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Tocolytic Effectiveness of Nifedipine in Management of Preterm Labor: A Tertiary Center Experience

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Abstract

Objective: This study aimed to compare the efficacy of nifedipine use in our clinic for treatment of preterm labor with diferent effacement degrees, and to compare our results with the literature.

Methods: 440 Singleton pregnant women with intact amnionic membrane pregnant women in their 23 and 36 weeks were retrospectively evaluated. Because of different criterias defining preterm labor in the literature, patients were divided into two groups as 4 or over contractions in 20 minutes and cervical opening at 2 cm and/or above and/or effachment at 80% or above (Group A, n = 230) and 4 or over contractions in 20 minutes and cervical opening below 2 min and effechment below 80% (Group B, n = 210). Descriptive statistics were conducted using chi-square and Mann Whitney U test, and statistically significance was $P < 0.05$.

Results: Demographics, reproductive history and pregnancy weeks of the groups were similar. The average time between the start of tocolysis and the birth was 4 times higer in Group B (0.1–99.2, mean 28.4) than that of Group A (0.1–78.9, mean 7.4 days, $P < 0.001$). Delay after tocoloysis at days 1 to 7 was statistically remarkable in Group B ($P < 0.001$, for each). Preterm labor resulting in early birth was more remarkable in Group A in both before 34 weeks and 37 weeks ($P < 0.001$, for each; n = 88, 38.3% vs n = 36, 17.1% and n = 171, 74.3% vs n = 98, 46.7%, respectively and n = 269/124, 28.2 vs 61.1%). Delay with nifedipine at day 1 (87.5%), day 2 (79.1%), day 3 (74.8%) and day 7 (65.5%) was also compatable with the literature.

Conclusions: Nifedipine is an effective tocolytic agent in preterm labor regardless of the effachment degree.
Keywords: Preterm labor, tocolysis, nifedipine, calcium channel blockers, pregnancy

Introduction

Preterm labor is one of the problems of obstetrics, and is one of the leading cause of neonatal morbidity and mortality. The incidence of preterm birth is around 7 to 9%.[1] The baby born is prone to respiratory, renal, neurologic and gastrointestinal problems. The etiology of this problem is not clear, so the preventive measures are important but ineffective since the insufficient diagnostic methods and uneffective medications. Other perinatal morbidity and mortality reasons decreased except preterm labor.[2] The general clinical approach to pregnant women admitted with pain and contractions should be verification of the preterm labor before entering the irreversible stage. The correct diagnosis should be followed by the early administration of the most effective tocolytic agent with least side effects for both mother and fetus.

Currently, there are some drugs in use preventing smooth muscle contractility.[3,4] Most of these agents have many side-effects and besides, the patient should be monitored closely. Calcium antagonists, beta-2 receptor blockers, prostaglandin synthesis inhibitors are among these agents, and all have severe pulmonary and cardiac side-effects.[4] The least side effect is recorded with a calcium channel blocker, nifedipine. Magnesium sulphate, ritodrin, terbutaline and indomethazine have all more side effects.[5,6] Furthermore, their success depends on the early diagnosis of preterm labor.

In the present study, we aimed to evaluate the success rate of tocolytic agent 'nifedipine' on the spontaneous preterm labor of singleton pregnant women with intact amnionic membrane.

Methods

Patients provided informed written consent to have data from their medical records used in research. After approval of study (SB-BakirkoyEAH-2005), we studied medical records of 440 pregnant women with diagnosis of preterm labor in whom nifedipine was used for preterm labor treatment. All pregnant women in our study were admitted to our clinic between January 2002 and January 2005. Preterm labor was diagnosed with regular uterine contractions and with a cervical dilatation documented at first examination or seen with observation. All patients were between 23 and 36 weeks of gestation, and with singular pregnancy. Because of different criterias used within other researchs in the literature, we divided patients with regular uterine contractions into two groups according to their vaginal examinations. We evaluated the efficacy of nifedipine according to the gestational week at the delivery; the period between the start on tocolysis and the time of delivery.

Inclusion criterias were singleton pregnant women with spontaneous preterm labor at their 23–36 weeks. Exclusion criterias were women with preterm early membrane rupture, chorioamnionitis, preterm labor without cervical change, multiple pregnancy, hypertension, intrauterine growth retardation, fetal anomaly, oligoanhidramniosis, placenta previa, decolman placenta and intrauterine fetal death.

Three capsule nidilat 10 mg soft capsule (Sanofi İlaç Sanayii, Istanbul, Turkey) was given in 1 hour (20 minute-intervals) sublingually (total dose 30 mg) and one capsule was given orally after in 2 to 4 intervals (10 mg or over). If contractions stopped and there no labor, drug was continued till the end of 37 week of pregnancy.

The measures before tocolysis were age, duration of marriage, number of marriage, gravida, parity, number of aborts, number of curretages, children alive, cervical opening (centimeter, cm), cervical effechmant (%), Bishop score, pregnancy week. Nominal measures recorded before tocolysis were the history of abortus within the first and second trimesters, previous preterm labor, smoking history, working history.

Measures during preterm labor were the start of tocolysis, birth interval (day), pregnancy week at birth. Delays after tocolysis were delay for 1 day, 2 days, 3 days and 7 days, birth before 34 weeks and birth before 37 weeks.

The criteria at the literature are different, we used 2 groups according to the vaginal exam findings as Group A; 4 or over contractions in 20 minutes and cervical opening at 2 cm and/or above and/or effachment at 80% or above, and Group B; 4 or over contractions in 20 minutes and cervical opening below 2 cm and effachment below 80%, but not responding to hidration and bed rest.

In statistical analyses, SPSS (1995, Illionis US) package was used. After calculations of means annd Standard deviations (SD); Mann Whitney U and chi square tests were used for group comparisons for both one way and variable changes. $P < 0.05$ was used as statistical significance value.

Results

There were 440 preterm labors. The maternal charasteristics of both groups are summarized in Table 1. Group B was a bit older than Group A ($P < 0.05$). Other criteria was not statistically different but the duration of marriage and number of children alive were higher in Group B ($P > 0.05$, for each). Nominal measures before tocolysis was summarized in Table 2. First trimester abortus number was higher in group B ($P < 0.05$). There was no difference in other measures.

Pregnancy week at birth was listed in Table 3; There was a difference of 2 weeks and 3 days between the groups ($P < 0.05$). Delay of birth after tocolysis was also summarized in Table 3. Delay after tocoloysis at days 1 to 7 was statistically remarkable in Group B ($P < 0.001$, for each). Preterm labor resulting in early birth was more remarkable in Group A in both before 34 weeks and before 37 weeks ($P < 0.001$, for each; 88, 38.3% vs 36, 17.1% and 171, 74.3% vs 98, 46.7%, respectively, In total, 269/124–28.2% and 61.1%).

Tocolysis and birth interval is seen at Table 4, and a 4 times longer period was remarkable for group B (0.1–99.2, mean 28.4 days vs Group A value of 0.1–78.9, mean 7.4 days, $P < 0.001$). The difference in delay of birth was statistically signiicant for days 1, 2, 3 and 7 (Table 5). Birth before 34 and 37 weeks was also significant (Table 6).

Discussion

Preterm birth rate in developed countires is around 6–7% and it is known as the main reason for perinatal morbidity and mortality.[1,2] However, the prolongation of pregnancy and use of corticosteroids aiding in the development of fetal pulmonary organs are found to be useful in decreasing this ratio.[2] Ritodrin, salbutamol and terbutaline, the most widely studied tocolytic agents, are all betamimetics and they are shown to prolong labor up to 7 days and they do not have any side effect on the fetal mortality.[5-7] However, their maternal side-effects are tachycardia, hypotension and some biochemical abnormalities.[4] Furthermore, maternal death is possible due to pulmonary edema.[5,6] These adrenergic agonists are the first line tocolytics, but calcium canal blockers are becoming more popular since they have less side effects and comparable efficcacy.

Calcium canal blockers are nonspecific smooth muscle relaxants used in adult hypertension treatment.[5,8] Their tocolytic effect depends on their inhibition of calcium ions into

Table 1. **Maternal features of groups**

Measure	A ($N = 230$) Least	Highest	25. percentile	50. percentile	75. percentile	B ($N = 210$) Least	Highest	25. percentile	50. percentile	75. percentile
Age	17	40	22	25	29	18	43	23	26	31
Gravida	1	9	1	2	3	1	7	1	2	3
Parity	0	6	0	1	1	0	5	0	1	1
Number of abortus	0	4	0	0	0	0	3	0	0	0
Number of curettage	0	5	0	0	0	0	3	0	0	0
Number of living children	0	6	0	0	1	0	4	0	0	1
Pregnancy (week)	23	35.4	30.5	32.4	34.1	23.4	35.6	30.2	32.4	34.1

Table 2. **Nominal numbers in previous history of patients before tocolysis**

Measure	A (*N* = 230) (*N*, %)	B (*N* = 210) (*N*, %)	Both (*N*, %)
Number of abortus in first trimester	25, 10.9	40, 19	65, 14.8
Number of abortus in second trimester	16, 7	13, 6.2	29, 6.6
Previous history of early birth	44, 19.1	34, 16.2	78, 17.7
Smoking (cigarette)	34, 14.8	26, 12.4	60, 13.6
Working (active professional life)	30, 13	30, 14.3	60, 13.6

Table 3. **Pregnany week at birth**

Pregnancy week at birth	Lowest	Highest	25. percentile	50. percentile	75. percentile
Group A	23.3	42.5	32.2	34.5	37
Group B	24.1	43.3	35	37.1	38.5

Table 4. **Time interval from tocolysis until birth (hour/hours)**

Tocolysis-birth interval hour(s)	Lowest	Highest	25. percentile	50. percentile	75. percentile
Group A	1	78.9	1.6	7.4	25.2
Group B	1	99.2	13.4	28.4	43.9

Table 5. **Time interval from tocolysis to birth. Chi square test, 1 day delay; *P* = 0,001, 2 days delay; *P* = 0,000, 3 days delay; *P* = 0,000, 7 days delay; *P* = 0,000**

Delay	A (*N*, %)	B (*N*, %)	Both (*N*, %)
1 day	189, 89.2	196, 93.3	385, 87.5
2 days	160, 69.6	188, 89.5	348, 79.1
3 days	143, 62.2	186, 88.6	329, 74.8
7 days	118, 51.3	170, 81	288, 65.5

Table 6. **Distribution of early births among groups; <34 wk *P* = 0,000, <37 wk *P* = 0,000**

Early birth	A (*N*, %)	B (*N*, %)	Both (*N*, %)
Before 34 weeks	88, 38.3	36, 17.1	124, 28.2
Before 37 weeks	171, 74.3	98, 46.7	269, 61.1

the myometrial cells. In vitro studies have shown that they have strong relaxant effects on human myometrium. The previous experimental studies showing its decreasing effects on fetal and placental circulation were not proved. In a Dutch study, Ulmsten et al have shown that nifedipine delayed the preterm labor for at least 3 days in 10 women at 33 weeks and before.[9] Other following studies have also shown that nifedipine is as effective as ritodrin and has no side-effects on the fetus. Similarly, Read and Wellby compared their patients taking nifedipine or ritodrin and not.[10] Nifedipine started at 30 mg induction dose and 20 mg per 8 hours as meantenance resulted in 48 hours delay; these ratios were 55% for ritodrin and 25% for controls. Ferguson et al applied these agents also to their pregnant pateints in 20–36 weeks having more than 8 contractions in 1 hour and ongoing cervical changes.[11] Nifedipine started at 10 mg sublingual dose and 10 mg per 20 min till contractions cease. The maximum dose was 40 mg in one hour and meantenance dose as 20 mg per 4–6 hours. Delay of birth for 48h (84%), 7 days (70%) and 36 weeks (41%). In a prospective randomized study, 24–34 weeks pregnants with preterm labor defined as uterine contractions together with cervical changes, delaty at 48h 84%, 7 days 67% and till 36 wk (50%), but no difference with ritodrin.[12]

Papatsonis et al defined preterm labor as 10 min-intervals regular uterine contractions for at least 1 hour and/or membrane rupture.[13] 10 mg sublingual dose and 10 mg second dose if contractions go on in 15 min, they repeated two more for each 15 min, max dose 40 mg in 1 hand meantenance dose as retard dose of 60–160 mg daily. The dose reduced gradually after day 3 and minimum dose 20 mg three times per week till 34 weeks. In membrane-intact patients, delay was 39.2 days (89.7% at 24h 80.9 at 48h, 72% at 7 days and delay till 34 weeks 55% and till 37 weeks as 42.6%. Nifedipine was found to have less side effects and have more effects.

In studies of Ferguson, Meyer and Kupferminc, nifedipine and ritodrin have similar effects since nifedipine dose were lower.[11,14,15] Koks et al also evaluated prelabor patients before 34 weeks and defined preterm laboras regular contractions 6 or more per hour with or without cervical changes and found nipedipine effective.[16] They defined preterm labor as 3 or more regular contractions in half an hour and plus cervical dilatation as 2 cm. In a systemic review of several randomized controlled studies 1029 cases at 20–36 weeks were evaluated, calcium blockers were effective in both 7 day delay

and birth before 34 weeks.[17-21] Ease of medication for maternal side effects were also lower. It was also effective in lowering neonatal comlications such as jaundice, necrotizing enterocolitis, respiratory distress and stay in intensive care units (ICU). When compared with beta-mimetics, 9 more studies support its use for distress and ICU stay, as well.

In our study, primary spontaneous preterm labor in 440 singleton pregnants at 23–36 weeks, excluding the prematüre early membrane rupture and multiple pregnancies, was treated with nifedipine tocolytic. Since the definition of preterm labor in literature is inconclusive, our 2 groups were constructed according to the vaginal exam findings as Grup A (≥ 4 contractions in 20 min + ≥ 2 cm cervical opening and or ≥ % 80 effachment) and Grup B (< 4 contractions in 20 min + < 2 cm cervical opening and < % 80 effachment). Pregnancy weeks in each group did not show statistically significant difference. When the delay from tocolysis start to birth; in group B median delay was 28.4 days, and in group A with 4 times longer (most significant at 7.4 days; $P < 0.001$). The gained days till birth in our study was similar to other studies published in English-written literature, and nifedipine delayed birth in both groups but more in group B. In conclusion, nifedipine is an effective tocolytic agent in delaying preterm labor regardless of the effachment degree.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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