Tocolysis in women with preterm labor between 32 0/7 and 34 6/7 weeks of gestation: A randomized controlled pilot study

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Objective: The purpose of this study was to determine whether intravenous magnesium sulfate ($MgSO_4$) followed by oral nifidepine tocolysis in women with preterm labor between 32 0/7 and 34 6/7 weeks' gestation reduces neonatal hospital stay.

Study design: Fifty-four women between 32 0/7 and 34 6/7 weeks with preterm labor were randomized to receive either $MgSO_4$ and oral nifidepine (n = 24) or no tocolysis (n = 30). All women received betamethasone and prophylactic antibiotics. The primary outcome was total neonatal hospital stay. Data were analyzed using Chi-square and Mann Whitney U test.

Results: The 2 groups had similar mean cervical dilation and gestational age at enrollment. There were no statistically significant differences in total neonatal hospital stay (5.8 ± 7.2 days; median of 3 days in the no tocolysis vs. 7.5 ± 8.6 days; median of 3 days in the tocolysis group), rate of preterm delivery (57% vs. 75%) or need for oxygen supplementation (7% vs. 21%, p < 0.23). The neonatal complications were similar in each group.

Conclusion: Tocolysis after 32 weeks gestation does not reduce neonatal hospital stay.
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Preterm birth is the leading cause of infant morbidity and mortality and it accounts for 35% of all health care spending on infants.[1] Preterm birth affects about 12.3% of births in the USA[2] and of these 40-50% have been attributed to preterm labor.[2-4] The use of tocolytic therapy in an attempt to reduce preterm delivery has not reduced the overall preterm birth rate. Furthermore, there are no

established guidelines regarding the upper limits of gestational age beyond which tocolysis is not indicated, with recommendations ranging from 32 to 36 completed weeks.[5] The goals of tocolytic therapy in women with preterm labor are 1) to allow maternal transport to a tertiary care center, 2) to prolong pregnancy for at least 48 hours to optimize the beneficial effect of steroids for fetal lung maturation and 3) to prolong pregnancy in an attempt to improve perinatal outcomes. It is well established that tocolytic therapy can prolong pregnancy for at least 48 hours.[6] Beyond this benefit, there is little evidence that prolonged tocolytic therapy improves

perinatal outcomes at any gestational age (GA).[5,7] Despite this, tocolysis beyond 48 hours is commonly prescribed.

Magnesium sulfate ($MgSO_4$) is the tocolytic drug of choice in many centers.[5,7] The use of oral nifedipine, as maintenance tocolytic therapy after the initial episode of preterm labor, has been shown to provide symptomatic relief and decrease the number of triage visits, and is common practice among many obstetricians.[8] However, Sanchez-Ramos et al,[7] in a recent meta-analysis reported that the use of oral nifedipine did not improve maternal or neonatal outcomes. We conducted a randomized controlled trial to determine if aggressive tocolysis with $MgSO_4$ followed by maintenance therapy with oral nifedipine, in women with preterm labor at 32 0/7 weeks to 34 6/7 weeks, will reduce the total neonatal length of hospital stay.

Material and methods

This trial was performed at the University Hospital, Cincinnati, Ohio between August 2002 and July 2005. Pregnant women with singleton gestation, who were in preterm labor between gestational age of 32 0/7 and 34 6/7 weeks with intact amniotic membranes, a diagnosis of preterm labor and a cervical dilation of ≤4 cm were considered for the study. Preterm labor (PTL) was defined as progressive cervical dilation or effacement associated with regular uterine contractions (≥6/hr). At our institution, fetal fibronectin (FFN) and/or cervical length evaluation by ultrasound are not used for confirming the diagnosis of preterm labor. In addition, amniocentesis to assess lung maturity or infection is not routinely performed for women in PTL. Exclusion criteria were: cervical dilation >4 cm, multifetal gestation, obstetrical contraindications to tocolysis (known fetal anomalies, suspect chorioamnionitis, non-reassuring fetal heart tracings, preeclampsia, placenta previa and bleeding or abruptio placenta), preterm premature rupture of membranes, known HIV, and refusal to participate. Institutional review board approval was obtained before initiation of patient enrollment. After informed consent was obtained, patients were randomly assigned to receive either tocolysis or no tocolysis. Random assignments were made by picking sealed, opaque, sequentially numbered envelopes using a computer-generated random number.

Women assigned to tocolysis received $MgSO_4$ 6 gm IV load over 30 minutes followed by 2-5 g/hr of maintenance $MgSO_4$ IV to achieve uterine quiescence (<6 contractions/hr). All women received a course of 2 doses of betamethasone 12 mg IM 24 hrs apart and prophylactic antibiotics for GBS prophylaxis. After 24 hrs and following the administration of the second dose of betamethasone, if patients remained without contractions, they were given nifedipine 10-20 mg orally every 4-6 hrs until 36 6/7 weeks or delivery. If these women started contracting again, after initial therapy and before 35 0/7 weeks; $MgSO_4$ tocolysis was reinstituted as described. Women assigned to no tocolysis (control group) only received betamethasone and prophylactic antibiotics, no tocolytic agents were allowed in these women.

Women who received IV $MgSO_4$ for less than 6 hours prior to transfer from referring hospitals were eligible for randomization. All women were instructed on signs and symptoms of preterm labor and had weekly follow up with their primary physician. Data regarding patient's age, race, parity, risk factors, gestational age, and cervical exam were recorded from the charts. Maternal and neonatal outcomes were collected after delivery.

Data Analysis and Sample Size

The primary outcome of the trial was the total length of neonatal hospital stay. The secondary outcomes were rate of preterm delivery (<37 weeks), rate of neonatal intensive care unit (NICU) and transitional neonatal care unit (TCN) admissions, % of neonates requiring oxygen supplementation (continuous positive airway pressure (CPAP) or oxygen tent), neonatal death, % of neonates with hyperbilirubinemia and feeding issues, respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NEC). In order to justify administration of IV $MgSO_4$ in these women with PTL between 32 and 34 completed weeks, we considered 40% reduction in neonatal length of stay as clinically significant. Prior to our sample size calculation, we were informed by our Neonatologist that the average length of neonatal stay of infants between 32 and 34 completed weeks at our institution is 15 ± 7 days. Twenty eight patients per group were needed to detect a 40% difference in the total neonatal length of hospital stay with $\alpha = 0.05$ (2 tailed and power = 80%). Statistical analysis was by intention to treat and the data from all randomized women were included in the analysis. Data analysis included Mann Whitney U test for continuous variables and Chi-square or Fisher exact test for categorical variables. A p value of <0.05 was considered significant.

Results

A total of 54 women were enrolled; 30 were randomized to the control group (no tocolysis) and 24 were randomized to the treatment group (IV and oral tocolysis). There were 2 (7%) women in the no tocolysis group and 4 (17%) women in the tocolysis group who were maternal transfers from other institutions. Table I reports the baseline characteristics for the women at randomization. There were no statistically significant differences with regard to maternal demographics, mean cervical dilation and mean gestational age at enrollment between the 2 groups. Table II summarizes

Table I   Maternal demographics

Characteristics	No tocolysis (n = 30)	Tocolysis (n = 24)	P value
Maternal age (y)	22.0 ± 5.0	21.6 ± 3.5	NS
	20.5 (14-32)	21.0 (16-30)	
Race			
White n (%)	9 (30)	10 (42)	NS
1st pregnancy n (%)	7 (23)	8 (33)	NS
Previous preterm delivery n (%)	10/23 (44)	7/16 (44)	NS
Gestational age at enrollment (wk)	33.1 ± 0.8	33.1 ± 0.8	NS
	33.2 (32.0-34.5)	33.3 (32.0-34.5)	
Cervical dilation at enrollment (cm)	2.8 ± 1.1	2.7 ± 0.9	NS
	3 (1-4)	3 (1-4)	

Data are presented as mean ± SD, median (range) unless otherwise noted.

Table II   Latency period according to cervical dilation at enrollment

	Delivery					
Dilation	≤1 wk	1-2 wk	2-3 wk	>3 wk	Mean (d)	Median (d)
No tocolysis						
3 cm (n = 13)	2	2	0	9	25.0	26.0
4 cm (n = 7)	2	1	2	2	16.0	19.0
Tocolysis						
3 cm (n = 13)	2	2	4	1	16.6	16.0
4 cm (n = 7)	1	0	1	2	17.2	21.0

Table III   Frequency distribution of cervical dilation by centimeter and % effacement at enrollment in each group

Dilation (cm)	No tocolysis n (%)	Tocolysis n (%)
<2	5 (17)	3 (13)
2-2.9	5 (17)	8 (33)
3-4	20 (67)	13 (54)
Median dilation (cm)	3	3
Effacement (%)	No tocolysis n (%)	Tocolysis n (%)
0-25	1 (3)	0
50-75	23 (77)	18 (75)
80-100	6 (20)	6 (25)
Median effacement	70%	55%
Mean effacement	66%	63%

the latency period according to cervical dilation at enrollment and Table III shows the frequency distribution of cervical dilation by cm and % effacement at enrollment in each group. One (3%) woman in the no tocolysis group and 3 (12%) women in the tocolysis group had a diagnosis of gestational diabetes. Twenty-five (85%) women in the no tocolytic group and 19 (79%) women in the tocolysis group were discharged home undelivered after randomization. Three (10%) women in the no tocolysis group and 1 (4%) woman in the tocolysis group were delivered at one of our affiliated hospitals, allowing us to obtain both maternal and neonatal outcome data. Table IV reports the neonatal outcome. The primary outcome, total length of neonatal hospital stay, was not significantly different between the two groups (5.8 ± 7.2 days in the no tocolysis group and 7.5 ± 8.6 days in the tocolysis group). The median total neonatal hospital stay for both groups was 3 days (range, 1-26 and 1-27, for no tocolysis group and tocolysis group, respectively). The main reason for prolonged neonatal stay for the majority of infants in both groups was feeding issues; 4 (13%) neonates in the no tocolysis group and 5 (21%) neonates in the tocolysis group stayed for more than 2 weeks whereas 1 (3%) neonates in the no tocolysis group and 1 (4%) neonate in the tocolysis group stayed for more than a week but less than 2 weeks. In addition, there were no significant

differences regarding the rate of preterm delivery and neonatal complications between the 2 groups. Thirteen (43%) women in the no tocolysis group and 6 (25%) women in the no tocolysis group delivered at term. One patient in each group were delivered for nonreassuring fetal heart tracing. All other women delivered due to PTL or PPROM.

There were no cases of neonatal death, RDS, IVH or NEC in either group. Oxygen supplementation was required in the form of CPAP at delivery in 2 (7%) neonates in the no tocolysis group and 5 (21%) neonates in the tocolysis group (p < 0.23). The maximum duration on CPAP was 14 hours. Of the 5 neonates in the tocolysis group who required oxygen supplementation, only 1 neonate required oxygen tent for 23 hours, this neonate was delivered at 35 weeks; he stayed in the NICU for 22 days and was treated with antibiotics for probable sepsis due to findings of bandemia and thrombocytopenia. Hyperbilirubinemia was diagnosed in 3 (10%) neonates in the no tocolysis group and 7 (29%) neonates in the tocolysis group (p < 0.09).

Table V reports maternal outcome for the 2 study groups. There were no significant differences regarding any of the maternal outcome. There were no cases of adverse maternal outcome related to tocolytics.

Table IV Primary and other secondary neonatal outcome

Characteristics	No tocolysis (n = 30)	Tocolysis (n = 24)	P value
Total neonatal stay (d)	5.8 ± 7.2	7.5 ± 8.6	NS
	3.0 (1-26)	3.0 (1-27)	
Length of NICU stay (d)	3.8 ± 8.1	4.9 ± 8.4	NS
	0 (0-26)	0 (0-26)	
Length of TCN stay (d)	0.3 ± 0.8	1.1 ± 5.5	NS
	0 (0-3)	0 (0-27)	
Delivered with 48 n (%)	5 (17)	3 (13)	NS
Delivered <7 days n (%)	7 (23)	7 (29)	NS
<37 weeks n (%)	17 (57)	18 (75)	NS
Birth weight (g)	2794 ± 601	2507 ± 431	NS
	2755 (1853-4058)	2514 (1700-3494)	

Data are presented as mean ± SD, median (range) unless otherwise noted.

Table V Maternal outcome

Characteristics	No tocolysis (n = 30)	Tocolysis (n = 24)	P value
Gestational age at delivery (wk)	36.5 ± 2.2	35.7 ± 1.8	NS
	36.5 (32.6-40.1)	35.5 (33.0-40.1)	
Latency (d)	23.9 ± 15.9	17.8 ± 12.0	NS
	25.5 (0-52)	18.5 (1-47)	
Total no. of maternal	5.3 ± 5.3	7.8 ± 4.4	NS
hospital days	4 (2-31)	7 (2-22)	
Recurrent preterm contractions n (%)	14 (48)	15 (65)	NS
Require readmission n (%)	11 (37)	12 (50)	NS
C-section n (%)	4 (13)	4 (17)	NS

Data are presented as mean ± SD, median (range) unless otherwise noted.

Comments

Principal Findings of the Study

In this prospective, randomized clinical trial we evaluated the efficacy of aggressive tocolysis with IV $MgSO_4$ followed by maintenance oral nifedipine in women determined to be in preterm labor between 32 0/7 and 34 6/7 weeks gestational age. Our results indicate that aggressive tocolysis does not improve neonatal outcome as measured by the total length of neonatal hospital stay. In addition, we found that neonatal morbidity is minimal at this gestational age following administration of steroids irrespective of the use of tocolytic agents.

Clinical Implications of the Study

Several studies suggest that acute tocolytic therapy does not prevent preterm birth or significantly reduce gestational age dependent morbidity when given for women in preterm labor.[6] In general, data from randomized trials suggest that tocolytic agents prolong pregnancy up to 48 hours,[6] thus treatment is being given on the basis that tocolysis will prevent delivery in the first 24 to 48 hours to optimize the effect of steroids. However, most studies are plagued by a variety of confounding variables, such as lack of progressive cervical change before randomization,[9-18] inclusion of women with preterm rupture of membranes,[11,14,16] large range of gestational age (20 to 36 weeks' gestation) at enrollment,[5,7] the inclusion of near term deliveries between 35 and 36 weeks' gestation with little risk for significant infant morbidity and mortality,[9-18] and inadequate power to assess infant morbidity and mortality.[9-11,13,15-18]

Parenteral magnesium sulfate is the most commonly utilized tocolytic agent in the treatment of preterm labor in North America. A recently published meta-analysis by Crowther et al[19] revealed no evidence of clinically important tocolytic effect for $MgSO_4$ and concluded that treatment with $MgSO_4$ does not substantially increase the proportion of women delivering within 48 hours (RR 0.85, 95% C.I. 0.58-1.25, 11 trials, 881 women), and it does not substantially reduce infant morbidity.

The critical importance of preterm birth is its relationship to infant morbidity and mortality. The majority of perinatal mortality is directly related to complications of prematurity. Long term sequelae, including cerebral palsy, blindness, deafness, and chronic lung disease are

directly linked to preterm birth, particularly in infants born before 32 weeks gestation or under 1500 grams.[20,21] Although survival is almost 100% and perinatal morbidity is less common (<5-10%) with preterm birth after 32 weeks of gestation, some of these neonates will require prolonged hospitalization due to acute complications including transient tachypnea of the newborn, hyperbilirubinemia, temperature instability, apnea and bradycardia of prematurity and poor feeding.[22,23]

Strengths and Weaknesses of the Study

One major strength of this study is limiting the sample of women to those with preterm labor between 32 to 34 6/7 weeks' gestation. A large proportion of women presenting with preterm labor fall into this gestational age range.[5,7] Other studies have used much larger ranges for gestational age. The inclusion of such a large range of gestational age adds possible confounding variables such as complications due to the younger gestational age.

Another strength of this study is the requirement of the presence of progressive cervical dilations and effacement to diagnose preterm labor. Indeed, at randomization 61% of all enrolled patients had cervical dilation ≥ 3 cm and/or 20-25% had cervical effacement of $\geq 80\%$. By including only women who are in actual labor, we reduce potential bias in the true effects of tocolytics in women who may not have been in active labor.

One limitation of our study is the lack of placebo. Although there is the potential for biased treatment by managing physicians, all physicians provided a standard management protocol with the same home care instructions to patients. Doing a double-blind placebo trial would have required extensive resources. In addition, in clinical practice it is very difficult to mask the side effects of IV $MgSO_4$ that are obvious to patients, nurses and physicians.

There is the potential for patients to be biased regarding their subsequent behavior after randomization; however, we found no differences between the 2 groups in the number of women returning to the hospital for triage visits or in the number of women who were readmitted to the hospital for subsequent contractions. Therefore, the likelihood of bias due to the unblinded design of the study is low.

A second weakness of our study is the small sample size and corresponding low power (power = 37%) of this study make it difficult to draw inferences regarding the effects of aggressive tocolysis after 32 weeks' gestation. A post hoc analysis of our data revealed that 306 patients per group are needed to detect a difference in the total length of neonatal hospital stay between the no tocolysis (5.8 ± 7.2 days) versus tocolysis (7.5 ± 8.6; effect size = .24) groups at $\alpha = 0.05$ and power of 80%.

In addition, the low rates of RDS and IVH in this population limit our ability to draw conclusions about the effects of tocolysis on these conditions. There were no cases of RDS or IVH in our study. However, since these complications are infrequent in this gestational age range and several thousand patients would be required, it is unlikely that a trial will be performed to evaluate these issues.

Future areas of investigation

Future studies with larger sample sizes are needed to evaluate the benefits of tocolytic agents in women with preterm labor prior to 32 weeks'gestation. A large multi-center randomized trial will be required to further investigate the efficacy and clinical usefulness of aggressive tocolysis after 32 completed weeks of gestation regarding neonatal length of hospital stay.

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