# Methyldopa Supplement for Resistant Essential Hypertension : A Prospective Randomized Placebo Control Crossover Study

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**Abstract**

**Background :** Resistant hypertension is an important public health problem, its prevalence varies between 30 to 50 per cent. However, there is no definite recommendation for the treatment of resistant hypertension (HT).

**Material and Method :** A prospective randomized placebo control crossover study in resistant HT was designed to compare safety and efficacy between methyldopa 250 mg twice daily and placebo using ambulatory blood pressure monitoring.

**Results :** 87 from 1,112 cases (7.82%) from the hypertension clinic of Vajira Hospital were found to have clinical resistant HT and 40 cases were accepted to enrolled in the study. 23 cases of true resistant HT proceeded to the treatment phase of the study and all of them completed the study. Methyldopa reduced systolic blood pressure (BP) from 153.67 to 135.23 mmHg, or -18.44 mmHg (95% confidence interval 15.13-21.75). Diastolic BP was reduced from 86.42 to 74.90 mmHg, or -11.52 mmHg (95% confidence interval 9.41-13.63).

**Conclusion :** The addition of methyldopa to the optimal medical therapy contributed to the improvement of BP control among patients with resistant HT.

**Key word :** Resistant Hypertension, Methyldopa, Ambulatory Blood Pressure Monitoring

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Resistant hypertension (HT) is an important public health problem and a common reason for referral of patients to specialized hypertension clinics. Patients with uncontrolled HT are at are increased risk of stroke, myocardial infarction, congestive heart failure and renal failure. Resistant, or refractory HT is defined

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as the inability to reach target blood pressures of less than 140/90 mmHg in patients who are complying with an adequate dosage of triple-drug regimens (including a diuretic)[1]. According to data from large clinical trials, nearly 50 per cent of patients receiving antihypertensive agents fall into this category (resistant HT)[2]. Trends in awareness, treatment, and control of high blood pressure in adults reported in the Joint National Committee-7 found that since 1976 to 2000, BP control of less than 140/90 mmHg could be achieved with increasingly better results, but 10 per cent in 1976 to 34 per cent in 2000 is still not impressive[3]. Not all of those who were classified to have resistant HT really have uncontrolled BP. In one study, the authors evaluated 27 patients determined to be resistant to treatment based on clinic blood pressures. Over 50 per cent were found by ambulatory blood pressure monitoring (ABPM) to be well controlled with their current drug regimens, suggesting a frequent white-coat effect[4]. Such cases may be called white-coat resistant HT and those found by ABPM to be uncontrolled are defined as true resistant HT.

Treatable causes of resistant HT can be found somewhere else,[3] and should be discovered and corrected before patients are defined as resistant HT. According to the above data, one-fourth of all hypertensive patients will be defined as being in the true resistant HT category. However, there is no definite recommendation for treatment of resistant HT.

Methyldopa is a central alpha2-agonist which was once used as an antihypertensive agent for more than twenty years. Unfortunately today it is not recommended as the initial monotherapy in HT due to its side effect of postural hypotension, depression, and erectile dysfunction[1]. However, methyldopa is cheap and maintains its role as an antihypertensive agent in some situations; for example, gestational HT. Then it may be suitable for use as a supplementation in resistant HT, but so far there is no study using methyldopa in such situations.

### Objective

The primary objective of the study was to test the hypothesis that efficacy of low dose methyldopa for resistant HT is more effective than a placebo. Secondary objectives were to test the safety and side effects of methyldopa in the same conditions. If the hypothesis is correct, using of methyldopa as a fourth drug therapy in difficult-to-treat HT can be implemented by physicians who deal with such conditions.

## MATERIAL AND METHOD

The present study was designed to compare the efficacy and safety of treatment between methyldopa and placebo. The study was conducted according to good clinical practice and was approved by the Bangkok Metropolitan Administration ethics committee, and written informed consent was obtained from all patients.

### Patients

The patients enrolled in the present study participated in a double-blinded crossover clinical protocol aimed at comparing the effect of six weeks treatment with methyldopa 250 mg twice daily or a placebo in difficult-to-treat hypertensive patients. This study was carried out between November 2002 and May 2003.

### Design

Prospective analysis of hypertensive population.

Inclusion criteria was as follows: 1. Previously diagnosed hypertension of any degree; those who were taking three kinds of antihypertensive agents which were diuretic, calcium channel blocker and angiotensin converting enzyme inhibitor or beta-blocker. 2. All medications were prescribed as the usual recommended doses; for example hydrochlorothiazide 25 mg per day, felodipine 10 mg per day, metoprolol 50 mg twice a day or perindopril 4 mg per day.

Exclusion criteria was as follows: 1. Patients younger than 20 years, or those over 80 years; 2. Treatment with more than three antihypertensive agents with well controlled BP; 3. Secondary hypertension; 4. Concurrent disease or concomitant therapy that could complicate the drug evaluation or reduce patient compliance; e.g. chronic renal failure, cirrhosis, morbid cerebrovascular disease; 5. Current pregnancy or lactation; 6. Allergy or known hypersensitivity to methyldopa; 7. Inability to obtain pre-entry day-time average systolic BP more than 130 mmHg or diastolic BP more than 85 mmHg from ABPM.

### Method

Patients from the hypertension clinic of Vajira Hospital were reviewed. Subjects who had systolic BP over 140 mmHg and/or diastolic BP over 90 mmHg with adequate triple drug regimens for two consecutive times, two weeks apart, were classified as resistant HT and were enrolled in the study. Triple drugs

were thiazide diuretic, calcium channel blocker and the third possibly as a beta-blocker or angiotensin converting enzyme inhibitor (ACEI), all being prescribed in usual adequate doses.

ABPM study was completed. A patient whose day-time systolic BP was over 130 mmHg and/or diastolic BP over 85 mmHg were considered as having resistant hypertension, and the protocol was studied. Other patients whose day-time BP was less than 130/85 mmHg were considered as well controlled (white-coat resistant HT), and were encouraged to continue with their previous medication. Then the subjects were randomized to be given a placebo or 250 mg methyldopa orally twice daily. At the end of the six week's treatment, ABPM was taken and the subjects were prescribed either a placebo or methyldopa as a cross-over study. After six weeks of crossover treatment, ABPM was taken again at the end of the study.

## Instrument

Quiettrak model 5100-01 Welch Allyn NC USA was used as the instrument for measuring ABPM. Data recording was analysed using Qtrak software.

## Statistical analysis

Mean day-time (7 am to 11 pm) systolic BP and diastolic BP were calculated. Mean systolic BP and diastolic BP from the placebo group and methyldopa group were compared by means of paired student *t*-test using SPSS pc software 10.0.

**Table 1. Demographic data of the patients.**

| Group | Male | Female | Average age | ACEI/BB | DM | CAD/VD |
|---|---|---|---|---|---|---|
| White-coat resistant HT | 7 | 10 | 66.18 | 9/8 | 3/17 | 1 |
| Resistant HT | 15 | 8 | 61.83 | 15/8 | 10/23 | 1 |
| All | 22 | 18 | 64 | 24/16 | 13 | 2 |

ACEI = angiotensin converting enzyme inhibitor, BB = betablocker,
DM = diabetes mellitus, CAD = coronary artery disease, VD = vascular disease.

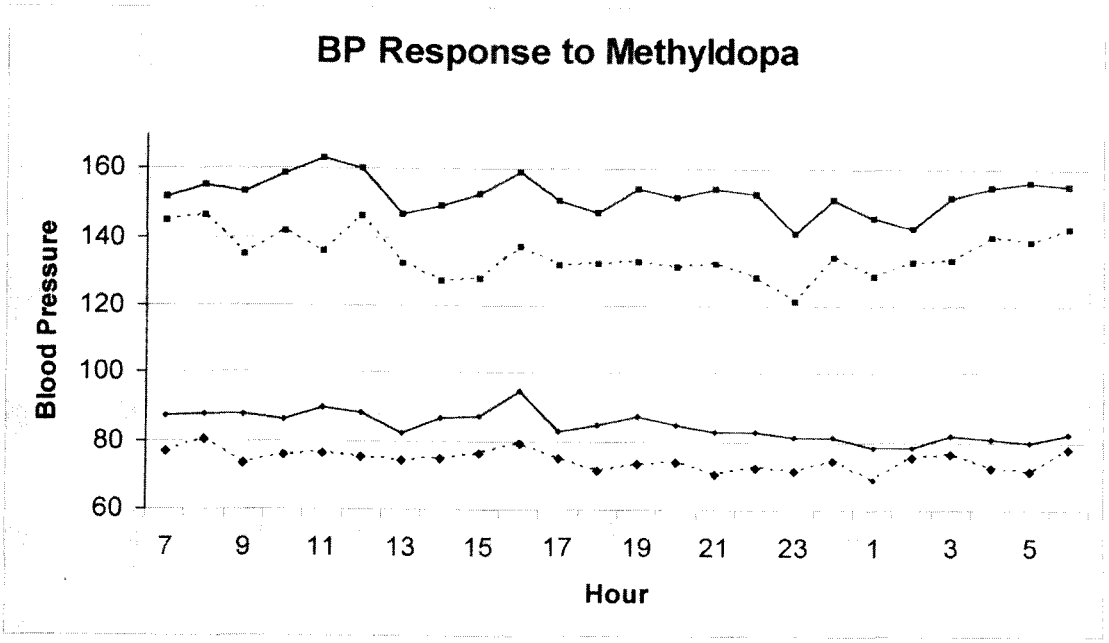


**Fig. 1. Systolic and diastolic BP reduction with placebo (solid line) compared to methyldopa (dot line).**

## RESULTS

A total of 1,112 cases with hypertension as the primary disease in the hypertension clinic Vajira Hospital were screened. 87 cases (7.82%) found to have clinical resistant HT and 40 cases were accepted to enroll in the study. Demographic data of patients are presented in Table 1. 17 cases were found to have good control of their day-time BP as measured by ABPM and classified to be white-coat resistant HT (5). 23 cases of true resistant HT proceeded to the treatment phase of the study and all of them completed the study.

BP response to methyldopa in both systolic and diastolic BP demonstrate in Fig. 1 shows a reduction in both systolic and diastolic BP, at approximately the same level in 24 hours. This also implies that methyldopa 250 mg, twice daily, is adequate for control of BP up to 24 hours. Day-time systolic BP was controlled 130 mmHg or less in 14 of 23 cases. Day-time diastolic BP controlled 85 mmHg or less in 9 of 12 cases (systolic resistant HT - 11 cases).

Average BP reduction in day-time is demonstrated in Fig. 2. Methyldopa reduced systolic BP from 153.67 to 135.23 mmHg, or -18.44 mmHg (95% confidence interval 15.13-21.75). Diastolic BP was reduced from 86.42 to 74.90 mmHg, or -11.52 mmHg (95% confidence interval 9.41-13.63).

Side effects are described in Table 2. There was no serious adverse event during the study. There were no other significant differences between the treatment group in the number of patients with changes in laboratory variables that met prespecified criteria for abnormally low or high values.

## DISCUSSION

The prevalence of HT (> 140/90 mmHg) varies between 15-35 per cent in urban adult popula-

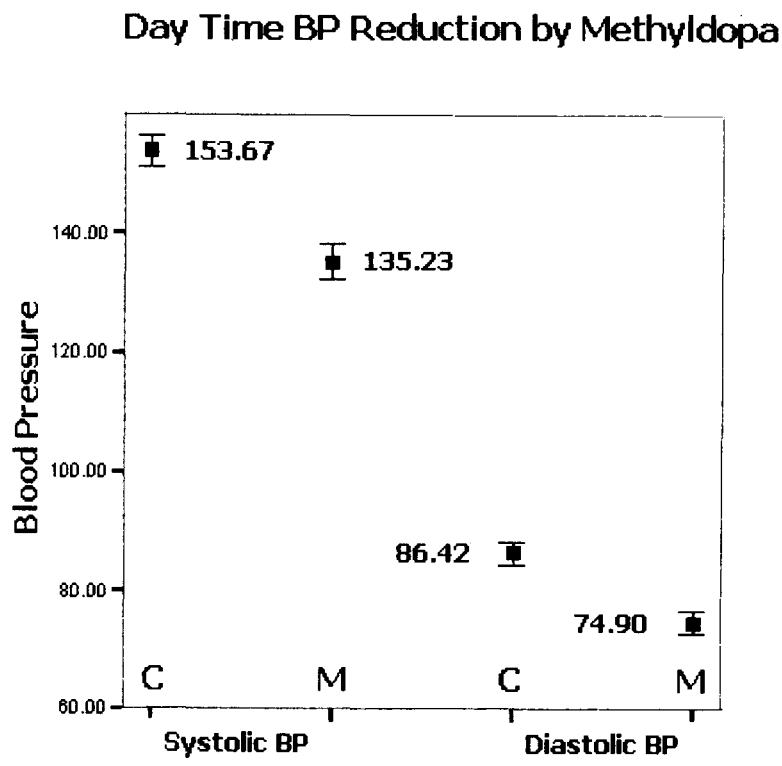


**Fig. 2. Response of systolic and diastolic BP reduction by methyldopa.**

**C = placebo control group,**
**M = methyldopa group, bar shows 95% confidence interval.**

**Table 2. Side effects found in the study.**

| Side effect | Placebo | Methyldopa |
|---|---|---|
| Headache and dizziness | 4 | 6 |
| Nausea | 2 | 3 |
| Postural hypotension | 1 | 4 |
| New erectile dysfunction | 2 | 3 |
| Depression | 0 | 0 |

tions in Asia. In rural populations, the prevalence is two to three times lower than in urban subjects[6, 7]. This may be as high as 36.5 per cent in elderly populations[8]. Prevalence of resistant HT varies according to primary care or referral centers. Reporting of resistant HT from referral centers may be as high as 30 per cent or more. Most cases are older, have higher systolic BP, and predominately male which is similar to the present study[9]. Inadequacy of BP control in Thailand as reported by Phoojaroenchanachai M, was 30.7 per cent in an HT clinic and 50.7 per cent in a general medicine clinic but cannot be classified as resistant HT[10]. Adhering strictly to the definition, 7.82 per cent of clinical resistant HT was found in the present study.

The addition of methyldopa 250 mg twice daily in patients with resistant HT resulted in a reduction of both elevated systolic and diastolic BP during daytime of -18.44/-11.52 mmHg evaluated by ABPM. This regimen also allows for BP reduction throughout 24 hours with acceptable side effects not significantly different from a placebo. The relationship between BP and risk of cardiovascular disease events is continuous, consistent, and independent of other risk factors. The higher the BP, the greater the chance of heart attack, heart failure, stroke, and kidney disease. For individuals 40-70 years of age, each increment of 20 mmHg in systolic BP or 10 mmHg in diastolic BP doubles the risk of cardiovascular disease across the entire BP range from 115/75 to 185/115 mmHg [11]. Methyldopa is now a generic drug and is very cheap, thus adding methyldopa to resistant HT may have some benefit of reducing hypertensive related complications mentioned above with very high cost-effectiveness.

## SUMMARY

23 cases of resistant HT, confirmed by ABPM study, was double-blinded and randomized to placebo or methyldopa 250 mg twice daily. Response of BP reduction was found to be -18.44/-11.52 mmHg in daytime by ABPM and well controlled BP was found over a 24-hour period. Tolerability and safety of methyldopa is acceptable with experimental dosage. The response was significantly better than a placebo with modest side effects. The addition of methyldopa to optimal medical therapy contributed to the improvement of BP control among patients with resistant HT. The present study was supported by a grant from Vajira Hospital Foundation.

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# การให้เมธิลโดปาเป็นยาเสริมในผู้ป่วยความดันโลหิตสูงรักษายากเทียบกับยาหลอก

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**ที่มาของการศึกษา** : ภาวะความดันโลหิตสูงดื้อต่อการรักษา (ได้รับยาลดความดันโลหิตสามชนิด) พบได้ร้อยละ 30-50 และเป็นปัญหาทางสาธารณสุขที่สำคัญ ปัจจุบันยังไม่มีแนวทางรักษาที่เป็นมาตรฐานสำหรับผู้ป่วยกลุ่มนี้ เมธิลโดปาเป็นยาลดความดันโลหิตที่มีใช้มานานและราคาถูกแต่มีข้อด้อยคือผลข้างเคียงที่พบได้บ่อยจึงอาจมีบทบาทในการรักษาเป็นยาเสริมชนิดที่สี่เพื่อควบคุมความดันโลหิต

**วิธีการศึกษา** : เป็นการศึกษาชนิดไปข้างหน้าแบบสุ่มเปรียบเทียบกับยาหลอกในผู้ป่วยความดันโลหิตสูงดื้อต่อการรักษา โดยใช้ยาเมธิลโดปา 250 มก วันละสองครั้ง เปรียบเทียบผลการรักษาด้วยการตรวจวัดความดันโลหิต 24 ชั่วโมงและการเปรียบเทียบความปลอดภัยและผลข้างเคียงจากการรักษา

**ผลการศึกษา** : ได้ทำการทบทวนผู้ป่วย 1,112 ราย ในคลินิกความดันโลหิตสูงวิทยาลัยแพทยศาสตร์กรุงเทพมหานครและวชิรพยาบาล พบมีผู้ป่วยความดันโลหิตสูงดื้อต่อการรักษา 87 ราย (ร้อยละ 7.82) ผู้ป่วย 40 รายเข้าร่วมการศึกษาและพบว่า 17 รายมีภาวะดื้อต่อการรักษาเทียม 23 รายมีภาวะดื้อต่อการรักษาจริงและได้เข้าทำการศึกษาด้วยเมธิลโดปาเปรียบเทียบกับยาหลอก พบว่าเมธิลโดปาสามารถลดความดันโลหิตซิสโทลิกจาก 153.67 เป็น 135.23 มม.ปรอท, หรือลดได้ 18.44 มม.ปรอท (ด้วยความเชื่อมั่นร้อยละ 95 เท่ากับ 15.13-21.75). ลดความดันโลหิตไดแอสโทลิกจาก 86.42 เป็น 74.90 มม.ปรอท, หรือลดได้ 11.52 มม.ปรอท (ด้วยความเชื่อมั่นร้อยละ 95 เท่ากับ 9.41-13.63).

**สรุป** : การให้ยาเมธิลโดปาเป็นยาเสริมในผู้ป่วยความดันโลหิตสูงดื้อต่อการรักษาสามารถลดความดันโลหิตได้เป็นที่น่าพอใจโดยมีผลข้างเคียงไม่รุนแรงและพบได้ไม่บ่อย

**คำสำคัญ** : ความดันโลหิตสูงดื้อต่อการรักษา, เมธิลโดปา, ความดันโลหิต 24 ชั่วโมง

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