใหญ่ได้รับยาเดกซาเมทาโซล รวมทั้งไม่พบอาการไม่พึงประสงค์ที่รุนแรงของยาทั้งสองต่อทารก

คำสำคัญ : เทอร์บูทาลีน, แมกนีเซียมซัลเฟต, ภาวะเจ็บครรภ์ก่อนกำหนด

ประยงค์ สุริย์จามร
จดหมายเหตุทางแพทย์ ฯ 2544; 84: 98–104

* กลุ่มงานสูติ-นรีเวชกรรม, โรงพยาบาลสิงห์บุรี, สิงห์บุรี 16000