Nifedipine Versus Nitroglycerin in the Inhibition of Preterm Labour

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Abstract

Aim of Work: To compare the safety & efficacy of oral nifedipine with transdermal nitroglycerin in the inhibition of preterm labour.

Methods: This study included 60 women in preterm labour, randomly divided into two groups, the first 30 patients received oral nifedipine and the second 30 patients used transdermal nitroglycerin (NTG).

Patients in preterm labour with a single gestation, between the 26th and the 34th week and no contraindication for tocolysis were selected.

Women with fetal malformation and medical or obstetric diseases were excluded. The variables analyzed were: Delay in delivery for 48 hours, 7 days or more than 7 days, period of gestation at delivery, side effect profile of drugs & neonatal outcomes.

Results: Mean prolongation of pregnancy was more with NTG (30.13 ± 3.0 days) compared to that of nifedipine (29.57 ± 3.6 days). Nifedipine was more successful in prolonging pregnancy beyond 48 hours. Failure of acute tocolysis, defined as delivery within 48 hours, was more common with NTG (33.3%) as compared to nifedipine (23.3%). Headache was higher in the NTG group (3.3%) compared to nifedipine group (0%). The neonatal outcomes in terms of respiratory distress was higher in nifedipine (76.7%) than NTG group (63.3%). There was no statistically significant difference between both groups.

Conclusions: Transdermal nitroglycerin is as safe and effective tocolytic agent compared with oral nifedipine.

Key Words: Preterm labour – Nifedipine – Transdermal nitroglycerin-tocolysis.

Introduction

PRETERM birth remains one of the main causes of perinatal mortality and long-term morbidity. More than 70% of the total perinatal mortality can be attributed to preterm birth [1].

In spite of that only 5% of infants are born <37 gestational weeks in Sweden, they account for nearly half of all cases with cerebral palsy (CP). In addition, the risk of CP is inversely proportional to gestational age meaning that the risk of CP is 60 times higher at gestational age <28 compared to term. Long-term follow up studies indicate that a high proportion of infants born very preterm suffer from a high risk of neuropsychological impairment, school problems and behavioral abnormalities [2].

It is now clear that the causes of preterm labor are multifactorial and vary according to gestational age, commonly recognized etiologies include systemic and intrauterine infection, stress uteroplacental thrombosis, implantation error, uterine overdistension, and cervical insufficiency.

Identification of patients at risk for preterm delivery has its pivotal role in the prevention and management of preterm, the risk factors include:

1- A previous history of preterm labor is the strongest risk marker [3].
2- There is now evidence to support an association between severe periodontal disease and spontaneous preterm labor [4].
3- Maternal infection e.g. Asymptomatic bacteruria Pyelonephritis, Genital infections (Syphilis, gonorrhea, chlamydia Group B streptococcal infection, Bacterial vaginosis, Ureaplasma urealyticum, mycoplasma hominis).
4- Cigarette smoking, the study showed that the impact of maternal smoking on very preterm birth appears to be complex: It lowers the risk of very preterm birth due to gestational hypertension, but increases the risk of very preterm birth due to other mechanisms. These findings might explain why maternal smoking is more closely related to preterm birth among multiparous women than among nulliparous women [8].
5- Low body mass index, Ghrelin is a peptide that regulates maternal appetite and energy expenditure as well as playing a role in fetal nutrition. Mark et al. (2008) did a study that found that Ghrelin exerted an inhibitory effect on contractility, compared with control strips. This inhibitory effect of ghrelin on uterine contractions suggests that it plays a physiologic role in regulation of myometrial activity. These findings highlight the emerging role of metabolic modulation of myometrium, and particularly at extremes of body mass index measurements [6].

6- Multiple pregnancy [7].

7- Cervical incompetence.

8- Uterine anomalies.

9- Uterine over-distension (polyhydraminos, macrosomia, fibroids).

10- Young or advanced maternal age.

11- Short interval between pregnancies (less than 12 months) [8].

12- Domestic violence, especially injury due to physical abuse, was found to be significantly associated with both preterm birth and low birth weight, independently from a large set of sociodemographic and behavioral characteristics usually recognized as determinants of preterm birth [9].

Unfortunately, most of these risk markers are poor predictors of preterm labor as they have variable sensitivities (35-60%) and positive predictive values (15-30%).

Diagnosis of preterm labour:

Preterm labor must be considered whenever abdominal or pelvic symptoms occur after 18 to 20 weeks of gestation. Symptoms like pelvic pressure, increased vaginal discharge, backache, and menstrual-like cramps are common with advancing pregnancy and suggest preterm labor more by their persistence than by their severity [10].

The accurate diagnosis of early preterm labor is difficult because the symptoms and signs of preterm labor commonly occur in healthy women who do not deliver preterm and because digital examination of the cervix in early labor (less than 3cm of dilatation and less than 80 percent effacement) is not highly reproducible. Women whose symptoms are cervical dilatation of less than 2cm or effacement of less than 80 percent, or both, present a diagnostic challenge [10].

Other means of enhancing diagnostic accuracy in preterm labor include transvaginal sonographic measurement of cervical length and testing for fetal fibronectin in cervicovaginal fluid. Both of these tests improve the diagnostic accuracy by reducing the possibility of a false-positive diagnosis of labor [11].

According to the ACOG Committee on Obstetric Practice, the fetal fibronectin test is only appropriate for use in pregnant women with all of the following characteristics:

- Amniotic membranes intact; and
- Cervical dilatation is minimal (less than 3cm); and
- Sampling is performed no earlier than 24 weeks, 0 days and no later than 34 weeks, 6 days of gestation.

The detection of fetal fibronectin at levels greater than 50 nanograms (ng) per milliliter (mL) between 22-35 weeks of gestation is considered abnormal. Ultrasound evaluation of the cervix is being used increasingly to assist in the management of preterm labor and as a screen to identify patients at high risk for preterm delivery. Funnelling must be associated with a residual length that is less than 25mm to be clinically significant [11].

Many tocolytic agent have been described for inhibition of preterm labour, it includes beta-adrenergic agonist, magnesium sulphate progesterone, oxytocin antagonist, calcium channels blockers, nitric oxide donors [12].

Material and Methods

This prospective randomized study was carried at the Casualty Department at Cairo University during the period from March 2013–July 2014.

This study included 60 women in preterm labour between 26 and 34 weeks of gestation, randomly divided into two groups.

Group 1: It included the first 30 patients receiving oral nifedipine, they were administered 10mg nifedipine capsules orally every 15 minutes up to 40mg in the first hour, and were subsequently given 1 tablet of 20mg nifedipine slow release.

Group 2: It included the second 30 patients receiving transdermal nitroglycerin (NTG) (5mg/day).

Patients in preterm labour with a single gestation, between the 26th and the 34th week determined by reliable history of regular cycles and/or ultra-
sonography at 8 to 12 weeks and no contraindication for tocolysis were selected. Women with fetal malformation and medical or obstetric diseases were excluded. The baseline characteristic of the selected groups included informed consent was obtained from each study participant. The variables analyzed were: Delay in delivery for 48 hours, 7 days or more than 7 days, side effect profile of drugs & neonatal respiratory distress.

Statistical method:

Data were statistically described in terms of means ± standard deviation and percentage when appropriate.

Comparison of numerical variables between the study groups was done using student t-test for independent samples for comparing categorical data. Chi square (X^2) test was performed exact test was used instead when the expected frequency is less than 5. p-values less than 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

Table (1): Demographic characters.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Nifedipine (n 30)</th>
<th>NTG (n 30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maternal age:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± Std. Deviation</td>
<td>30.58±2.2</td>
<td>28.13±3.06</td>
<td>0.518</td>
</tr>
<tr>
<td>Gestational age (days):</td>
<td>214.4±2.2</td>
<td>204.3±3.1</td>
<td>0.925</td>
</tr>
<tr>
<td>Parity:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± Std. Deviation</td>
<td>0.93 ±0.74</td>
<td>0.83±0.74</td>
<td>0.604</td>
</tr>
<tr>
<td>Vital signs:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SBP (Mean ± SD)</td>
<td>109.6±9.6</td>
<td>107.3±13.3</td>
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<tr>
<td>DBP (Mean ± SD)</td>
<td>70±7.4</td>
<td>67.6±7.2</td>
<td>0.224</td>
</tr>
<tr>
<td>Puls (Mean ± SD)</td>
<td>73.2±5.5</td>
<td>74.2±4.3</td>
<td>0.410</td>
</tr>
<tr>
<td>Temp (Mean ± SD)</td>
<td>37.007±0.03</td>
<td>37±0</td>
<td>0.321</td>
</tr>
</tbody>
</table>

Discussion

Preterm birth, defined as birth occurring between 26 and 36 completed weeks of gestation is a major contributor to perinatal morbidity and mortality [13]. The rate of preterm birth is increasing across low- and middle-income countries, affecting 8.6% of births in high-income countries and between 7.4% to 13.3% in low- and middle-income countries [14].

Preterm birth is a leading cause of perinatal morbidity including respiratory distress syndrome (RDS), chronic lung disease, intraventricular hemorrhage, sepsis, cerebral palsy and other forms of neuro-developmental impairment [15].

Results

This study was carried out on 30 women who received oral nifedipine for prevention of preterm labour, their mean age was (30.58±2.2) years, mean gestational age (214.4±2.2) days, mean parity (0.93±0.74) as well as 30 women who received transdermal nitroderm patch for prevention of preterm labour, their mean age was (28.13±3.06) years, mean gestational age (204.3±3.1) days, mean parity (0.83±0.747). There was no statistically significant difference between both groups.

Mean prolongation of pregnancy duration was more with NTG (30.13±3.06 days) as compared to that of nifedipine (29.57±3.65 days). Nifedipine was more successful in prolonging pregnancy beyond 48 hours. Failure of acute tocolysis, defined as delivery within 48 hours, was more common with NTG (33.3%) as compared to nifedipine (23.3%). Headache was higher in the NTG group (3.3%) compared to nifedipine group (0%). The neonatal outcomes in terms of respiratory distress was higher in nifedipine (76.7%) than NTG group (63.3%). There was no statistically significant difference between both groups.

Table (2): Maternal and neonatal outcome.

<table>
<thead>
<tr>
<th></th>
<th>Nifedipine (n 30)</th>
<th>NTG (n 30)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delivery timing:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Within 48h</td>
<td>23.3%</td>
<td>33.3%</td>
<td>0.567</td>
</tr>
<tr>
<td>Within 7 days</td>
<td>13.3%</td>
<td>0%</td>
<td>0.112</td>
</tr>
<tr>
<td>- Mean prolongation of gestational age</td>
<td>29.57±3.65</td>
<td>30.13±3.06</td>
<td>0.518</td>
</tr>
<tr>
<td>- Discontinuation of drug due to side effect</td>
<td>3.3%</td>
<td>0%</td>
<td>0.317</td>
</tr>
<tr>
<td>- Neonatal respiratory distress</td>
<td>76.7%</td>
<td>63.3%</td>
<td>0.385</td>
</tr>
</tbody>
</table>

Numerous studies described the role of several tocolytic drugs in eliminating the incidence of preterm labor, but only few studies compared drugs of the same group. Several agents have been used for the inhibition of uterine contractility, but it remains unclear what the first-line tocolytic agent should be [16].

Code-Aquedelo et al., agrees with the authors who proposed that nifedipine, a calcium channel blocker, could be used as a first line tocolytic agent [17-20].

A Cochrane review regarding calcium channel blockers (CCBs) for acute tocolysis in preterm labor including 12 randomized controlled trials...
concluded that nifedipine reduce the risk of delivery within 7 days of initiation of treatment and delivery before 34 weeks gestation with relative improvements in neonatal outcomes [21].

A more recent Cochrane review of 38 trials, involving 3550 women, concluded that CCBs, especially nifedipine is better than no tocolytics for postponing preterm birth for 48 hours in comparison with betamimetics and oxytocin receptor antagonists. Another type of CCB, nicardipine, was only used in three trials, but was not more effective than other tocolytics [13].

As for nitroglycerine (NTG), Lees et al. [22], found that NTG prolonged gestation beyond 2 days in 84% of patients compared with 88% in the ritodrine group. Wani et al. [23], found the prolongation beyond 2 days to be 91% with NTG versus 88% in ritodrine group. However, In the RNOTT multicentric trial [24], NTG showed a lower (63%) efficacy in prolonging labor beyond 48 hours against 71% with ritodrine.

A direct comparison of NTG with nifedipine by Amorim et al., showed that the rate of preterm delivery within 48 hours after start of tocolysis was 15.4% in tocolysis with NTG and 12.5% in the nifedipine group [25].

Dhawle et al. [26], concluded that nifedipine was significantly better than NTG in pregnancy prolongation beyond 48 hours (88.4% women in nifedipine group versus 68.3% in the NTG group). Nifedipine delayed delivery beyond 7 and 14 days in 72.1% and 62.8% respectively which was not significantly different to that seen with NTG (65.9% and 58.6% respectively). The mean prolongation was 29.04 days in the NTG group against 34.46 days in the nifedipine group, which was similar to the results of Papatsonis et al. [27], who reported 39.2 days with nifedipine versus 22.1 days with ritodrine, and Lees et al. [22], who reported 35.8 days with NTG versus 36.9 days with ritodrine.

Our study demonstrates that nifedipine was more successful in prolonging pregnancy beyond 48 hours. Failure of acute tocolysis was more common with NTG (33.3%) as compared to nifedipine (23.3%). Mean prolongation of pregnancy duration was more with NTG (30.13 days) compared to that of nifedipine (29.57 days).

Lees et al. [22], compared the side effects of NTG and ritodrine, and found that the only side effect with NTG was headache, which was common when 2 patches were worn simultaneously. Bisits et al. [24], found similar results. Wani et al. [23], observed the incidence of headache to be 25% and total incidence of side effects with NTG to be 30%.

Kashanian et al. [28], found that nifedipine was associated with side effects in 40% of patients as compared to 17.5% with atosiban. They also found the incidence of hypotension with nifedipine to be 27.7%. Dhawle et al. [26], found a total incidence of side effects was 48.7% with NTG against 34.88% with nifedipine. Headache significantly more associated with NTG (41.5% versus 4.7%).

This comes in coodrance with our study that established an incidence of headache 3.3% in the NTG group compared to 0% in the nifedipine group.

Dhawle et al. [26], reported an incidence of RDS 17.1% in the NTG group and 9.3% in the nifedipine group, and the difference was not statistically significant. In our study, the incidence of RDS was 76.7% in the nifedipine group and 63.3% in the NTG group, and showed no statistical significant difference between both groups.

In conclusion, the results of our study showed the superiority of NTG in the mean prolongation of pregnancy compared to that of nifedipine but Nifedipine was more successful in prolonging pregnancy beyond 48 hours. Failure of acute tocolysis, defined as delivery within 48 hours, was more common with NTG as compared to nifedipine. However headache was higher in the NTG group compared to nifedipine group. The neonatal outcomes in terms of respiratory distress was higher in nifedipine than NTG group however non of these differences had any statistic significance so transdermal nitroglycerin is as safe and effective tocolytic agent compared with oral nifedipine and further prospective studies are still needed to evaluate the value of both drugs in prevention of preterm labour.

**Conclusion:** Transdermal nitroglycerin is as safe and effective tocolytic agent compared with oral nifedipine.

**References**


الملخص العربي

إن الولادة المبكرة لا تنسب فقط في الإعاقة الدائمة للأطفال بل إنها تعتبر من أهم أسباب الوفيات في الأطفال حديثي الولادة مما يجعلها من أهم المشكلات الطبية التي تحتاج إلى البحث والتحليل.

أما بالنسبة لإسباب الولادة المبكرة فإنها مختلفة ومتنوعة، مما أن طرق التشخيص والتنبؤ بعدوث الولادة المبكرة ما زالت في مراحلها الأولى، فأن الدراسات المبكرة لحالة انتقالها بسهولة مساعد في تحديد جودة فعالية العلاج.

على الرغم من وجود موارد علاج متعددة للولادة المبكرة، فإنه لا يوجد علاج واحد يعد الأفضل وتظل كل حالة يجب أن تتعامل على حدة بناء على التاريخ المروري للحالة.

وإلى الآن فإن الإجماع المتفق عليه أنه التأكد من توافر القليل من الأدوية الفاعلة واقتراحات في الأمراض الجانبية والتأثير السلبي على الأم والجنين.

وتقدم هذه الدراسة المقارنة بين كل من عقار التقسيم والنباتوغريس كعلاج للولادة المبكرة وترصد قدرة كل منها على إبطال فترة الحمل والأعراض الجانبية التي قد تتسبب في إصابة المريضات المتوقف عن العلاج. كما تدرس التأثير السلبي لكل من العقاقير على الأطفال حديثي الولادة.

أما عن طريق الولادة، فإن الولادة القصيرة ليست هي البديل الوحيد المطروح لكل حالات الولادة المبكرة بل من الممكن اللجوء للطبيعة في بعض الحالات على حسب العمر والوزن المتوقع للطفل.