ORIGINAL ARTICLE

# Terbutaline for acute tocolysis prior to emergency caesarean delivery for suspected foetal compromise

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**ABSTRACT**

**Introduction: Terbutaline has been used as a foetal resuscitation measure to improve the intrapartum foetal heart rate abnormalities and neonatal outcome for suspected foetal compromise. Unfortunately, till date, the available data are limited to draw any recommendation.**

**Material and Methods: This was a double-blind, placebo-controlled trial conducted among women planned for emergent caesarean delivery for suspected foetal compromise where 100 were randomised to receive subcutaneous terbutaline or placebo. The primary outcomes were the neonatal acid–base status, while the 5-minute Apgar score, admission to the intensive care unit and the maternal outcomes were recorded as secondary outcomes.**

**Results: Data from a total of 96 women were analysed and showed a lower incidence of neonatal acidemia (4.4% vs 10.4%) and fewer neonates born with umbilical artery pH of less than 7.20 (12.5% vs 27.1%) and 7.10 (4.2% vs 6.2%) after terbutaline injection. However, the difference in the incidence of neonatal acidaemia, mean cord pH and base excess, Apgar score or admission to the intensive care unit did not differ significantly. No difference was seen in the maternal mean arterial pressure, estimated blood loss or haematocrit after the surgery between the study groups. The only significant maternal effect was tachycardia which was more common after terbutaline injection (54.2% vs 25.0 %, p=0.003).**

**Conclusion: The study shows that acute tocolysis with subcutaneous terbutaline prior to caesarean delivery has the potential to improve the neonatal outcome in suspected intrauterine foetal compromise and should be further investigated.**

**KEYWORDS:**
*Foetal resuscitation; acute tocolysis; foetal compromise; terbutaline; caesarean section*

## INTRODUCTION

The National Institute for Clinical and Health Excellence (NICE) has recommended that emergency caesarean section should be completed within 30–75 minutes of decision depending on the risk assessed.[1] These targets may not be achieved for various reasons, including the unavailability of the operation theatre. In such a situation, intervention(s) that can increase the oxygen delivery to the placenta and umbilical blood flow, alleviating the insult(s) and improving the outcome of the neonate would be of tremendous value. One of these is acute tocolysis which by relaxing the myometrium could reduce the ischaemic effect of contraction on the uteroplacental blood flow.[2] Numerous medications had been investigated, such as terbutaline, atosiban, hexoprenaline, sildenafil, fenoterol bromhydrate, ritodrine, magnesium sulphate and nitroglycerine but the outcome varies.[3-9]

Improvement in the cardiotocography (CTG) patterns and neonatal umbilical artery pH had been demonstrated after subcutaneous terbutaline injection in a small randomised trial.[4] Similar results were also demonstrated in a retrospective cohort study comparing intravenous terbutaline and no intervention, where significantly fewer neonates with low Apgar score and higher umbilical cord pH were seen in the intervention group.[10] In another trial, acute tocolysis with subcutaneous terbutaline was associated higher percentage of abnormal cardiotocography resolution and fewer babies with umbilical cord pH of less than 7.20, compared with intravenous magnesium sulphate.[11] However, these studies were limited by the small sample sizes, retrospective study design and/or non-placebo controlled.[12] Here, we present results of a double-blind, placebo-controlled, randomised trial using subcutaneous terbutaline as a form of intrauterine resuscitation for cases of suspected foetal compromise.

## MATERIALS AND METHODS

Between January and December 2017, all women with a singleton pregnancy at term admitted in the active phase of labour in our hospital were invited to participate in a placebo-controlled, randomised trial. Once the diagnosis of suspected foetal compromised in first stage of labour was made based on the abnormal foetal heart rate monitoring (cardiotocography) according to NICE 2014 guideline and the delivery via caesarean section was planned, the participants were randomised to receive either subcutaneous terbutaline or equivalent volume of placebo.[13]

The women were excluded if they have cardiomyopathy, hyperthyroidism, abruptio placentae or other placental accidents, hypertensive disease of pregnancy, hyperstimulation with oxytocin, multiple gestation, abnormal foetus planned for conservative management,

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evidence of intrauterine growth restriction or on medication that will interact with terbutaline (tricyclic antidepressants, beta-blockers, diuretics and sympathomimetic medicine).

Consented women in the intervention group received 0.25 mg subcutaneous terbutaline while the control group was injected an equivalent volume (0.5 mls) of placebo by a nurse who prepared the solutions in a treatment room, separated from the labour suites. The obstetricians who ordered the intervention, the surgeons who performed the caesarean section, the anaesthetists, the neonatologists and the patients themselves were blinded to the injection given.

The primary objective was to determine if the pre-caesarean delivery tocolysis can reduce the incidence of acidosis in the neonatal umbilical artery. Acidosis in the umbilical artery is defined as pH level 7.00 or less and a base excess (BE) < –8 mmol/L.[14] The mean pH value, base excess, low Apgar score (less than 7) at 5 minutes of life and the need for admission to the neonatal intensive care unit (NICU) or special care nursey (SCN) were recorded as secondary outcomes. Other investigated outcomes were the maternal effects related to the interventional drug, which are the changes in mean arterial pressure and heart rate (before and 10 minutes after the drug or placebo injection), the estimated blood loss and the changes in the haematocrit level before and after the surgery. Maternal characteristics such as age, parity and gestational age were also recorded, together with induction and augmentation of labour. The neonatal birthweight, the colour of the amniotic liquor and interval between the decision for caesarean delivery, subcutaneous injection and the delivery of the neonate were also analysed. This trial methodology was based on the Consolidated Standards of Reporting Trials statement (http://www.consortstatement.org/consort-statement/).

Reported incidence of neonatal umbilical artery acidosis varies, depending on the level of cord pH and/ base excess used in the definition, ranging from 1.4% to 20%.[15,16] Taking the estimated neonatal acidaemia in cases of suspected foetal distress as 18%, samples required to show 50% reduction with the intervention, were calculated to be 247 in each arm (with 80% power and at 95% confidence) and was estimated to take more than 2 years to complete in our centre. Compromising on these, we had decided to include 110 women in each arm to achieve the study power of 50% and the recruitment was expected to be completed within a year. However, the Medical Research and Ethics Committee only approved 100 participants in total. The randomisation sequence was in random blocks of ten with a 1:1 ratio, generated by using a computerised random generator (www.random.org) and the blinding was secured using sealed opaque envelopes containing a random number and instruction for active drug or placebo administration. Mean and standard deviation were calculated for the qualitative variables and analysed using Student t test while the qualitative data were reported as percentage and analysed using chi-square test or Fisher exact test when necessary. Data handling and analysis were performed using Statistical Package for Social Science (SPSS) version 22 (SPSS Inc, Chicago, IL, USA) software with p-value of less than 0.05 considered to indicate statistical significance.

The study is registered with National Medical Research Register, Ministry of Health Malaysia (NMRR-16-1985-33115 (IIR)) and had received the approval of Medical Research & Ethic Committee, Ministry of Health Malaysia on 20th February 2017 (((23) KKM/NIHSEC/ P16-1613). The protocol was registered in Clinical Trail Registry (NCT05326269) and the study complies with the Declaration of Helsinki.

## RESULTS

In 2017, there were 4063 deliveries in our centre where 136 (from a total of 649) were caesarean section for foetal distress in 1st stage of labour. Of the 100 women randomised in this trial, one in the control group delivered vaginally in the operation theatre and three others (one from the control and two from the intervention group) had incomplete data, hence were excluded from the analysis. The women's characteristics and delivery progress are depicted in Table I, where no significant differences were seen between these two groups. More women in the terbutaline group had received labour induction and augmentation but the differences were not significant. It is to note that the average interval between the injections and delivery of the babies was 39 minutes in both groups while the mean decision to delivery time was 50 minutes in the terbutaline group and 48 minutes in the control group ($p$=0.755).

Neonates delivered in both groups had a similar mean birthweight, although more babies in the terbutaline group were small for gestational age ($p$=0.140). The incidence of neonatal acidosis was 4.2% and 10.4% in the terbutaline and placebo group, respectively; however, this difference was not statistically significant. The mean umbilical cord pH and base excess also did not differ between the groups (Table II). Two neonates had an umbilical cord pH of 7.00 or less at delivery (one in each group) and 25 had a base excess of less than -8.0 (thirteen in the terbutaline group). Even though there was no difference in mean cord pH and base excess, there were less babies in the intervention cohort that had the cord pH of less than 7.20 and 7.10 (Table III).

All 96 neonates had Apgar score of at least 7 at 5 minutes of life, and there was no significant difference in mean score between the groups. There was no perinatal death recorded in this study and no difference in the percentage of babies requiring admission to the NICU and SCN (Table II). Majority of these admissions were for respiratory-related issues such as suspected congenital pneumonia, meconium aspiration syndrome and transient tachypnoea of newborn.

Table IV shows the maternal outcomes related to the use of subcutaneous terbutaline or placebo. We found that significantly more women had tachycardia in the intervention group but the mean pulse rate and arterial pressure after the injections did not differ. Five women who were given terbutaline and four receiving the placebo had the estimated blood loss of more than 1000 ml, with highest blood lost recorded in both groups was 2 L. Despite so, no differences in the mean estimated blood loss and haematocrit changes after the surgery were noted.

**Table I: Maternal demographic and labour characteristics**

| | Terbutaline (n=48) | Placebo (n=48) | *p* value |
|---|---|---|---|
| Maternal age (years), mean (SD) | 27.4 (5.6) | 28.8 (5.8) | 0.444 |
| Gravidity, mean (SD) | 2.3 (1.7) | 2.1 (1.1) | 0.559 |
| Nulliparous, n (%) | 24 (50.0) | 22 (45.8) | 0.683* |
| Gestational age at delivery (weeks), mean (SD), | 39.1 (1.1) | 39.4 (1.1) | 0.598 |
| Duration of first stage of labour (minutes), mean (SD) | 239.2 (117.4) | 239.0 (186.2) | 0.059 |
| Induction of labour, n (%) | 20 (41.7) | 15 (31.3) | 0.298* |
| Oxytocic augmentation, n (%) | 34 (70.8) | 27 (56.2) | 0.138* |
| Interval of injection to delivery (minutes), mean (SD) | 39.4 (13.2) | 39.5 (14.2) | 0.880 |
| Interval of decision to delivery (minutes), mean (SD) | 50.0 (16.1) | 48.7 (14.8) | 0.755 |
| Decision to delivery 30 minutes or less, n (%) | 4 (8.3) | 2 (4.2) | 0.399* |
| Meconium-stained amniotic liquor, n (%) | 9 (18.7) | 10 (20.8) | 0.798* |
| Atypical variable deceleration, n (%) | 30 (62.5) | 26 (54.2) | 0.408* |

Analysed with t-test unless stated; *Chi-square test.

**Table II: Neonatal outcomes**

| | Terbutaline (n=48) | Placebo (n=48) | *p* value |
|---|---|---|---|
| Birth weight (gm), mean (SD) | 2922 (436) | 3039 (335) | 0.970 |
| Small for gestational age, n (%) | 4 (8.3) | 2 (4.1) | 0.140* |
| Acidosis, n (%) | 2 (4.2) | 5 (10.4) | 0.435** |
| Umbilical cord pH, mean (SD) | 7.25 (0.80) | 7.23 (0.12) | 0.269 |
| Umbilical cord base excess, mean (SD) | -6.42 (3.74) | -6.11 (3.50) | 0.673 |
| Neonatal Apgar score at 5 minutes of life, mean (SD) | 9.8 (0.7) | 9.7 (0.8) | 0.580 |
| Number of NICU admission, n (%) | 27 (56.2) | 28 (58.3) | 0.837* |
| Admission for respiratory problem, n (%) | 24 (50.0) | 25 (52.1) | 0.838* |

Analysed with t-test unless stated; *Chi-square test; ** Fisher exact test.

**Table III: Neonatal umbilical artery parameters**

| | Terbutaline (n=48) | Placebo (n=48) | *p* value |
|---|---|---|---|
| Umbilical cord pH | | | |
| < 7.2 | 12.5% | 27.1% | 0.073* |
| <7.1 | 4.2% | 6.3% | 0.500** |
| <7.0 | 2.1% | 2.1% | - |
| Umbilical cord base excess | | | |
| <-12.0 | 8.3% | 4.2% | 0.677** |
| <-10.0 | 12.5% | 14.6% | 0.765* |
| <-8.0 | 27.1% | 25.0% | 0.816* |

*Chi-square test; ** Fisher exact test.

**Table IV: Maternal outcomes**

| | Terbutaline (n=48) | Placebo (n=48) | *p* value |
|---|---|---|---|
| Maternal mean arterial pressure (mmHg), mean (SD)¥ | 95.6 (15.3) | 96.2 (12.2) | 0.228 |
| Maternal heart rate (bpm), mean (interquartile range)¥ | 100 (90-108) | 90 (80-99) | 0.425 |
| Maternal tachycardia, n (%)¥ | 26 (54.2) | 12 (25.0) | 0.003* |
| Additional uterotonic, n (%) | 6 (12.5) | 7 (14.6) | 0.765* |
| Estimated blood loss (mL), mean (interquartile range), | 597.9 (325-800) | 584.4 (300-600) | 0.693 |
| Postpartum hemorrhage > 1 L, n (%) | 5 (10.4) | 4 (8.3) | 0.726* |
| Maternal haematocrit difference (%), mean (SD) | 4.8 (3.8) | 4.3 (3.2) | 0.923 |

Analysed with t-test unless stated. bpm, beat per minute; ¥ At 10 minutes after injection; *Chi-square test.; Significant p value indicated in bold.

## DISCUSSION

The study was conceived to investigate the use of acute tocolysis to improve the neonatal outcome in cases of suspected intrapartum foetal compromise, as it was one of the most common indications for caesarean delivery. In 2016-17, more than one-third of the caesarean sections in Malaysia was performed for this indication.[17] A positive result would tremendously help the management of intrapartum foetal distress especially in hospitals without dedicated obstetric operation theatre such as ours. During the trial, the mean decision to delivery time was 49 minutes, and only 6.3% of the deliveries were completed within 30 minutes. Effective intrapartum resuscitation would also benefit cases from non-specialist hospitals that need to be transferred to other facilities for operative deliveries.

Terbutaline was chosen as it had been shown to be effective in reducing uterine tone in low-dose subcutaneous administration, of which the effect can be seen within 2 minutes of the injection.[10] Furthermore, studies have shown that a single subcutaneous dose is also associated with minimal side effects.[10,18] Our results support the safety of subcutaneous administration with no significant maternal effects except for tachycardia, which did not cause a significant prolonged effect.

Earlier evidence had shown that terbutaline was associated with improvement or resolution of abnormal CTG patterns in more than 70% of intrapartum foetal distress.[8,10] Our study was designed to look a step further, that is, the neonatal outcomes, where the number of neonates with umbilical cord acidosis in the intervention group was less than half of the placebo group. Even though the difference is not statistically significant, the finding did show the possible positive effect of an intrauterine intervention.

The mean umbilical cord pH and base excess, however, are not statistically different. Similar findings were also seen in a recent prospective audit report from Sydney.[19] Buckley et al investigated the neonatal outcomes after the introduction of a practice of administrating subcutaneous terbutaline prior to emergent caesarean delivery. The authors reported no difference in neonatal cord pH and base excess before and after the policy implementation. However, the study was not a randomised trial and only about 60% of the caesarean deliveries were performed for foetal distress; hence, drawing a definite conclusion is not possible.

Previous workers had demonstrated that acute tocolysis with terbutaline prior to caesarean delivery could reduce the incidence of low neonatal Apgar score at 5 minutes of life (from 14% to 6.8%).[5] In contrary, none of the neonates born within our trial had low Apgar score and no difference was seen in the mean 5 minutes Apgar score and NICU/ SCN admission. A larger study population could, however, give a different picture.

Despite these findings, the strength of this study lies in its design, of which to date, is the only published double-blind, placebo-controlled randomised trial investigating subcutaneous terbutaline for acute tocolysis prior to emergency delivery. It was, unfortunately, limited by the small sample size allowed by the ethic committee and the lower-than-expected incidence of neonatal acidosis (7.3%). In fact, if a lower base excess value is used for the definition of neonatal acidosis (pH < 7.00 and base deficit >12 mmol/l), the incidence would be much lower at 2.1%.[20]

Yet, it is not all lost concerning acute tocolysis for suspected foetal distress. Data from other investigators did show significantly higher mean neonatal umbilical cord pH in groups receiving terbutaline for foetal compromised diagnosed with foetal scalp pH, especially when the pH is less than 7.25.[4,11] Other than the lower incidence of neonatal acidosis, our data demonstrated that fewer babies were born with cord pH of less than 7.10 and 7.20 in the terbutaline group. These findings suggest that further research with larger samples could shed some light on this promising intervention. We hope these findings could motivate other researchers to pursue this subject.

## CONCLUSION

Acute tocolysis with subcutaneous terbutaline prior to caesarean section is a safe intervention and has the potential to improve the acid–base status of suspected compromised foetuses. Even though our data could not confidently support this postulation, further trials with refined protocols and bigger sample sizes may give a different result.

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