# Oral Salbutamol for Treatment of Preterm Labor

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***Objective :*** *The aim of this study was to assess the value of oral salbutamol for the inhibition of preterm labor.*
***Material and Method :*** *Medical records of the department from January 1, 1991 to December 31, 1999 were reviewed for all idiopathic preterm labors that were inhibited by oral salbutamol and statistically analyzed.*
***Results :*** *Of 132 pregnancies, 81.1% (95%CI, 74.4, 87.7) were prolonged for more than 24 hours, 59.8% (95%CI, 51.5, 68.2) for more than 2 days, 32.6% (95%CI, 24.6, 40.6) for more than 1 week, and 8.3% (95%CI, 4.2, 14.4) for more than 4 weeks. Tachycardia (pulse rate > 100 beats/min) occurred in 85.6% of the patients, but those with a pulse rate higher than 140 beats/min occurred in only 3%. Hypotension occurred in only 0.8%. Neonatal complications occurred in 28%, while respiratory distress syndrome occurred in 22.7% of the babies. Perinatal mortality in the present study was 7.6 per 1,000 births. When comparing the pregnancy outcome between groups regarding the prolongation time, the pregnancy outcome was significantly better in the group that had a prolongation time of at least 48 hours.*
***Conclusion :*** *Oral salbutamol proved to be another effective method that inhibits preterm labor and consequently prolongs pregnancy. Because it requires no intensive medical nursing care and observations, and no discomfort of an intravenous line, oral salbutamol may be an alternative drug in the management of preterm labor.*

***Keywords :*** *Salbutamol, Oral form, Preterm labor, Tocolysis, Inhibition*

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Preterm birth is defined as a delivery that takes place before 37 complete weeks' gestation[1]. It is the leading cause of perinatal mortality and morbidity. The incidence varies between 6-15%[2,3]. The perinatal mortality and morbidity associated with preterm birth decreases with advancing gestational age. Only 20% of the babies born at 24 weeks survive[4]. A delay of delivery for 1 week between the gestational age of 23 and 26 weeks can increase neonatal survival by 3% per day, with a concordant reduction of neonatal morbidity[5]. Because high perinatal mortality and morbidity are associated with preterm birth, significant effort is directed toward inhibiting and preventing it. Several tocolytic drugs such as beta-sympathomimetics, magnesium sulfate, antiprostaglandins, calcium channel blockers, and oxytocin antagonists have been recommended for this purpose[3]. They can delay labor sufficiently to allow the administration of antepartum corticosteroids. The incidence of respiratory distress syndrome (RDS), intraventricular hemorrhage (IVH) and necrotizing enterocolitis (NEC) in neonates are reduced when tocolytics and corticosteroids are co-administrated[6].

Beta-sympathomimetic drugs are widely used for prophylaxis[7] and treatment of preterm labor[8]. Oral salbutamol, one of beta-sympathomimetic drugs, has been used for treatment of preterm labor in Europe since 1979[9], and at the authors' department since 1984[10]. The aim of this study was to assess the value of oral salbuta-mol as inhibitor of preterm labor.

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## Material and Method

The authors reviewed the case records of pregnant women who were diagnosed as preterm labor and subsequently treated with oral salbutamol as tocolysis at the Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University

from January 1, 1991 to December 31, 1999. All recruited women in the study met the following criteria: preterm labor between the gestational age of 28 and 34 weeks; all had live singleton fetuses at their onset of labor; no cause of preterm labor had been found; none had medical and obstetric complication; all were treated with oral salbutamol 32 mg/day with 4 divided doses and received 4 doses of 6 mg dexamethasone intramuscularly at 12 hour intervals. All of them had regular uterine contractions, at least 4 contractions in 20 minutes or 8 in 60 minutes plus progressive change of cervix (cervical dilatation greater than 1 cm and/or effacement at least 80%)[1].

The following variables were extracted from the records: maternal age, weight, gestational age at diagnosis, cervical dilatation and effacement at diagnosis, gestational age at delivery, prolongation time, side effects, maternal and neonatal outcomes. Prolongation time is defined as the time between oral salbutamol administration and delivery. Neonatal complications include RDS, IVH, NEC, pneumonia and sepsis. The authors also divided the cases into two groups according to the prolongation time. Group 1 had a prolongation time less than 48 hours while group 2 had at least 48 hours of prolongation time.

Statistical analysis was assisted by computer software (SPSS version 10.0 for Windows, SPSS Inc, Chicago, USA). Data were summarized applying descriptive statistics and expressed in term of mean, standard deviation, percent, and 95% confidence interval (CI). Chi square or Fisher's exact tests for comparison of proportions, and student t-tests for comparison of means were used. $P < 0.05$ was considered statistically significant.

**Table 1.** Data of maternal and obstetric characteristics

| | Mean±SD (Range) | 95%CI |
|---|---|---|
| Maternal age (years) | 24.7±6.0 (14-41) | 23.7, 25.7 |
| Gravidity | 1.8±0.9 (1-6) | 1.6, 2.0 |
| Parity | 0.5±0.7 (0-5) | 0.4, 0.7 |
| Gestational age at admission (weeks) | 31.7±1.8 (28-34) | 31.4, 32.0 |
| Gestational age at delivery (weeks) | 33.1±2.4 (28-40) | 32.7, 33.5 |
| Length of admission (days) | 10.1±6.7 (2-45) | 9.0, 11.3 |
| Prolongation time (days) | 8.8±12.1 (0.1-64) | 6.7, 10.9 |

**Table 2.** Success rate in prolongation of pregnancy

| Pregnancy prolonged | Number of patients (%) | 95% CI |
|---|---|---|
| < 24 hours | 25 (18.9%) | 12.3, 25.6 |
| 24-48 hours | 28 (21.2%) | 14.2, 28.2 |
| 2-7 days | 36 (27.3%) | 19.7, 34.9 |
| 7-28 days | 32 (24.2%) | 16.9, 31.6 |
| > 28 days | 11 (8.3%) | 4.2, 14.4 |

**Table 3.** Maternal side effects

| Side effects | Number of patients (%) | 95% CI |
|---|---|---|
| Tachycardia (beats/min) | 113 (85.6%) | 79.6, 91.6 |
| > 110 | 100 (75.6%) | 68.4, 83.1 |
| > 120 | 35 (26.5%) | 19.0, 34.0 |
| > 130 | 10 (7.6%) | 3.7, 13.5 |
| > 140 | 4 (3.0%) | 0.8, 7.6 |
| Hypotension (< 90/60 mmHg) | 1 (0.8%) | 0.02, 4.1 |

## Results

A total of 132 women met the inclusion criteria: 43 women had a prolongation time less than 48 hours (Group 1), and while 89 women had at least 48 hours of prolongation time (Group 2).

Maternal and obstetric characteristics are shown in Table 1. The success rate of prolongation of pregnancy is shown in Table 2. Pregnancies were prolonged for more than 24 hours in 81.1% (95%CI, 74.4, 87.7), for more than 2 days in 59.8% (95%CI, 51.5, 68.2), for more than 1 week in 32.6% (95%CI, 24.6, 40.6), and more than 4 weeks in 8.3% (95%CI, 4.2, 14.4) of the patients.

Maternal side effects are shown in Table 3. The most common side effect was tachycardia which occurred in 85.6% of the patients. However, a pulse rate higher than 140 beats per minute occurred in only 3% of the patients. This was considered intolerable, then the administration of the drug was delayed for half an hour. Hypotension (blood pressure less than 90/60 mmHg) occurred in only 0.8% of the patients. There was no maternal death in this study.

Neonatal outcomes are shown in Table 4. The most common neonatal complication was RDS which occurred in 22.7% of the babies. There was no IVH in the present study and Only one baby died. She was born at 29 weeks after 12 hours of oral salbutamol and intramuscular dexamethasone administration. The cause of death was pneumonia and sepsis that took place 5 days after birth.

Maternal and obstetric characteristics, maternal side effects and neonatal outcomes were

**Table 4.** Neonatal outcomes

| Outcomes | | 95% CI |
|---|---|---|
| Birth weight (grams) | 2,056.5±474.6 (1,050-3,250) | 1974.8, 2138.2 |
| Apgar score at 1 min | 8.0±1.8 (0-9) | 7.7, 8.3 |
| Apgar score at 5 min | 9.4±1.2 (1-10) | 9.2, 9.6 |
| Apgar score < 7 at 1 min | 25 (18.9%) | 12.3, 25.6 |
| Apgar score < 7 at 5 min | 4 (3.0%) | 0.8, 7.6 |
| Total newborn admission day (days) | 14.8±19.1 (2-85) | 11.5, 18.1 |
| Complications | 37 (28.0%) | 20.4, 35.7 |
| RDS | 30 (22.7%) | 15.6, 29.9 |
| NEC | 2 (1.5%) | 0.2, 5.4 |
| Pneumonia | 11 (8.3%) | 4.2, 14.4 |
| Sepsis | 8 (6.1%) | 2.7, 11.6 |
| Need NICU | 36 (27.3%) | 19.7, 34.9 |
| Death | 1 (0.76%) | 0.02, 4.1 |

Data expressed as Mean±SD (range) or proportion

**Table 5.** Comparison between groups, according to the prolongation time

| | Group 1(N=43) | Group 2(N=89) | 95% CI of the difference | P value |
|---|---|---|---|---|
| Maternal age (years) | 23.4±6.3 | 25.3±5.8 | -4.1, 0.3 | NS |
| Gravidity | 1.7±1.0 | 1.8±0.9 | -0.4, 0.2 | NS |
| Parity | 0.5±0.9 | 0.5±0.7 | -0.3, 0.3 | NS |
| Gestational age at admission (weeks) | 31.3±2.0 | 31.9±1.7 | -1.3, 0.1 | NS |
| Gestational age at delivery (weeks) | 31.7±2.1 | 33.8±2.3 | -2.9, -1.3 | < 0.05 |
| Length of admission (days) | 7.2±4.3 | 11.6±7.2 | -6.4, -2.4 | < 0.05 |
| Prolongation time (days) | 1.0±0.6 | 12.5±13.2 | -14.4, -8.8 | < 0.05 |
| Tachycardia (beats/min) | 33 (76.7%) | 80 (89.9%) | -0.3, 0.01 | NS |
| Hypotension (mmHg) | 0 | 1 (1.1%) | - | - |
| Birth weight (grams) | 1817.2±411.6 | 2172.1±461.5 | -518.8, -191.1 | < 0.05 |
| Apgar score < 7 at 1 min | 12 (27.9%) | 13 (14.6%) | -0.02, 0.3 | NS |
| Apgar score < 7 at 5 min | 2 (4.7%) | 2 (2.2%) | -0.05, 0.09 | NS |
| Total newborn admission day (days) | 22.4±23.8 | 11.1±15.2 | 3.4, 19.3 | < 0.05 |
| Complications | 18 (41.9%) | 19 (21.3%) | 0.03, 0.4 | < 0.05 |
| RDS | 12 (27.9%) | 18 (20.2%) | -0.08, 0.2 | NS |
| NEC | 1 (2.3%) | 1 (1.1%) | -0.04, 0.06 | NS |
| Pneumonia | 8 (18.6%) | 3 (3.4%) | 0.03, 0.3 | < 0.05 |
| Sepsis | 5 (11.6%) | 3 (3.4%) | -0.02, 0.2 | NS |
| Need NICU | 19 (44.2%) | 17 (19.1%) | 0.08, 0.4 | < 0.05 |
| Death | 1 (2.3%) | 0 | - | - |

compared between the two groups (Table 5). The difference of maternal age, gravidity, parity and gestational age at admission were not significant in either group. Gestational age at delivery, length of admission, and prolongation time were significantly longer in group 2. The birth weight was significantly lower in group 1, whereas the total newborn admission day was significantly shorter in group 2. Neonatal complications, pneumonia and the need for neonatal intensive care unit (NICU) were significantly lower in group 2. However, RDS, NEC and sepsis were not significantly different.

## Discussion

In the present study, oral salbutamol administration for inhibition of preterm labor appears to give satisfactory outcomes with 81.1% success rate of prolongation time of more than 24 hours. The neonatal outcome was good when the prolongation time was at least 48 hours.

The oral form of salbutamol was used in our department because it offers advantage both to the patients and the nurses. It does not require intensive medical nursing care and observations, together with the discomfort of an intravenous line. The dosage of

oral salbutamol used in the department was 8 mg every 6 hours, similar to the report by Hastwell, et al[11]. The serum concentration of the dosage is equivalent to that commonly used in intravenous salbutamol infusion dose 6-30 μg/min to inhibit preterm labor[12]. This dosage was considered tolerable for patients because of its lower incidence of maternal side effects. In the present study, there was an incidence of 0.8% of hypo-tension and 3% of tachycardia that was higher than 140 beats/min.

Fifty-nine point eight percent of the patients in the present study had their pregnancies prolonged for more than 48 hours. This result was less than the reports of Hastwell, et al[11] and Witoonpanich, et al[10] that oral salbutamol could prolong pregnancy more than 48 hours in 85-89.4%. The difference may come from the difference of the inclusion criteria employed by Haswell, et al and the small sample size in the study of Witoonpanich, et al. The result was also less than the regimen that consisted of intravenous salbutamol followed by oral salbutamol[13]. The 48-hour delay was used to allow the benefit of corticosteroids to increase fetal lung maturity. The present study confirmed that a 48-hour delay of onset of labor resulted in a lower incidence of neonatal complications.

The incidence of RDS in this study was higher than that of Hastwell, et al[11]. This may be explained by the difference of inclusion criteria. The study from Hastwell, et al[5] included preterm labor gestational age between 20-36 weeks with intact or ruptured membranes, and had more cases delivered after 34 weeks than in the present study. However, the perinatal death in the present study was 0.76% which was lower than that reported by Hastwell, et al[11]. The higher perinatal loss may be due to the higher number of cases of congenital malformation in their study.

The neonatal outcomes were more significantly better in the patients that had at least 48 hours of prolongation time (Table 5). This confirmed the use of tocolytic drugs to inhibit preterm labor which allows more time for corticosteroids to enhance fetal lung maturation[3]. The difference of the number of RDS and NEC between the two groups was not significant. This may come from the benefit of corticosteroids that can decrease morbidity despite short term or even after one dose administration[6].

This is a retrospective study and as such suffers the limitations of retrospective studies. As is true for all retrospective studies, the authors cannot assure that all potential factors influencing outcome were controlled. Within these recognized limitations of retrospective studies, the data support the contention that oral salbutamol is an effective method to inhibit preterm labor and prolong pregnancy. Although this study is retrospective, there is a large number of Thai patients with preterm labor.

In conclusion, oral salbutamol has been proved to be an effective method to inhibit preterm labor and prolong pregnancy. Because it requires no intensive nursing care and observations, and no discomfort of an intravenous line, oral salbutamol may be an alternative drug in management of preterm labor.

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## การใช้ยาซาลบูทามอลชนิดรับประทานสำหรับการรักษาการเจ็บครรภ์คลอดก่อนกำหนด

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***วัตถุประสงค์:*** *เพื่อประเมินถึงคุณค่าของการใช้ยาซาลบูทามอลชนิดรับประทานสำหรับระงับการเจ็บครรภ์คลอดก่อนกำหนด*

***วัสดุและวิธีการ:*** *ทำการทบทวนเวชระเบียนของหญิงตั้งครรภ์ที่มีภาวะการเจ็บครรภ์คลอดก่อนกำหนดโดยไม่พบสาเหตุที่ได้รับการระงับการเจ็บครรภ์คลอดก่อนกำหนดด้วยยาซาลบูทามอลชนิดรับประทานตั้งแต่ 1 มกราคม พ.ศ. 2534 ถึง 31 ธันวาคม พ.ศ. 2542 และทำการวิเคราะห์ข้อมูลทางสถิติ*

***ผลการศึกษา:*** *มีหญิงตั้งครรภ์ที่เข้าในการศึกษาทั้งหมด 132 คน พบว่าร้อยละ 81.1 (ระดับความเชื่อมั่นที่ร้อยละ 95, 74.4, 87.7) สามารถยืดระยะเวลาคลอดออกไปได้นานกว่า 24 ชั่วโมง, ร้อยละ 59.8 (51.5, 68.2) สามารถยืดระยะเวลาคลอดออกไปได้นานกว่า 2 วัน, ร้อยละ 32.6 (24.6, 40.6) สามารถยืดระยะเวลาคลอดออกไปได้นานกว่า 1 สัปดาห์, และร้อยละ 8.3 (4.2, 14.4) สามารถยืดระยะเวลาคลอดออกไปได้นานกว่า 4 สัปดาห์ ภาวะแทรกซ้อนที่พบคือ ภาวะหัวใจเต้นเร็ว (ซีพจรมากกว่า 100 ครั้งต่อนาที) พบได้ร้อยละ 85.6 แต่ถ้าซีพจรมากกว่า 140 ครั้งต่อนาทีพบได้เพียงร้อยละ 3 ภาวะความดันโลหิตต่ำพบได้เพียงร้อยละ0.8 พบภาวะแทรกซ้อนต่อทารกร้อยละ 28, โดยที่ภาวะการทำงานของปอดไม่สมบูรณ์พบได้ร้อยละ 22.7 อัตราการตายปริกำเนิดในการศึกษานี้เท่ากับ 7.6 ต่อ 1,000 ของการคลอด เมื่อเปรียบเทียบผลลัพธ์ของการตั้งครรภ์ระหว่างกลุ่มที่แบ่งตามระยะเวลาที่ยืดออกไปจนคลอด พบว่าผลลัพธ์ของการตั้งครรภ์ในกลุ่มที่ยืดเวลาออกไปอย่างน้อย 48 ชั่วโมงดีกว่าอีกกลุ่มอย่างมีนัยสำคัญทางสถิติ*

***สรุปผลการศึกษา:*** *ยาซาลบูทามอลชนิดรับประทานนั้นเป็นวิธีหนึ่งที่มีประสิทธิภาพดีในการระงับการเจ็บครรภ์คลอดก่อนกำหนด ยาซาลบูทามอลชนิดรับประทานอาจจะเป็นยาทางเลือกหนึ่งในการรักษาภาวะการเจ็บครรภ์คลอดก่อนกำหนดด้วยข้อดีที่ไม่จำเป็นต้องใช้การดูแลทางการแพทย์ที่ใกล้ชิดและไม่ต้องให้ยาทางเส้นเลือด*