

# Comparison of Treatment with Metoprolol and Nifedipine in Conservative Management of Preeclampsia

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## Abstract

**Objective:** The aim of this study was to investigate the efficiency of the short-term treatment with metoprolol and nifedipine in women with preeclampsia and to evaluate the maternal and fetal outcomes.

**Methods:** Seventy three preeclamptic women treated conservatively with metoprolol succinate 50 mg po (Beloc Zok®, Astra Zeneca) or nifedipine (Nidilat®, Sanofi-Synthelabo) were included in the study. Clinical characteristics, the mean blood pressure on admission and 48 hours after antihypertensive therapy, mode of delivery, birth weight, 1-minute Apgar score, and the rates of eclampsia and ablatio placenta were compared between preeclamptic women treated with metoprolol and those treated with nifedipine.

**Results:** Forty three of 73 preeclamptic women were conservatively treated with metoprolol and 30 with nifedipine. There was no statistically significant difference between groups in the rate of nulliparity, past history of preeclampsia and mode of delivery. Metoprolol and nifedipine groups were comparable with respect to gestational age at diagnosis (33.3±3.3 weeks in metoprolol group, 33.1±3.5 weeks in nifedipine group). The mean prolongation of pregnancy was 6.9±8.7 days in preeclamptic women treated with metoprolol, and 6.2±7.4 days in those treated with nifedipine; the difference was not statistically significant. There was significant decrease in both systolic and diastolic blood pressures 48 hours after the initiation of the antihypertensive therapy in both groups (systolic blood pressure from 152.8±14.4 mmHg to 131.1±11.3 mmHg, p=0.0001, diastolic blood pressure from 97.4±9.5 mmHg to 85.5±8.9 mmHg, p=0.0001 in metoprolol group; systolic blood pressure from 154.7±14.3 mmHg to 131.1±9.4 mmHg, p=0.003, diastolic blood pressure from 97±9.1 mmHg to 85.8±7.6 mmHg, p=0.004 in nifedipine group). In metoprolol group, the difference between the mean systolic blood pressure on admission and that measured 48 hours after antihypertensive therapy was 19.6±12.6 mmHg and the difference between diastolic blood pressures 12.3±9.9 mmHg; in nifedipine group these systolic and diastolic blood pressure differences were 21.1±14.1 mmHg and 11.5±10.7 mmHg, respectively. Both groups were comparable with respect to both systolic and diastolic blood pressure differences between pre- and post-treatment recordings.

**Conclusion:** Conservative management using metoprolol in preeclamptic women provides blood pressure control comparable to nifedipine, with a prolongation of pregnancy by 7 days. Maternal and fetal complications accompanying metoprolol treatment are comparable to those of nifedipine.

**Keywords:** Preeclampsia, metoprolol, nifedipine, conservative management.

## Preeklampsinin konservatif tedavisinde metoprolol ve nifedipin kullanımının karşılaştırılması

**Amaç:** Preeklampsi tanısı almış gebelerde metoprolol ve nifedipin ile kısa dönemli konservatif tedavinin etkinliği ile maternal ve fetal sonuçlarını değerlendirmek.

**Yöntem:** Çalışmada preeklampsi tanısı almış ve 50 mg, oral metoprolol suksinat (Beloc Zok®, Astra Zeneca) ve nifedipin (Adalat Crono® kontrollü salınım tableti, Bayer) ile konservatif yaklaşım uygulanmış toplam 73 gebenin sonuçları retrospektif olarak değerlendirildi.

rildi. Çalışmaya alınan gebelerin genel karakteristik özellikleri, yatış esnasındaki ve metoprolol ile nifedipin tedavisinden 48 saat sonraki kan basınçları, doğum şekli, doğum ağırlığı, yenidoğanın 1. dakika apgar skoru, eklampsi gelişimi ve ablasyo plasenta oranları retrospektif olarak değerlendirildi.

**Bulgular:** Çalışmaya dahil edilen 73 gebeden 43'ü metoprolol, 30'u nifedipin ile konservatif olarak takip edildi. Metoprolol ve nifedipin grupları arasında pozitif öykü ve nulliparite oranları arasında istatistiksel fark izlenmedi. Gruplar tanı esnasında gebelik haftası açısından benzer olarak gözlemlendi (metoprolol grubunda  $33.3 \pm 3.3$ , nifedipin grubunda  $33.1 \pm 3.5$ ). Metoprolol tedavisi ile gebelik süresindeki ortalama uzama  $6.9 \pm 8.7$  gün iken nifedipin grubunda  $6.2 \pm 7.4$  gün uzadı ve bu fark istatistiksel olarak benzer idi. Tedavi grupları arasında doğum şekli açısından fark gözlenmedi. Her iki tedavi grubunda da ilaç uygulamasının 48. saatinde sistolik ve diastolik kan basınçlarında anlamlı bir düşüş izlendi (metoprolol grubunda sistolik  $152.8 \pm 14.4$  mmHg'dan  $131.1 \pm 11.3$  mmHg'a,  $p=0.0001$ , diastolik  $97.4 \pm 9.5$  mmHg'dan  $85.5 \pm 8.9$  mmHg'a,  $p=0.0001$ ; nifedipin grubunda sistolik  $154.7 \pm 14.3$  mmHg'dan  $131.1 \pm 9.4$  mmHg'a,  $p=0.003$ , diastolik  $97 \pm 9.1$  mmHg'dan  $85.8 \pm 7.6$  mmHg'a,  $p=0.004$ ). Tedavi öncesi ve 48. saat kan basıncı ölçümleri arasında metoprolol grubunda  $19.6 \pm 12.6$  mmHg sistolik ve  $12.3 \pm 9.9$  mmHg diastolik, nifedipin grubunda ise  $21.1 \pm 14.1$  mmHg sistolik ve  $11.5 \pm 10.7$  mmHg diastolik mutlak fark izlendi. Her iki tedavi grubu arasında tedavi öncesi ve 48. saatteki sistolik ve diastolik mutlak kan basıncı farkları istatistiksel olarak benzerdi.

**Sonuç:** Metoprolol ile konservatif takip edilen preeklampşik gebelerde nifedipin ile konservatif takibe benzer şekilde etkin kan basıncı kontrolünün sağlandığı, gebelik süresinde yaklaşık 7 gün gibi bir uzama sağlanabildiği ve metoprolol ile konservatif tedavinin nifedipine oranla maternal ve fetal komplikasyon oranlarını arttırmadığı saptandı.

**Anahtar Sözcükler:** Preeklampsi, metoprolol, nifedipin, konservatif yaklaşım.

## Introduction

Preeclampsia is a disease that affect the 3% of the pregnancies characterizing with high blood pressure, proteinuria and common vasoconstriction.<sup>1,2</sup> Hypertension in pregnancy is the second reason of the maternal mortality following the embolic events in the developing countries and one of the most important reason of the perinatal morbidity and mortality.<sup>3</sup> Although the etiology of preeclampsia could not be enlightened yet in the last data it is reported that marked increase in the sympathetic activity causes a higher peripheral vascular resistance and as a result causes an increase in the blood pressure.<sup>4,5</sup> The definite treatment of preeclampsia is the termination of the pregnancy but a conservative approach can be done by using the antihypertensive agents<sup>6</sup> to provide the maturation of the immature fetuses that are over the border of the viability or to accelerate the lung maturation. Nifedipine is the most common used agent having the effect of calcium channel blockage for the conservative treatment of preeclampsia.<sup>7,8</sup> Recently, to balance the sympathetic activity, also the  $\beta$ -blockers are used for the treatment of

preeclampsia as an alternative agent to nifedipine in clinic.<sup>9</sup> Metoprolol, a second generation  $\beta$ -blocker, is a selective  $\beta$ -1 adrenergic receptor blocker. It neutralizes the effect of the catecholamines and decreases the blood pressure by reducing the vascular resistance. Metoprolol is one of the  $\beta$ -blocker used in the short term conservative treatment of preeclampsia to provide fetal maturation and to stabilize the pregnant.<sup>10</sup>

The aim of this study is to compare the efficacy of short term conservative treatment with metoprolol and nifedipine in the pregnant admitting to our clinic diagnosed as preeclampsia and to evaluate the maternal and fetal results of conservative treatment.

## Methods

This study included totally 73 women who admitted to our clinic between January 2003-December 2006 diagnosed as preeclampsia and who have been managed conservatively with oral metoprolol succinate (Beloc Zok®, Astra Zeneca) and nifedipine (Nidilat®, Sanofi-Synthelabo). The women whose clinical signs appear before 20 weeks of gestation, chronic

hypertension, mole hydatiform, fetal growth retardation, oligohydramnios and multiple gestation were excluded from the study. As well, at the admittance women who have been taken prophylactic  $MgSO_4$  treatment or another antihypertensive treatment except metoprolol were excluded.

The diagnosis of preeclampsia was done by the existence of  $>140$  mmHg systolic blood pressure or  $>90$  mmHg diastolic blood pressure in two measures at left side lying position at least 6 hours intervals and co-existence of proteinuria ( $>0,3$  g/24 hours). While beginning the antihypertensive treatment those criteria below were taken into account:

1. Existence of higher measures of blood pressure 160 mmHg systolic or 110 mmHg diastolic measured at lying position twice at least 6 hours intervals
2. Proteinuria ( $> 5$  g/24 hour)
3. Existence of platelet account lower than 100.000/mm<sup>3</sup> or microangiopathic hemolytic anemia
4. Elevation of the liver enzymes (ALT, AST)
5. Oliguria  $< 400$  ml/day
6. Headache or other cerebral and visual problems
7. Epigastric pain
8. Papillary edema or exuda, hemorrhage in the fundus
9. Lung edema or cyanosis
10. Increased serum creatinine level ( $>1.2$  mg/dl)
11. Increased LDH level ( $>600$  IU/l).

General characteristic features of the pregnant included in the study, blood pressures at the hospitalization time and 48 hours after metoprolol and nifedipine treatment, birth way, birth weight, 1. minute APGAR score of the newborn, growth of eclampsia and ratio of

ablatio placenta were evaluated retrospectively. To compare the ratio between the groups K square test, Fisher exact K square test when the case number was lower than 5, to compare the averages of independent groups Mann-Whitney U test, to compare the averages of the dependent groups (paired) Wicoxon test were used. For statistical computation SPSS 11.5 (SPSS, Inc, Chicago, IL, USA) programme was used and  $P<0.05$  was accepted as significant.

## Results

43 of 73 pregnant included in the study according to the defined criteria were followed with metoprolol and 30 were followed with nifedipine conservatively. The general characteristic features of the all study group and the two groups were shown in Table 1. In the 12,3% of the patients (n=9), it was seen that there was a history of pregnancy induced hypertension or preeclampsia previously. %65.8 of the pregnant (n=48) were nullipara and %34.2 (n=25) were multipara. There was no positive story between the groups of metoprolol and nifedipine and there was no statistical difference between nullipara ratios. At the time of admitting to the clinic the mean gestational week was  $33.2\pm3.4$  and the groups were considered as similar at the diagnosis ( $33.3\pm3.3$  in the group of metoprolol,  $33.1\pm3.5$  in the group of nifedipine) according to the gestational week. The mean delay of gestational period was  $6.9\pm8.7$  with treatment of metoprolol and was  $6.2\pm7.4$  with treatment of nifedipine and this was not statistically different. The mean gestational week at the termination of pregnancy of all of the study group was  $34.2\pm3.4$  week, mean birth weight was 2005,  $1\pm764.0$  g, the mean 1. minute APGAR score was  $6.3\pm2.3$ . Gestational week, birth weight and 1. minute APGAR score was similar between the study groups (Table 1). In only %9,6 of the patients (n=7), normal spontan

**Table 1.** The characteristics of the cases at admission and the outcomes.

	Metoprolol (n=43) Mean±SD*	Nifedipin (n=30) Mean±SD*
Age (year)	28.7±4.3	27.1±3.2
Gestational age	33.3±3.3	32.7±3.4
Gestational age at delivery	34.3±3.3	34.2±2.5
Delay (days)	6.9±8.7	6.0±7.0
Birth weight (gr)	2011.6±741.1	1995.7±808.5
Apgar 1. minute	6.3±2.2	6.0±2.1

\* SD: standard deviation

\*\* Previous history of preeclampsia or superimposed preeclampsia

birth was performed. In the other %90.4 (n=66) of the patients we preferred cesarean section. According to the birth way there were no difference between the groups of study. The gestational week of these patients was approximately 28.1±1.1 (minimum 26.5 week-maximum 29.6 week) at the time of hospitalization. Abruptio placenta was not seen in any patient while eclampsia was seen in 3 patients.

The blood pressure measures and absolute differences between pretreatment and 48 hours after treatment of all of the study group and the treatment groups were shown in Table 2. After 48 hours of drug applying a significant decrease was seen in systolic and diastolic blood pres-

**Table 2.** The blood pressure (BP) at admission and after treatment and differences.

	Metoprolol (n=43) Mean ± SD	Nifedipin (n=30) Mean ± SD	
<b>Systolic BP</b>			
At admission	152.8±14.4	154.7±14.3	
48 hour after	131.1±11.3	131.1±9.4	
P value	p<0.0001	p<0.0003	
Absolute changes	19.6±12.6	21.0 ± 14.1	p: not significant
<b>Diastolic BP</b>			
At admission	97.4±9.5	97.0±9.1	
48 hour after	85.5±8.9	85.8±7.6	
P value	p<0.0001	p<0.0004	
Absolute changes	12.3±9.9	11.6±10.7	p: not significant

ures in both treatment groups (systolic from 152.8±11.3 mmHg to 131.1±11.3 mmHg, p=0.0001, diastolic from 97.4±9.5 mmHg to 85.5±8.9 mmHg, p=0.0001, in metoprolol group; systolic from 154.7±14.3 mmHg to 131.1±9.4 mmHg, p=0.003, diastolic from 97±9.1 to 85.8±7.6, p=0.004, in nifedipine group). Absolute difference was seen in blood pressure measures with 19.6±12.6 mmHg systolic and 12.3±9.9 mmHg diastolic in the metoprolol group with 21.1±14.1 mmHg systolic and 11.5±10.7 mmHg diastolic in nifedipine group between pretreatment and 48 hours after treatment. There was no significant difference in the absolute blood pressure change with pretreatment and 48 hours after treatment between the both study group (Table 2).

## Discussion

In this study we observed that the majority of the preeclamptic pregnant who were conservatively observed with metoprolol and nifedipine were nullipar, gestation was delayed approximately 7 days with conservative observation, systolic and diastolic blood pressure were significantly decreased in preeclamptic pregnant compared to the pretreatment period and it was seen that the absolute systolic and diastolic blood pressure difference between the two treatment methods and maternal and perinatal complication ratios were similar.

The aim in the treatment of preeclampsia is to impede the potential cerebrovascular and cardiovascular complications which are the most reason of the maternal mortality and morbidity of the developed countries without damaging the uteroplacental perfusion.<sup>8</sup> It is shown in many studies that use of nifedipine in the conservative treatment is safe<sup>6,7</sup> but there has been little study about the metabolic effects, treatment results, efficacy and the use of selective  $\beta$ -blocker agents such as metoprolol. The use of the  $\beta$ -blockers in the pregnancy is con-

troversial because of the serious side effects such as fetal growth retardation, neonatal bradycardia and hypoglycemia,<sup>11</sup> neonatal respiratory depression<sup>12</sup> and increased perinatal mortality.<sup>13</sup> However the recent studies demonstrating insulin resistance, hyperinsulinemia, low levels of HDL and high levels of triglyceridia in preeclampsia,<sup>14</sup> points out the importance of the metabolic effects of the used antihypertensive agents. In the studies applied to men and non pregnant women although %14 decrease<sup>15,16</sup> was shown in insulin sensitivity with 3 months treatment of metoprolol there hasn't been seen negative effect on lipid profile and insulin sensitivity at the preeclamptic pregnant with metoprolol treatment.<sup>14</sup> In a recent study,<sup>17</sup> it is shown that the long use of  $\beta$ -blockers in the treatment of mild and moderate hypertension in pregnancy decreased significantly the risk of severe hypertension and the need for the other antihypertensive agents. Besides it is informed that when the treatment of metildopa and  $\beta$ -blocker is compared it is found that although they increase the ratio of SGA and they have the same efficacy, probably they have the similar safety.<sup>17</sup> In a study investigating the safety of short term use of metoprolol no differences were seen in the indexes of umbilical artery resistance and consequently uteroplacental blood flow in pregnant.<sup>14</sup> In the light of all these data the use of  $\beta$ -blocker agents in pregnant is limited at the present time with short term use before birth as in this study.<sup>10</sup> In this study effective blood pressure control was provided, there has been no need for extra antihypertensive agent and the similar blood pressure control was provided with nifedipine<sup>6,10</sup> which is used commonly and is investigated for the efficacy in many studies. It is known that preeclampsia is a pregnancy complication that affect nulliparae and the women who are at the extremes of the reproductive period (aged <20 or aged >35).<sup>18,19</sup> In a study investigating the eti-

ology of the preeclampsia, Caritis et al.<sup>20</sup> showed that nulliparity increases the risk of preeclampsia 1.5 times. In case controlled studies, Ekanazi et al.<sup>21</sup> and Mittendorf et al.<sup>22</sup> reported the odds ratio for preeclampsia development of multipara women to the nullipara women as 5.4 and 3.8 respectively as a result of multiple variable analysis. As well Chesley<sup>19</sup> reported that %75 of the preeclamptic women are nulliparae. Resembling that it is observed that %66 of the preeclamptic pregnant in this study are nullipar. It is known that the progress and the complications of the preeclampsia cannot be foreseen and for the postnatal complications most important parameter is the gestational week at the time of admittance to the hospital.<sup>23</sup> It is an estimated result that the gestational weeks of the women at the hospitalization time and at the time of termination of pregnancy in the severe preeclampsia group were lower than the mild preeclamptic group.

Today there is no consensus between the invasive and conservative approach yet.<sup>8</sup> However the idea of decreasing the fetal short term morbidity with conservative approach is seen dominant according to the last data.<sup>8</sup> Application of antihypertensive treatment at the conservative follow may cause complications such as fetal growth retardation, ablatio placenta, oligohydramnios and intrauterin exitus by affecting negatively the uteroplacental flow which is already poor.<sup>10</sup> In the severe preeclampsia cases it is shown that negative neonatal results at the weeks of 26-32 gestation are higher than the outcomes resulting from the only preterm birth.<sup>24</sup> Since 1990, when it is taken into consideration that only one maternal death<sup>6</sup> was seen during the conservative treatment of 1766 preeclamptic pregnant higher than 24 weeks, the idea that conservative approach in the severe preeclamptic pregnant lower than 33 weeks affect the perinatal out-



comes better with minimal risk in the mother has become widespread.<sup>25</sup> Odendaal et al.<sup>26</sup> and Sibai et al.<sup>25</sup> have found the ratio of ablatio placenta %22 and %4,1, the ratio of intrauterin exitus %16.6 and % 0 respectively, in their study. In the present observational studies it is reported that the ratio of ablatio placenta is %5.1–20, fetal death is %5.4–13.6.<sup>27,29</sup> These differences may result from the differences of the gestational weeks of the cases included in the study, fetal growth retardation, HELLP or presence of eclampsia. In this study no ablatio placenta case occurred and fetal death, all of them were lower than 30 weeks, occurred at the proportion of %9.

Another complication of preeclampsia is the increase of ratio of the cesarean section birth.<sup>18</sup> Even though the induction is successful, it is reported that %45 of the fetuses cannot tolerate and the pregnancy is terminated via cesarean sectio.<sup>18</sup> In our study this finding was confirmed once more and the pregnancies were found to be terminated via cesarean section.

## Conclusion

This study showed that in the preeclamptic pregnant who are followed conservatively with metoprolol the similar effective blood pressure control was provided like conservative follow with nifedipine, and that the gestational period achieved 7 days delay, and that conservative treatment with metoprolol in proportion to nifedipine did not increase the fetal complication ratios.

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