Maintenance Tocolysis with Nifidipine versus β-sympathomimeticsin Established Preterm Labour on Pregnancy Elongation

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Abstract: Background: This study aimed to compare the efficacy of Nifedipine versus β-sympathomimetic as tocolytic agents and effect of tocolysis on pregnancy elongation. **Methods:** This clinical trial was conducted at El Galaa Maternity Teaching Hospital and El Sayed Galal university hospital for women with preterm labour pain, intact membrane and singleton pregnancy between 28 weeks to 34 weeks. on 100 women divided in two groups each group 50 womens (1st group nifedipine-2nd group ritodrine). **Results:** There was significant difference between two groups regarding preterm labor after 48 hours. also there was significant difference between both groups regarding delivery after 1 week & regarding delivery at 37th weeks, there was significant difference between two groups regarding labor GA (weeks), episodes of recurrent preterm labor were statistically significant in ritodrine group compared to nifedipine group, vaginal delivery was more statistically significant in nifedipine group than in ritodrine group (88%,-70% respectively). **Conclusion:** The Use of Nifedipine as a maintenance tocolytic therapy in preterm birth is better than ritodrine. Also, Nifedipine was associated with less side effects than Ritodrine.

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Keywords: Nifedipine**,** β-sympathomimetics, Preterm labor

1. Introduction

Preterm birth is common, with an estimated 11% of infants being born at a gestational age of less than 37 weeks [(1)].

Preterm labor is defined as delivery of a live birth after 20 weeks gestation and before completed 37 weeks' gestation. The incidence of preterm birth ranges between 10% and 12.5% of all births [(2)].

The annual rate of preterm birth shows a steady increase over the past two decades worldwide. It was estimated in some studies in the United States, that the annual rates of preterm birth increased by 30% over only the past decade **[(3)].**

Maintenance tocolytic therapy with various agents including β-sympathomimetics, cyclo-oxygenase inhibitors, atosiban and calcium channel blockers have been studied with minimal benefit **[(4)]**.

Ritodrine is one of the widely used tocolytic agents. This drug binds to the β-2 receptors on the surface of the myocytes and mediates myometrial relaxation by stimulating cyclic AMP. However, it also has a stimulatory effect on the β-1 in the heart, liver, pancreas, and kidney which account for the side effects. Prolonged use of this drug would induce down-regulation of theβ-2 receptors and more drug (i.e. more side effects) is necessary to maintain the effect **[(5)].**

2. Patient and Methods:

This prospective randomized controlled study was held in the period from July 2018 till December2018 in Al-Galaa Teaching Hospital and El Sayed galal university hospitals. The study was approved by the Ethics Board of Al-Azhar University.

This study included 100 pregnant women with preterm labour pain, intact membrane and singleton pregnancy between 28 weeks to 34 weeks.

All patients were subjected to the following after taking a written consent from each patient:

❖ **History taking:**

- Name, age, parity occupation, residency and special habits.
- History of onset, course and duration of labor pains, vaginal gush of fluid, vaginal discharge, vaginal bleeding or febrile illness.
- History of previous preterm labor, previous abortion, previous full term deliveries, mode of delivery and fetal outcome.
- For estimation of gestational age using Naegele's rule, provided that she had regular cycles for the last three months before she got pregnant and was not taking contraceptive pills during this period and she was sure of her dates and by using first trimetric

ultrasound by estimation of CRL for accurate dating to pregnant women with unreliable LMP.

- History of medical disorders, abdominal surgeries, drug therapy or allergy or history of intake of other tocolytic drugs.

❖ **General examination**

- With special attention to blood pressure, pulse and temperature every 20 minutes until a stable dose was achieved and every 4 hours thereafter. Blood pressure for all the patients was above 80/50 mmHg before the commencement of treatment. Abdominal examination with particular emphasis on uterine contraction and abdominal enlargement.
- Abdominal examination to measure the fundal level, palpate the uterine contractions and monitoring of the fetal heart rate.
- Pelvic examination to assess the state of membranes and exclude their rupture through examination with a sterile Cusco speculum, to exclude vaginal bleeding and assess the state of the cervix and measure the bishop score.
- Sonographic assessment to estimate the gestational age, amount of liquor and to exclude placenta previa, placental abruption and major fetal congenital anomalies. Several ultrasound parameters were used to estimate gestational age including biparietal diameter (BPD), head circumference (HC), and femur length (FL).
- Electronic monitoring of uterine contractions and fetal heart rate until the uterine contractions disappeared. Afterwards, fetal heart rate and uterine contractions were monitored for 1 hour every 12 hours during hospital admission.

Inclusion criteria:

1. Age: 18 – 40 years old.
2. Gestational age: 28 – 34 weeks' gestation.
3. Diagnosis of established preterm labor and successful arrest of it by IV. Magnesium sulfate tocolytic therapy.
4. Intact fetal membranes.
5. The patient is medically free (no diabetes, nohypertension, no autoimmune disease, ect.).

The diagnosis of establishedpreterm labor is based on the American College of Obstetricians and Gyneacologists Guidelines (ACOG, 2003): presence of uterine contractions (at least 4 in 20 minutes or 8 in 60 minutes), cervical dilation ≥ 3 cm, and/or cervical effacement ≥ 80% (cervical changes).

Exclusion criteria:

1. Failed tocolysis.
2. Women with antepartum hemorrhage (whether placental abruption or placenta previa).
3. Multifetal pregnancy.
4. Evident intrauterine infection (uterine tenderness, foul vaginal discharge, maternal pyrexia ≥ 38°C, and/or maternal leucocytosis).
5. Presence of non- reassuring fetal status or fetal distress.
6. Presence of fetal anomalies incompatible with life.
7. Cervical cerclage.

Sample size

The population of this study comprised 100 pregnant women suffered from preterm labor pain.

3. Results

Table (1): Comparison between Nifedipine and Ritodrine groups as regards to preterm labor after 48 hours

	Nifedipine (N=50)	Ritodrine (N=50)	χ^2	P
Yes	6 (12.0%)	14 (28.0%)	4.000	0.046*
No	44 (88.0%)	36 (72.0%)		
Relative risk	0.4	95% CI	0.1–1.0	

χ^2: Chi square test, CI: Confidence interval, *Significant

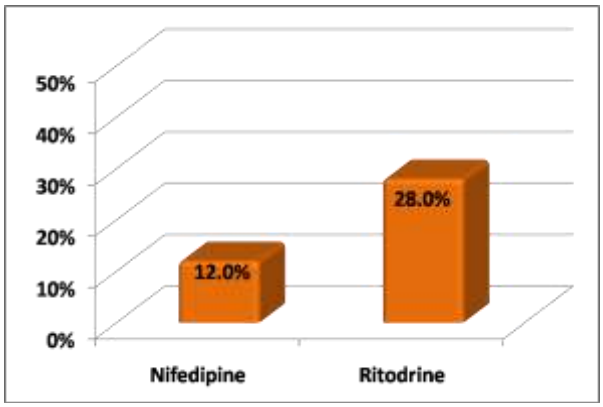

Figure (1): Comparison between Nifedipine and Ritodrine groups as regards to preterm labor after 48 hours.

This study was held in the period from July 2018 till December 2018 on 100 patients recruited from the causality unit of the Obstetrics & Gynecology Department, Al-Galaa Teaching Hospital with preterm labour pain, intact membrane and singleton pregnancy between 28 weeks to 34 weeks.

In this study, Demographic data including age, BMI, gestational age, parity & previous preterm delivery shows no significant statistical difference between the two groups. The mean age of Nifedipine group & Ritodrine group was (24.6±2.7) & (24.4±3.3) respectively with no statistically significant difference between the two groups.

Table (1) and figure (1) show that: Preterm labor after 48 hours was significantly less frequent in Nifedipine group than Ritodrine group.

Table (2): Comparison between Nifedipine and Ritodrine groups as regards to preterm labor after 1 week

	Nifedipine (N=50)	**Ritodrine (N=50)**	χ^2	**P**
Yes	14 (28.0%)	24 (48.0%)	4.244	**0.039***
No	36 (72.0%)	26 (52.0%)		
Relative risk	0.4	**95% CI**	0.1–1.0	

χ^2: Chi square test, CI: Confidence interval, *Significant

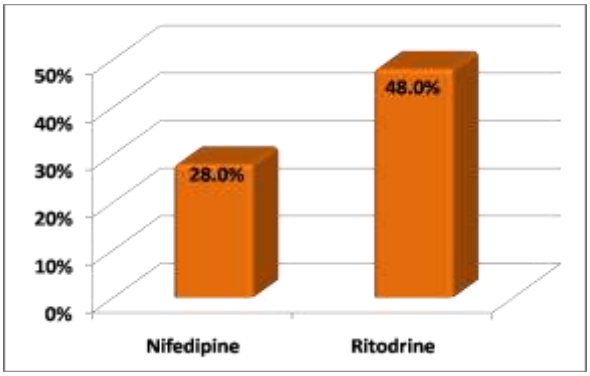

Figure (2): Comparison between Nifedipine and Ritodrine groups as regards to preterm labor after 1 week.

Table (2) and figure (2) show that: **Preterm labor after 1 week** was significantly less frequent in Nifedipine group than Ritodrine group.

Table (3): Comparison between Nifedipine and Ritodrine groups as regards to labor at 37th week gestational age

	Nifedipine (N=50)	**Ritodrine (N=50)**	χ^2	**p**
Yes	19 (38.0%)	29 (58.0%)	4.006	**0.045***
No	31 (62.0%)	21 (42.0%)		
Relative risk	0.4	**95% CI**	0.2–1.0	

χ^2: Chi square test, CI: Confidence interval, *Significant

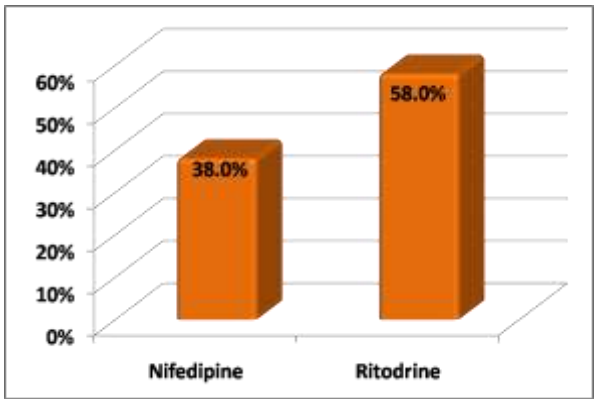

Figure (3): Comparison between Nifedipine and Ritodrine groups as regards to preterm labor at 37th week GA.

Table (3) and figure (3) show that: **Labor at 37th week GA** was significantly less frequent in Nifedipine group than Ritodrine group.

4. Discussion

Pre-term birth (PTB) is one of the main clinical problems in obstetrical practice. The incidence of PTB may differ in different regions, the rate varying worldwide in the range between 5–11%.

Despite of the availability of several drugs that inhibit pre-term contractions (tocolytics), the pharmacotherapy of PTB is inappropriate. Additionally, the maternal and fetal side-effects caused by high doses of such drugs may induce further complications; there is therefore a great need for

effective and well-tolerated drugs against PTB. Ca2+ channel blockers (CCBs), and especially nifedipine and nicardipine, are among the frequently used tocolytics. In our study, there was no significant difference as regard patient characteristics (age, weight, BMI, parity and gestational agebetween study and control groups.

In this study, Demographic data including age, BMI, gestational age, parity & previous preterm delivery shows no significant statistical difference between the two groups. The mean age of Nifedipine group & Ritodrine group was (24.6±2.7) & (24.4±3.3) respectively with no statistically significant difference between the two groups.

In this study, there was no statistically significant difference between BMI of both groups (28.2±3.6 for Nifedipine group & 29.3±3.9 for Ritodrine group). This was similar to a study done by Lyell [6] to assess the maintenance of nifedipinetocolysis compared with placebo found no significant difference between BMI of the two groups.

In this study, there was no significant statistical difference between two groups regarding mean gestational age by weeks (31.3±1.1 for nifedipine group) & (30.9±1.4 for ritodrine) Also, there was no statistical difference between two groups regarding mean parity (1.8±1.5 for nifedipine group) & (1.8±1.3 for ritodrine group).

In this study, there was significant difference between two groups regarding preterm labor after 48 hours, (nifedipine group 12.0%) & (ritodrine group 28.0%) with p value 0.046. also there was significant difference between both groups regarding delivery after 1 week & regarding delivery at 37th weeks this similar to study of Agarwal [7] done on 30 women per each group they found statistically significant difference between two groups. Also, Paptsonis [8] in a similar study found significant difference between two groups.

In this study, there was significant difference between two groups regarding labor GA (weeks), (in nifedipine group it was 35.6±2.3) & (in ritodrine group it was 34.0±3.0) with p value 0.05. This similar to study of Paptsonis [8] done on 80 women per each group they found statistically significant difference between two groups.

In this study, prolongation of pregnancy in weeks was reported with Nifedipine group than ritodrine (4.3±2.4 & 3.1±2.9 respectively) and was statistically significant with P value 0.033. This is similar to a study done by Agarwal [7] who reported a statistically significance value in nifedipine group with P value <0.05. In contrast, Lyell [6] in a study done on 33 women per each group found no statistical difference. But, we used a larger sample size.

In this study, episodes of recurrent preterm labor were statistically significant in ritodrine group compared to nifedipine group with p value <0.001.

In this study, vaginal delivery was more statistically significant in nifedipine group than in ritodrine group (88.0% & 70.0% respectively).

In addition to evaluation of efficacy, Safety profile of either method was assessed, our study was concerned with safety as side effects were strictly observed & recorded to allow for an appropriate comparison.

In this study, maternal flushing was statistically significant in nifedipine group than ritodrine group (14% & 2%) respectively with P value (0.027). Also, maternal headache was statistically significant in nifedipine group than ritodrine group (22% & 6%) respectively with P value (0.021). Agarwal [7] in his study found no significant statistical difference regarding maternal flushing & headache but he used smaller sample size than us.

In this study, maternal palpitations were reported more in ritodrine group & it was statistically significant with p value (0.05) this is in accordance with the result of a meta-analysis by Oei [9] & Al Qattan [10] on nifedipine versus ritodrinefor suppression of preterm labor.

While there was no significant statistical difference regarding maternal drowsiness & fainting between the two groups. This similar to study done by Agarwal [7] in a comparative study of oral nifedipine and intravenous ritodrine as tocolytic agents who reported the same results.

In this study, we found no significant statistical difference in both groups regarding neonatal respiratory distress, neonatal ICU admission, neonatal APGAR-1, APGAR-5 and neonatal birth weight. Also Lyell [6] found no significant statistical difference in both groups regarding neonatal side effects.

Conclusion:

Using Nifedipine as a maintenance tocolytic therapy in preterm birth is better than ritodrine. Also, Nifedipine was associated with less side effects than Ritodrine.

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