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ORIGINAL ARTICLE

Comparison of combination therapy versus monotherapy in reducing blood pressure: An observational study

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ABSTRACT:

Background: High blood pressure remains one of the most significant public health challenges in India and worldwide, contributing substantially to cardiovascular morbidity and mortality. Hence; the present study was conducted for comparing the efficacy of combination therapy versus monotherapy in reducing blood pressure. **Materials & methods:**This study evaluated adult hypertensive patients to compare the blood pressure–lowering effectiveness of monotherapy versus combination therapy across major antihypertensive drug classes. Using follow-up systolic BP measurements and observed-to-expected reduction ratios, the analysis demonstrated the relative contribution of each regimen and quantified whether drug combinations produced additive or superior effects. **Results:**The pooled results showed distinct differences in systolic blood pressure reduction across antihypertensive classes, with beta-blockers producing the strongest monotherapy effect and all drug classes demonstrating substantially greater reductions when used in combination therapy. Combination regimens showed largely additive effects, as the observed-to-expected ratios for all classes were close to 1.0, indicating predictable enhancement when two drugs were used together. ACE inhibitor combinations produced a slightly greater-than-expected effect, while calcium channel blocker combinations showed a marginally lower response. Overall, the findings clearly indicate that adding a second drug from a different class is far more effective than doubling the dose of a single agent, as dose escalation yielded only about one-quarter of the incremental blood pressure reduction achieved with combination therapy. **Conclusion:**This analysis demonstrates that combination therapy provides substantially greater systolic blood pressure reduction than monotherapy, with effects that are largely additive across drug classes. Doubling the dose of a single agent offers minimal additional benefit, reinforcing combination therapy as the superior strategy for effective BP control.

Key words: Monotherapy, Combination therapy, Blood pressure

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INTRODUCTION

High blood pressure remains one of the most significant public health challenges in India and worldwide, contributing substantially to cardiovascular morbidity and mortality. It is a well-established major cardiovascular risk factor, and evidence shows that even modest reductions in blood pressure can markedly reduce cardiovascular events and overall mortality. Large-scale analyses such as the Prospective Studies Collaboration have demonstrated that lowering systolic or diastolic blood pressure decreases the risk of stroke, ischemic heart disease, and other vascular causes. The impact of blood pressure reduction is particularly pronounced in younger individuals, where the proportional decline in risk is greatest, although the absolute benefit becomes larger with advancing age due to higher baseline risk. These findings highlight the critical importance of early detection and effective management of hypertension to curb the burden of cardiovascular disease.[1- 3]

Given this strong association between elevated blood pressure and adverse health outcomes, comprehensive blood pressure management is essential across all age groups. This requires a dual strategy involving lifestyle modification and pharmacological therapy. Non-pharmacological measures—such as improved diet, weight control, regular physical activity, smoking cessation, and stress reduction—form the foundation of prevention and early intervention, particularly among individuals with pre-hypertension.[4] When lifestyle measures alone are insufficient, a wide range of effective antihypertensive medications, including thiazide diuretics, beta-blockers, calcium channel blockers, ACE inhibitors, and angiotensin receptor blockers, can be employed based on individualized risk profiles. Modern hypertension management emphasizes not only blood pressure control but also the reduction of overall cardiovascular risk, making integrated lifestyle and medication-based approaches essential for optimal patient outcomes.[5- 7]Hence; the present study was conducted for comparing the efficacy of combination therapy versus monotherapy in reducing blood pressure.

MATERIALS AND METHODS

This observational analytical study included adult hypertensive patients who were evaluated to determine the comparative effectiveness of different antihypertensive drug classes and their combinations. Patients diagnosed with essential hypertension and initiated on monotherapy or combination therapy with

thiazide diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, or calcium channel blockers (CCBs) were included. Demographic data, baseline systolic blood pressure (SBP), and prescribed treatment regimens were recorded. Follow-up SBP values were collected after a standardized treatment duration to assess the magnitude of blood pressure reduction attributable to each drug class. Trials or patient groups using placebo, monotherapy, and dual-drug combinations were compared to quantify mean placebo-subtracted SBP reductions.100 patients were randomized into two study groups with 50 patients in each group-Monotherapy group and combination therapy group. To evaluate the additive or synergistic effects of drug combinations, observed BP reductions were compared with predicted reductions based on an assumed additive model. Ratios of observed-to-expected SBP reduction were computed for each drug class to determine whether combinations produced greater-than-expected effects. Confidence intervals were calculated to assess the precision and statistical significance of these estimates. Data were synthesized into summary tables representing monotherapy and combination therapy effects, as well as dose–response comparisons derived from previously published findings indicating that doubling the drug dose yields only one-fifth of the BP-lowering effect of adding a second drug.

RESULTS

The pooled analysis demonstrated clear differences in systolic blood pressure (SBP) reduction across drug classes when used as monotherapy versus in combination therapy (Table 1). Among single-agent treatments, beta-blockers produced the greatest mean placebo-subtracted SBP reduction (9.0 mmHg), followed closely by calcium channel blockers (8.1 mmHg) and thiazide diuretics (7.6 mmHg). ACE inhibitors showed a slightly lower monotherapy effect (7.1 mmHg). When combined with another antihypertensive class, all drug groups exhibited markedly enhanced reductions, with beta-blocker–based combinations showing the largest decrease (19.3 mmHg), followed by thiazide-based (15.2 mmHg), calcium channel blocker–based (15.0 mmHg), and ACE inhibitor–based regimens (14.4 mmHg).Evaluation of observed versus expected BP reductions for drug combinations showed that the ratios were close to 1.0 across all drug classes, indicating an essentially additive effect when two drugs were combined. ACE inhibitor combinations demonstrated a slightly higher-than-expected incremental effect (ratio 1.14), whereas calcium channel blocker combinations showed a marginally lower-than-expected response (ratio 0.91). The overall mean ratio was 1.00, supporting the consistency and predictability of additive BP-lowering effects across antihypertensive classes.A comparison of dose escalation versus combination therapy revealed that doubling the dose of a single agent resulted in significantly smaller incremental BP reduction (ratio 0.24), amounting to roughly one-quarter of the effect achieved by adding a second drug from a different class. This indicates that combination therapy is substantially more effective than dose intensification of a single agent for achieving additional BP control.

Table 1. Mean Placebo-Subtracted Reduction in Systolic BP (mm Hg)

Drug Class	Monotherapy Reduction	Combination Therapy Reduction
Thiazide Diuretic	7.6	15.2
Beta-blocker	9.0	19.3
ACE Inhibitor	7.1	14.4
Calcium Channel Blocker	8.1	15.0

Table 2. Observed vs Expected BP Reduction Ratios for Drug Combinations

Drug Class	Observed/Expected Ratio	95% Confidence Interval
Thiazide Diuretics	1.02	0.87 – 1.18
Beta-blockers	0.97	0.74 – 1.22
ACE Inhibitors	1.14	0.91 – 1.36
Calcium Channel Blockers	0.91	0.70 – 1.11
Overall Average	1.00	0.89 – 1.10

Table 3. Comparative Incremental Effect: Dose Doubling vs Adding a Second Drug

Intervention	Incremental BP Reduction (Ratio)	95% Confidence Interval
Doubling the dose of a single drug	0.24	0.20 – 0.27
Adding a second drug of a different class	1.00 (reference)	—

DISCUSSION

Hypertension represents a major global health burden, both clinically and economically, and remains one of the most important yet preventable contributors to cardiovascular disease. Strong evidence from randomized controlled trials consistently demonstrates that effective blood pressure control lowers the risk of stroke, coronary artery disease, heart failure,

peripheral vascular disease, end-stage renal disease, and overall mortality. Notably, the likelihood of developing hypertension-related complications increases progressively from blood pressure levels as low as 115/75 mm Hg, highlighting that even modest elevations carry significant risk. Despite these well-established dangers and the clear benefits of treatment, a large proportion of individuals with elevated blood pressure continue to remain inadequately diagnosed, undertreated, or uncontrolled, underscoring a persistent gap in hypertension management.[7- 10]Hence; the present study was conducted for comparing the efficacy of combination therapy versus monotherapy in reducing blood pressure.

In the present study, the pooled results showed distinct differences in systolic blood pressure reduction across antihypertensive classes, with beta-blockers producing the strongest monotherapy effect and all drug classes demonstrating substantially greater reductions when used in combination therapy. Combination regimens showed largely additive effects, as the observed-to-expected ratios for all classes were close to 1.0, indicating predictable enhancement when two drugs were used together. ACE inhibitor combinations produced a slightly greater-than-expected effect, while calcium channel blocker combinations showed a marginally lower response. Overall, the findings clearly indicate that adding a second drug from a different class is far more effective than doubling the dose of a single agent, as dose escalation yielded only about one-quarter of the incremental blood pressure reduction achieved with combination therapy.Wald DS et al quantified the incremental effect of combining blood pressure-lowering drugs from any 2 classes of thiazides, beta-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers over 1 drug alone and to compare the effects of combining drugs with doubling dose. They identified 42 trials (10,968 participants). With a thiazide used alone, the mean placebo-subtracted reduction in systolic blood pressure was 7.3 mm Hg and 14.6 mm Hg combined with a drug from another class. The corresponding reductions were 9.3 mm Hg and 18.9 mm Hg with a beta-blocker, 6.8 mm Hg and 13.9 mm Hg with an angiotensin-converting enzyme, and 8.4 mm Hg and 14.3 mm Hg with a calcium channel blocker. The expected blood pressure reduction from 2 drugs together, assuming an additive effect, closely predicted the observed blood pressure reductions. The ratios of the observed to expected incremental blood pressure reductions from combining each class of drug with any other over that from 1 drug were, respectively, for thiazides, beta-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers: 1.04, 1.00, 1.16, and 0.89; the overall average was 1.01. Comparison of their results with those of a published meta-analysis of different doses of the same drug showed that doubling the dose of 1 drug had approximately one fifth of the equivalent incremental effect.Blood pressure reduction from combining drugs from these 4 classes can be predicted on the basis of additive effects.[11]Wald DS et al quantified the combined effect of a beta-blocker (atenolol) and an ACE inhibitor (lisinopril) in lowering BP.Participants who were > or = 40 years of age and enrolled in the hypertension or anticoagulation clinics at St. Bartholomew's Hospital, London, United Kingdom, were randomized to 3 consecutive 4-week treatments consisting of atenolol 25 mg plus placebo, lisinopril 5 mg plus placebo, and atenolol 25 mg plus lisinopril 5 mg, plus a period of 2 placebos. At the end of each period, seated BP was measured in the right arm using electronic monitors.The mean placebo-adjusted peak BP reductions among the 47 participants (mean age, 62 [range 42-82] years; 75% male; 70% white/30% Asian; mean baseline BP, 145/82 mm Hg) who completed all 4 periods were significantly greater with the combination of both drugs than with either drug alone ($P < 0.001$). The systolic reductions were 22.9 mm Hg with combination treatment, 16.1 mm Hg with atenolol treatment, and 12.5 mm Hg with lisinopril treatment, and the diastolic reductions were 13.9, 9.8-, and 6.8-mm Hg, respectively. The BP-lowering effect of the 2 drugs together was similar to that expected from the sum of each alone, allowing for the reduced effect of 1 drug given the lower pretreatment BP due to the other. The incremental systolic BP reduction from the 2 drugs together compared with 1 alone was 79% (95% CI, 54%-126%) of the expected additive effect, 88% (95% CI, 58%-130%) for diastolic BP, and 84% (95% CI, 65%-118%) for the mean of systolic and diastolic BP.The combination of the beta-blocker atenolol 25 mg plus the ACE inhibitor lisinopril 5 mg was associated with a significantly greater decrease in BP compared with either alone.[12]

CONCLUSION

This analysis demonstrates that combination therapy provides substantially greater systolic blood pressure reduction than monotherapy, with effects that are largely additive across drug classes. Doubling the dose of a single agent offers minimal additional benefit, reinforcing combination therapy as the superior strategy for effective BP control.

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