EFFECTIVENESS OF ORAL MAINTENANCE TERBUTALINE THERAPY AFTER THREATENED PRETERM LABOR

Supakit Wongwiwatthananukit[1,*], Rawadee Dhumma-Upakorn[2] and Ketkanok Kaenboon[3]

[1]Department of Pharmacy Practice, College of Pharmacy, University of Hawaii at Hilo, Hilo, Hawaii 96720, USA
[2]Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok 10330, Thailand [3]Department of Pharmacy, Pattani Hospital, Pattani 94000, Thailand

ABSTRACT: The purpose of this study was to compare the effectiveness of oral maintenance terbutaline with no therapy after successful intravenous tocolysis in reducing the rate of preterm labor and identify predictors of preterm labor. A historical cohort study was conducted in 91 pregnant women with 28 to 35 weeks' gestation who were admitted with threatened preterm labor. After successful treatment with intravenous terbutaline sulfate, 46 patients participated to receive oral maintenance terbutaline therapy and 45 patients received no therapy. The dose of terbutaline was given orally 2.5 mg every 6 hour and was continued until the 36 weeks of completed gestation. There was no significantly different between oral terbutaline and no therapy groups with respect to term delivery (76.09% vs 66.67%, p=0.32), incidence of recurrent preterm labor (26.09% vs 31.11%, p=0.60), time gained (31.33 ± 16.92 vs 28.11 ± 14.96 days, p=0.34) and neonatal outcome. Kaplan-Meier and log-rank test revealed that survival time to term delivery was not significant difference between two groups (p=0.34). Adverse effects during oral terbutaline treatment were palpitation and fetal tachycardia. Logistic regression indicated that only recurrent preterm labor was a significant predictor of preterm labor. Oral maintenance terbutaline therapy after successful parenteral tocolysis appeared to be ineffective tocolytic agent for pregnancy prolongation or a reduction in the incidence of recurrent preterm labor in women with 28 to 35 weeks' gestation.

Keywords: Preterm labor, Terbutaline, Tocolysis, Historical Cohort Study

INTRODUCTION: Preterm labor is a premature delivery occurring prior to 37 completed weeks of gestation[1)]. It occurs in 7-10% of pregnancies worldwide and continues to be the major cause of neonatal morbidity and mortality[1,2)]. Infants born prior to 28 weeks of gestation are complicated with mortality, severe handicap, low birth weight, and long-term cognitive impairment[1,2)]. The incidence of severe neonatal morbidities, such as respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage is well documented and its incidence is decreased with increasing gestational age[1)]. Prevention of threatened preterm labor is still a primary goal in obstetric practice, and the efficacy of parenteral tocolytic agents (i.e., magnesium sulfate, ritodrine sulfate) in prolongation of pregnancy for 24 to 48 hours has been shown to be useful and clearly studied[3)]. Since patients with an episode of threatened preterm labor are at increased risk for the incidence of recurrence, it has become common practice to prescribe oral tocolytic therapy after successful parenteral tocolysis as maintenance therapy in an attempt to reduce the rate of recurrent preterm labor.

However, the efficacy and use of oral maintenance tocolytic therapy, such as terbutaline sulfate, magnesium chloride, and indomethacin in preventing recurrent preterm labor and preterm delivery remain controversial and the studies have conflict results[4,5)]. The use of these agents is often associated with adverse effects, such as terbutaline includes palpitation, tremor, nausea and vomiting, hyperglycemia and hypokalemia and is able to cross the placenta which may affect the infant[3,5-8)]. There has been no consensus and clinical practice guideline specified which oral maintenance tocolytic therapy should be used for pregnancy prolongation after successful parenteral tocolysis[5)]. Therefore, the use of these oral agents totally leave the burden on the judgment and experience of individual physicians and patients. In addition, the effectiveness of oral maintenance terbutaline sulfate in preventing

*To whom correspondence should be addressed.
E-mail: supakit@hawaii.edu,
Tel: +1-808-933-2947, Fax: +1-808-933-2974

recurrent preterm labor after successful administration intravenous terbutaline sulfate, which is commonly used in some institutions, has not been well studied. Our objectives were to compare the effectiveness and adverse effects of oral maintenance terbutaline sulfate with no therapy after successful intravenous terbutaline sulfate in reducing the rate of preterm labor and identify predictors of preterm labor.

MATERIALS AND METHODS: A historical cohort study was conducted from January 2007 to February 2008 at the labor ward of Pattani Hospital, Pattani Province, Thailand. Patients admitted with the diagnosis of preterm labor between 28 and 35 weeks of pregnancy (determined by the date of the last menstrual period when known or by early ultrasound), were evaluated for intravenous terbutaline sulfate tocolysis. Inclusion criteria for initiating intravenous terbutaline sulfate were: regular uterine contractions at least four contractions occurring within 20 minutes or eight contractions occurring within 60 minutes, with documented cervical change. Exclusion criteria were the presence of preterm premature rupture of the membranes, cervical dilatation > 4 cm, high-order pregnancy carrying > 2 fetuses, major antepartum hemorrhage, blood pressure less than 90/50 mmHg, preeclampsia, a fetus with lethal congenital anomalies, known terbutaline allergy or contraindications, need of oral terbutaline for other medical indications. A 0.25-mg loading of terbutaline was administered intravenously, followed by an infusion of 2 mg until the cessation of uterine contraction. This then was followed by a subcutaneous 0.25-mg dose of terbutaline every four hours for the total of six doses.

Patients who were successfully treated with intravenous terbutaline were eligible for inclusion in the study and inform consent was obtained. Four hours after parenteral tocolysis, patients were assigned to receive either oral maintenance terbutaline or no therapy, depending on routine practice of each obstetrician. The terbutaline group was given oral terbutaline sulfate 2.5 mg every 6 hour (four times per day) until the 36 weeks of completed gestation. If preterm labor recurred and there was no contraindication, the oral medication was discontinued, intravenous terbutaline was repeated, and terbutaline or no terbutaline treatment was reinitiated and maintained until the 36 week of gestation or labor. Signs and symptoms of preterm labor, terbutaline side effect, and adherence were discussed before discharge from the hospital and reiterated by telephone contact weekly. The primary outcome in this study was term delivery (gestation age at delivery). Other outcomes included incidence of recurrent preterm labor, time gained, $\geq$ 37 weeks at delivery, recurrent uterine contractions, survival time to 37 weeks of gestation, neonatal outcomes (i.e., birth weight, APGAR score < 7[9]), nursery admissions, incidence of respiratory distress syndrome), and adverse effects. APGAR score is the evaluation of neonates after delivery[9], in which score is given for each sign (activity, pulse, grimace, appearance and respiration) at one minute and five minutes after delivery. A score of 7-10 is considered normal, while 4-7 might require some resuscitative measures, and 0-3 requires immediate resuscitation. Adherence was assessed by using pill counts in a pillbox and the patients presenting for follow-up as scheduled. Patients were instructed to leave any missed doses in the pillbox and were examined by the investigators at the end of the 36 weeks of gestation. Good adherence to follow-up was defined as patients take the pills at least 90% of the total pills.

An estimated sample of 82 patients (41 patients in each group) was calculated to determine a mean difference of 1.5 weeks of gestational age between the oral maintenance terbutaline and no therapy groups[10] and pooled variance of 5.86 weeks[10] at an α significance level of 0.05 and a power of 80%. The analyses were intention-to-treat. Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) software, version 15.0. Both descriptive and inferential statistics were determined. Baseline and outcome variables were compared by χ^2 tests or Fisher's exact test or independent *t*-test, as appropriate. Univariate logistic regression was used to analyze the

predictors of preterm labor. Kaplan-Meier Method was used to analyze the survival probability of preterm labor and log-rank test was used to compare survival time to 37 weeks of gestation between the two groups. The study and the study design were approved by the Research Ethics Committee of The Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand and the consent of the medical director of Pattani Hospital.

RESULTS: Ninety-one patients were enrolled in the study. Forty-six patients received oral terbutaline for maintenance therapy after threatened preterm labor and 45 patients had no therapy. Adherence of 100% for the patients who completed the study was demonstrated by pillbox examination at the end of the 36 weeks of gestation. There was no statistically significant difference in baseline maternal demographic data between those receiving terbutaline versus no therapy (Table I). Table II depicts a comparison of maternal outcome between the two groups. There were no significant difference between two groups regarding gestation age at delivery (term delivery), undelivered time gained, $\geq$ 37 weeks at delivery, incidence of recurrent preterm labor, and recurrent uterine contraction.

Table III shows neonatal outcomes between two groups. There was no significant difference in any neonatal outcomes. One infant in terbutaline group had APGAR score of 5 at one minute of delivery. However, the score of APGAR score assessment increased to seven at five minutes after delivery. Adverse effects during oral terbutaline treatment are noted in Table IV. There was no case requiring reduction of dosage or discontinuation of oral terbutaline. Univariate logistic regression was performed with preterm delivery as the dependent variable. The following variables were entered: maternal age, gestation age at entry, gravidity, parity, history of abortion, initial cervical dilation, twin gestation, recurrent preterm labor and terbutaline therapy. Only recurrent preterm labor was a significant independent predictor for preterm labor (Odds ratio = 378.00, 95% confidence interval: 50.37-2836.87). A survival analysis demonstrated that there was no statistically significant difference of survival time to 37 week of gestation between patients receiving oral terbutaline and no therapy (Figure1).

DISCUSSION: Previous studies had examined the efficacy of oral maintenance terbutaline therapy after successful parenteral tocolytic therapy in patients with threatened preterm labor. Brown and Tejani[11] conducted the first trial on maintenance terbutaline therapy. They randomized 46 patients to either oral terbutaline or placebo after tocolysis with intravenous ethanol. Results

Table 1 Maternal demographic data

	Terbutaline (N=46)	No Therapy (N=45)	p value
Age (yr) (mean ± SD)	26.17 ± 6.17	27.20 ± 5.48	0.404 [a]
Gestational age (wk) (mean ± SD)	32.91 ± 1.71	32.80 ± 1.66	0.750 [a]
Parity			
nulliparous	29 (63.04)	21 (46.67)	0.287 [b]
primigravid	9 (19.56)	12 (26.67)	
multigravid	8 (17.39)	12 (26.67)	
History of abortion			
No history	29 (63.04)	31 (68.89)	0.802 [b]
1 time	10 (21.74)	9 (20.00)	
2 times	7 (15.22)	5 (11.11)	
Twin gestation	3 (6.52)	2 (4.44)	1.000 [c]
Cervical dilation			
No dilation	29 (63.04)	32 (71.11)	0.710 [b]
1.0 cm	9 (19.56)	6 (13.33)	
1.5 cm	5 (10.87)	3 (6.67)	
2.0 cm	3 (6.52)	4 (8.89)	

Values in parentheses indicate percent.

[a]independent *t* test, [b]Chi-square test, [c]Fisher's Exact test

Table 2 Maternal outcomes

Maternal outcome	Terbutaline (N=46)	No Therapy (N=45)	p value
Gestational age at delivery (wk) (mean± SD)	37.41 ± 1.75	36.91 ± 1.98	0.202 [a]
Time gained (day) (mean ± SD)	31.33 ± 16.92	28.11 ± 14.96	0.340 [a]
≥ 37 wk at delivery	35 (76.09)	30 (66.67)	0.320 [b]
Recurrent preterm labor	12 (26.09)	14 (31.11)	0.596 [b]
Recurrent uterine contraction	3 (6.52)	3 (6.67)	1.000 [c]

Values in parentheses indicate percent.

[a]Student Unpaired t test, [b]Chi-Square test, [c]Fisher's Exact test

Table 3 Neonatal outcomes

Neonatal outcome	Terbutaline (N=49)[d]	No Therapy (N=47)[e]	p value
Birth weight (gm) (mean ± SD)	2770.20 ± 512.81	2723.62 ± 492.30	0.651 [a]
Birth weight < 2,500 gm.	17 (34.69)	14 (29.79)	0.607 [b]
APGAR score < 7	1 (2.04)	0 (0.00)	1.000 [c]
Nursery admissions	2 (4.08)	3 (6.38)	0.674 [c]
Respiratory distress syndrome	2 (4.08)	2 (4.26)	1.000 [c]

Values in parentheses indicate percent.

[a]Student Unpaired t test, [b]Chi-Square test, [c]Fisher's Exact test, [d]three patients had twin delivery, [e]two patients had twin delivery

demonstrated a significant increase in latency and a decrease in the incidence of neonatal respiratory distress syndrome, with the use of maintenance oral terbutaline therapy. A prospective randomized trial of terbutaline versus placebo by Parilla, Dooley, Minoque *et al*[12]. did not demonstrate a significant reduction in preterm delivery with the use of oral terbutaline after intravenous tocolysis. How, Hughes, Vogel *et al*[13]. investigated pregnancy outcome in patients given oral terbutaline versus no therapy and results indicated no improvement in pregnancy outcome. Rust, Bofill, Arriola *et al*[14]. conducted a randomized double-blind study and it was found that once preterm labor was ceased with intravenous magnesium sulfate, the use of either oral terbutaline or a placebo did not result in any significant differences in the maternal outcome and neonatal outcome.

Lewis, Mercer, Salama *et al*[15]. in a randomized double-blind study protocol suggested that using oral maintenance terbutaline after successful parenteral tocolysis did not reduce the incidence of delivery at 1 week, the incidence of preterm delivery, or the recurrence of preterm labor. In addition, they were unable to demonstrate a significant improvement in neonatal outcomes or birth weight with this therapy. This was confirmed by a systematic review[4], which assessed the effects of oral betamimetics for maintenance therapy after threatened preterm labor. Results demonstrated that available evidence did not support the use of oral betamimetics for maintenance therapy after threatened preterm labor[4]. Our study has also failed to demonstrate a significant beneficial effect of oral maintenance terbutaline therapy. It is important to note that the dosage regimen of oral terbutaline in our study was quite low when compared with the standard dose of 5-10 mg every 6 hours from previous studies and was not adjusted to achieve and maintain a maternal pulse rate of 90-120 beats/min[13]. Although this pulse rate was the indicator for the appropriate serum therapeutic level of terbutaline, a study[13] which adjusted dosage of oral terbutaline, 5-10 mg. every 4-6 hours, to keep the pulse rate

Table 4 Adverse effects associated with terbutaline

Adverse effect	Total N = 46
Complaint of at least one adverse effect	3 (6.52)
Maternal tachycardia (>100 beats/min.)	1 (2.17)
Palpitation	2 (4.35)
Fetal tachycardia (>160 beats/min.)	1 (2.17)

Values in parentheses indicate percent.

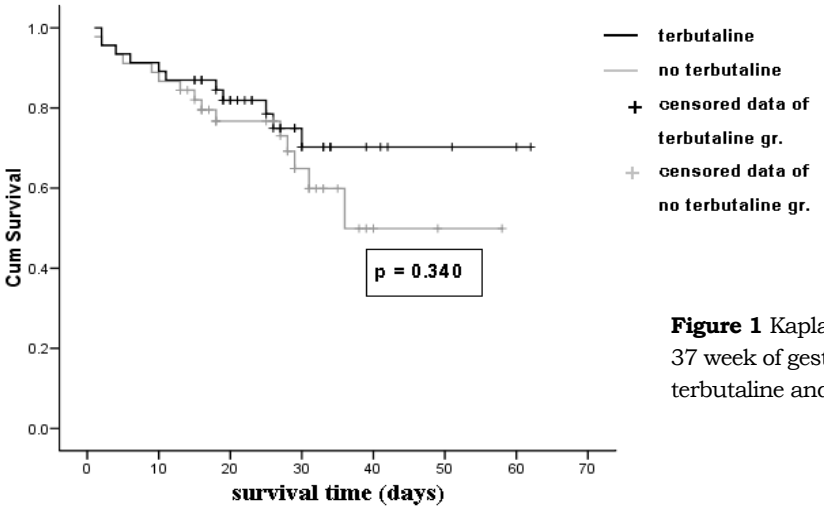

Figure 1 Kaplan-Meier survival curve of time to 37 week of gestation between oral maintenance terbutaline and no therapy groups.

between 90 and 120 beats/min still did not demonstrate an improvement in maternal and neonatal outcomes.

Terbutaline binds to beta-1 and beta-2 receptors. This leads to a variety of adverse effects and complications[8]. Stimulation of the beta-1 receptor can lead to increased cardiac output both by increasing heart rate as well as stroke volume by direct effect on the heart. In addition, beta-2 receptor stimulation in the vasculature can cause vasodilatation. This can lead to hypotension and further tachycardia[16]. The most common adverse effects in the previous studies attributed to oral terbutaline (5 mg. every 4-6 hours) were palpitation (13.1-16.6%) and maternal tachycardia (65.22%)[11,14]. In our study, as expected adverse effect of oral terbutaline appeared to be minimal and were manifested as mild maternal and fetal tachycardia when compared with the previous studies[11,14]. This may be explained by the low dose of oral terbutaline in this study.

Recurrent preterm labor was a significant independent predictor for preterm delivery. However, our confidence interval is relatively wide and is not particularly precise. This may be explained by our limited small sample size when performing logistic regression analysis. However, this result would generate more hypotheses for future study and guide providers to closely monitor patient with recurrent preterm labor to prevent preterm delivery. Our initial analysis of survival time to 37 weeks of gestation demonstrated no statistically significant difference between two groups, which was difference from Lewis, Mercer, Salama *et al*[15]. Their study found that post hoc evaluation of 96 patients enrolled before 32 weeks of gestation suggested pregnancy prolongation with oral maintenance terbutaline. Although data on patients randomized at <32 weeks of gestation appeared promising, the authors argued that it was obtained as a post hoc analysis[15]. A prospective, randomized trial will be needed to answer the question related to survival time when terbutaline is used in patients at an earlier gestational age. Our study was also not designed to answer the survival time of oral terbutaline and probably not powered to detect a survival time difference between two groups (only eight and 10 patients at < 32 weeks of gestation in those receiving oral terbutaline and no therapy, respectively).

CONCLUSIONS: Our data suggest that maintenance oral terbutaline therapy after threatened preterm labor does not improve maternal outcome or neonatal outcome in a population of women with 28 to 35 weeks of gestation. In addition, oral terbutaline produces adverse effects such as tachycardia, palpitation and fetal tachycardia.

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