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CLINICAL OUTCOMES OF MULTI-DRUG THERAPY VERSUS MONOTHERAPY IN HYPERTENSION MANAGEMENT

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Abstract

Background: Hypertension remains a leading cause of cardiovascular morbidity and mortality worldwide. While monotherapy is often the initial approach, many patients require multiple antihypertensive agents to achieve blood pressure control.

Methods: A prospective cohort study was conducted involving 284 patients with essential hypertension recruited from two tertiary care hospitals. Patients were divided into two groups: monotherapy (n=142) receiving single antihypertensive agents and multi-drug therapy (n=142) receiving two or more agents. Primary outcomes included systolic blood pressure (SBP), diastolic blood pressure (DBP), and blood pressure control rates. Secondary outcomes included adverse events and quality of life scores.

Results: The multi-drug therapy group demonstrated significantly greater reductions in SBP (−28.4 ± 8.2 mmHg vs. −18.6 ± 7.4 mmHg, $p<0.001$) and DBP (−16.8 ± 5.6 mmHg vs. −10.2 ± 4.8 mmHg, $p<0.001$) compared to monotherapy. Blood pressure control (<140/90 mmHg) was achieved in 78.2% of multi-drug therapy patients versus 52.1% in monotherapy ($p<0.001$). Adverse events were comparable between groups (24.6% vs. 21.1%, $p=0.486$). Quality of life scores improved significantly in both groups, with no significant difference between them ($p=0.124$).

Conclusion: Multi-drug therapy demonstrated superior efficacy in blood pressure reduction and achieving target control compared to monotherapy, without a significant increase in adverse events. These findings support the use of combination therapy for patients requiring intensive blood pressure management.

Keywords: Hypertension, multi-drug therapy, monotherapy, blood pressure control, combination therapy, clinical outcomes

1. Introduction

Hypertension affects approximately one billion individuals worldwide and is recognized as a primary risk factor for cardiovascular disease, stroke, chronic kidney disease, and premature mortality **[1]**. Despite advances in pharmacological management, blood pressure control rates remain suboptimal in many populations, with fewer than half of treated patients achieving recommended targets **[2]**. The persistent challenge of inadequate blood pressure control has significant implications for public health and necessitates optimization of treatment strategies.

Monotherapy, the traditional initial approach to hypertension management, involves the use of a single antihypertensive agent from various drug classes including angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, diuretics, and beta-blockers **[3]**. While monotherapy offers advantages such as simplicity, lower cost, and potentially better adherence,

clinical trials have demonstrated that most hypertensive patients require two or more medications to achieve adequate blood pressure control **[4]**.

Multi-drug therapy, involving the concurrent use of two or more antihypertensive agents with complementary mechanisms of action, has gained increasing recognition as an effective strategy for blood pressure management **[5]**. The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) demonstrated that combination therapy provided superior blood pressure reduction compared to monotherapy in high-risk patients **[6]**. Furthermore, the use of fixed-dose combinations has been shown to improve medication adherence and reduce treatment costs **[7]**.

Recent guidelines from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure have recommended initial combination therapy for patients with stage 2 hypertension or those with blood pressure more than 20/10 mmHg above goal **[8]**. However, debate continues regarding the optimal timing of combination therapy initiation and the comparative effectiveness of different multi-drug regimens in diverse patient populations **[9]**.

Despite the growing body of evidence supporting combination therapy, there remains a paucity of comparative studies examining clinical outcomes, adverse effects, and quality of life between multi-drug therapy and monotherapy in real-world clinical settings **[10]**. Most existing studies have focused on blood pressure reduction as the primary endpoint, with limited attention to patient-centered outcomes and long-term safety profiles.

The aim of this study was to comprehensively evaluate the clinical outcomes of multi-drug therapy versus monotherapy in patients with essential hypertension over a 12-month follow-up period. We hypothesized that multi-drug therapy would demonstrate superior efficacy in blood pressure control while maintaining acceptable safety and tolerability profiles compared to monotherapy.

2. Materials and Methods

2.1 Study Design and Setting

This prospective cohort study was conducted tertiary care hospital between January 2008 and March 2009.

2.2 Study Population

Patients were recruited from outpatient cardiology and internal medicine clinics. Inclusion criteria were: (1) age 35-75 years; (2) diagnosis of essential hypertension defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg on at least three separate occasions; (3) either treatment-naïve or willing to undergo treatment modification; and (4) ability to attend regular follow-up visits. Exclusion criteria included: (1) secondary hypertension; (2) history of myocardial infarction or stroke within the preceding six months; (3) severe hepatic or renal impairment (creatinine >2.5 mg/dL); (4) pregnancy or lactation; (5) known hypersensitivity to antihypertensive medications; and (6) concurrent participation in other clinical trials.

2.3 Sample Size and Group Assignment

Sample size calculation was based on an expected mean difference in systolic blood pressure reduction of 10 mmHg between groups, with a standard deviation of 15 mmHg, 80% power, and alpha of 0.05. This yielded a required sample size of 142 patients per group. Patients were assigned to treatment groups based on their treating physician's clinical judgment and guideline recommendations. The monotherapy group (n=142) received single antihypertensive agents, while the multi-drug therapy group (n=142) received two or more agents from different classes.

2.4 Interventions and Follow-up

In the monotherapy group, agents included angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, thiazide diuretics, or beta-blockers at standard therapeutic doses. The multi-drug therapy group received combinations of two or more agents selected based on guideline recommendations and individual patient characteristics. Drug dosages were titrated during the first three months to optimize blood pressure control.

Patients were evaluated at baseline, 3, 6, and 12 months. At each visit, blood pressure measurements were obtained after five minutes of rest using standardized automated oscillometric devices. Three consecutive readings were taken at one-minute intervals, and the average was recorded. Additional assessments included body mass index, laboratory tests (lipid profile, fasting glucose, serum creatinine), medication adherence evaluation, and adverse event monitoring.

2.5 Outcome Measures

Primary outcomes were: (1) change in systolic blood pressure from baseline to 12 months; (2) change in diastolic blood pressure from baseline to 12 months; and (3) proportion of patients achieving blood pressure control (<140/90 mmHg). Secondary outcomes included: (1) incidence of adverse events; (2) medication adherence rates; and (3) quality of life assessed using the Short Form-36 Health Survey.

2.6 Statistical Analysis

Data were analyzed using SPSS version 16.0. Continuous variables were expressed as mean ± standard deviation and compared using independent t-tests. Categorical variables were expressed as frequencies and percentages and compared using chi-square tests. Repeated measures ANOVA was used to assess blood pressure changes over time. A p-value <0.05 was considered statistically significant. Intention-to-treat analysis was performed for all efficacy endpoints.

3. Results

3.1 Baseline Characteristics

A total of 284 patients were enrolled and completed the 12-month follow-up. Table 1 presents the baseline characteristics of both groups. There were no significant differences in age, gender distribution, body mass index, baseline blood pressure, or comorbidities between the monotherapy and multi-drug therapy groups, indicating balanced baseline characteristics.

Table 1. Baseline Characteristics of Study Participants

Characteristic	Monotherapy (n=142)	Multi-drug Therapy (n=142)	p-value
Age (years), mean ± SD	56.8 ± 10.4	57.2 ± 11.1	0.752
Male gender, n (%)	78 (54.9)	82 (57.7)	0.629
Body mass index (kg/m²), mean ± SD	28.4 ± 4.6	28.9 ± 4.8	0.368
Baseline SBP (mmHg), mean ± SD	162.4 ± 12.8	164.2 ± 14.2	0.256
Baseline DBP (mmHg), mean ± SD	96.8 ± 8.4	97.6 ± 9.2	0.432
Diabetes mellitus, n (%)	38 (26.8)	42 (29.6)	0.587
Dyslipidemia, n (%)	54 (38.0)	58 (40.8)	0.621
Current smoking, n (%)	32 (22.5)	28 (19.7)	0.554
Family history of hypertension, n (%)	68 (47.9)	72 (50.7)	0.631

SBP = systolic blood pressure; DBP = diastolic blood pressure; SD = standard deviation

3.2 Blood Pressure Outcomes

Table 2 summarizes the blood pressure changes at different time points. The multi-drug therapy group demonstrated significantly greater reductions in both systolic and diastolic blood pressure at all follow-up intervals compared to the monotherapy group. At 12 months, the mean reduction in systolic blood pressure was 28.4 ± 8.2 mmHg in the multi-drug therapy group versus 18.6 ± 7.4 mmHg in the monotherapy group (p<0.001). Similarly, diastolic blood pressure decreased by 16.8 ± 5.6 mmHg in the multi-drug therapy group compared to 10.2 ± 4.8 mmHg in the monotherapy group (p<0.001).

Table 2. Blood Pressure Changes at Follow-up Intervals

Parameter	Monotherapy (n=142)	Multi-drug Therapy (n=142)	p-value
3 Months			
SBP (mmHg), mean ± SD	152.8 ± 10.6	145.2 ± 9.8	<0.001
SBP reduction, mean ± SD	-9.6 ± 5.2	-19.0 ± 6.4	<0.001
DBP (mmHg), mean ± SD	90.4 ± 7.2	85.6 ± 6.8	<0.001
DBP reduction, mean ± SD	-6.4 ± 3.8	-12.0 ± 4.6	<0.001
6 Months			
SBP (mmHg), mean ± SD	148.2 ± 9.8	139.4 ± 8.6	<0.001
SBP reduction, mean ± SD	-14.2 ± 6.8	-24.8 ± 7.8	<0.001
DBP (mmHg), mean ± SD	88.6 ± 6.8	82.4 ± 6.2	<0.001
DBP reduction, mean ± SD	-8.2 ± 4.4	-15.2 ± 5.2	<0.001
12 Months			
SBP (mmHg), mean ± SD	143.8 ± 8.4	135.8 ± 7.8	<0.001
SBP reduction, mean ± SD	-18.6 ± 7.4	-28.4 ± 8.2	<0.001
DBP (mmHg), mean ± SD	86.6 ± 6.4	80.8 ± 5.8	<0.001
DBP reduction, mean ± SD	-10.2 ± 4.8	-16.8 ± 5.6	<0.001

SBP = systolic blood pressure; DBP = diastolic blood pressure; SD = standard deviation

3.3 Blood Pressure Control and Secondary Outcomes

Table 3 presents the proportion of patients achieving blood pressure control and secondary outcomes. At 12 months, 78.2% of patients in the multi-drug therapy group achieved the target blood pressure of <140/90 mmHg compared to 52.1% in the monotherapy group (p<0.001). Medication adherence was high in both groups, with no significant difference (88.7% vs. 91.5%, p=0.431). The incidence of adverse events was comparable between groups (24.6% vs. 21.1%, p=0.486). Common adverse events included dizziness, headache, peripheral edema, and dry cough. Quality of life scores improved significantly from baseline in both groups, with no significant difference between groups at 12 months (p=0.124).

Table 3. Blood Pressure Control and Secondary Outcomes at 12 Months

Outcome	Monotherapy (n=142)	Multi-drug Therapy (n=142)	p-value
BP control (<140/90 mmHg), n (%)	74 (52.1)	111 (78.2)	<0.001
Medication adherence ≥80%, n (%)	126 (88.7)	130 (91.5)	0.431
Any adverse event, n (%)	35 (24.6)	30 (21.1)	0.486
Dizziness, n (%)	14 (9.9)	12 (8.5)	0.673
Headache, n (%)	8 (5.6)	6 (4.2)	0.591
Peripheral edema, n (%)	6 (4.2)	8 (5.6)	0.591
Dry cough, n (%)	7 (4.9)	4 (2.8)	0.356
QoL score (SF-36), mean ± SD	74.2 ± 12.6	76.8 ± 11.8	0.124
Change in QoL from baseline	+12.4 ± 8.2	+14.6 ± 9.4	0.058

BP = blood pressure; QoL = quality of life; SF-36 = Short Form-36 Health Survey; SD = standard deviation

4. Discussion

This prospective cohort study demonstrates that multi-drug therapy provides superior blood pressure reduction and higher control rates compared to monotherapy in patients with essential hypertension, without a significant increase in adverse events. These findings have important implications for clinical practice and support current guideline recommendations favoring combination therapy for many hypertensive patients.

The superior efficacy of multi-drug therapy observed in our study is consistent with previous landmark trials. The ALLHAT study demonstrated that most patients required multiple antihypertensive agents to achieve blood pressure targets, with combination therapy providing

additive effects **[6]**. Similarly, the Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial showed that combination therapy achieved better blood pressure control than monotherapy in high-risk patients **[11]**. Our findings extend these observations to a broader patient population in a real-world clinical setting.

The mechanism underlying the superior efficacy of multi-drug therapy relates to the complementary actions of different antihypertensive drug classes **[12]**. Combining agents that act on different pathways of blood pressure regulation can produce synergistic effects while potentially minimizing dose-dependent adverse effects of individual drugs. For instance, the combination of an angiotensin-converting enzyme inhibitor with a calcium channel blocker addresses both renin-angiotensin system activation and peripheral vascular resistance.

The blood pressure control rate of 78.2% achieved with multi-drug therapy in our study compares favorably with rates reported in other clinical trials. The Valsartan Antihypertensive Long-term Use Evaluation trial reported control rates of approximately 70% with combination therapy **[13]**. The higher control rate in our study may reflect the individualized approach to medication selection and dose titration, as well as close monitoring during follow-up visits.

Importantly, our study found that the incidence of adverse events was comparable between multi-drug therapy and monotherapy groups. This finding challenges the common assumption that combination therapy necessarily increases adverse effects. Previous studies have shown that using lower doses of multiple agents may actually reduce side effects compared to high-dose monotherapy **[14]**. The types of adverse events observed in our study were mild and consistent with the known safety profiles of antihypertensive medications.

The lack of significant difference in quality of life scores between groups is noteworthy. While both groups experienced improvements in quality of life, presumably due to better blood pressure control and reduced symptoms, the multi-drug therapy group did not experience inferior quality of life despite taking multiple medications. This suggests that concerns about the burden of polypharmacy may be outweighed by the benefits of improved blood pressure control **[15]**.

Several limitations of this study should be acknowledged. First, the non-randomized design may have introduced selection bias, although baseline characteristics were well balanced between groups. Second, the 12-month follow-up period, while substantial, may not capture long-term outcomes such as cardiovascular events and mortality. Third, the study was conducted in tertiary care centers, which may limit generalizability to primary care settings. Fourth, the specific combinations of antihypertensive agents varied among patients in the multi-drug therapy group, precluding conclusions about optimal drug combinations.

Future research should focus on randomized controlled trials comparing specific multi-drug regimens with appropriate monotherapy controls, with extended follow-up to assess cardiovascular outcomes. Additionally, cost-effectiveness analyses would be valuable to inform policy decisions regarding initial combination therapy versus sequential monotherapy approaches. Studies examining the impact of fixed-dose combination pills on adherence and outcomes would also contribute to optimizing hypertension management strategies.

5. Conclusion

This study demonstrates that multi-drug therapy achieves significantly greater blood pressure reduction and higher control rates compared to monotherapy in patients with essential hypertension. The superior efficacy was attained without a significant increase in adverse events, and quality of life improved comparably in both groups. These findings support the use of combination antihypertensive therapy for patients requiring intensive blood pressure management and align with current guideline recommendations. Multi-drug therapy represents an effective and safe strategy for optimizing blood pressure control and potentially reducing long-term cardiovascular risk in hypertensive patients. Healthcare providers should consider early initiation of combination therapy in appropriate patients to maximize the likelihood of achieving blood pressure targets and improving clinical outcomes.

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