The adjuvant effect of allopurinol with valsartan on the treatment of essential hypertension

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ABSTRACT

**Background:** Hyperuricemia is thought to contribute to development of hypertension, an elevation of uric acid in hypertension could be a consequence of reduced renal function, or elevated renal vascular resistance.

**Objective:** This paper aims to evaluate the adjuvant effect of allopurinol on blood pressure in newly diagnosed essential hypertensive patients with hyperuricemia.

**Design:** Double-blind randomized controlled clinical trial.

**Patients and methods:** Sixty newly diagnosed essential hypertensive patients with hyperuricemia in private clinic were enrolled in the study. They were randomly divided into two equal groups, group 1 was put on valsartan and allopurinol therapy, and group 2 was given valsartan and placebo therapy. Both groups were followed for four weeks duration. Blood pressure and serum uric acid levels were measured in both groups, before and after therapy.

**Results:** The systolic and diastolic blood pressures showed a significant reduction in group 1 with a mean difference of -24.20 ± 2.00 mmHg, for systolic blood pressure and -16.93 ± 4.73 mmHg for diastolic blood pressure. The reduction in serum uric acid was -3.25 ± 0.18, while the patients group that received valsartan and placebo did not show the same improvement.

**Conclusion:** The administration of allopurinol had beneficial effect on blood pressure, and can be used as adjunctive therapy for patients with hypertension, particularly if they have coexistent hyperuricemia.

**Keywords:** Adjuvant effect, allopurinol, essential hypertension, valsartan.

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التأثير المساند لعقار الألوبيورينول مع الفالسارتان في علاج ارتفاع ضغط الدم الشرياني

فاخر يوسف حسين

فرع الطب، كلية الطب، جامعة الموصل، الموصل، العراق

الخلاصة

**الخلفية:** يساهم فرط حمض البول في الدم في ارتفاع ضغط الدم الشرياني، قد يكون نتيجة لانخفاض وظائف الكلى، أو ارتفاع

**الهدف:** مراقبة لقياس التأثير المساند للألوبيورينول على ضغط الدم الأساسي مع عقار الفالسارتان.

**المريض وطريقة العمل:** إن المسجلين في هذه الدراسة ستون مريضا تم تشخيصهم حديثاً بارتفاع ضغط الدم الأساسي مع ارتفاع حمض البول في الدم في عيادة خاصة، وقمتمت العينة عشوائياً إلى مجموعتين متساويتين، المجموعة الأولى أتمت عقار الألوبيورينول، والجمعية الثانية على عقار الفالسارتان والعلاج الوهمي، وتم متابعة كلتا المجموعتين لمدة أربعة أسابيع. تم قياس ضغط الدم ومتوسط حمض البول في المجموعة قبل وبعد العلاج.

**نتائج:** أظهرت هذه الدراسة أن لعقار الألوبيورينول تأثير مفيد على ضغط الدم، وأظهرت أيضاً أن استخدام عقار الفالسارتان كان له تأثير مساعد في تقليل ضغط الدم. في المجموعتين التي تلقت عقار الفالسارتان هي مجموعتين متساويتين من حيث ضغط الدم الأساسي، وكان الإختلاف بينهما غير ملحوظ، بينما كان انخفاض ضغط الدم في المجموعة التي تلقت عقار الفالسارتان أعلى من المجموعة التي لم تلتقه.

**الاستنتاجات:** بانعكاس الدراسة أن لعقار الألوبيورينول تأثير مفيد على ضغط الدم، ويمكن استخدامهما كعلاج مساعد في المرضى الذين يعانون من ارتفاع ضغط الدم وفرط حمض البول.

**الكلمات المفتاحية:** التأثير المساند، الألوبيورينول، فارسارتان.
INTRODUCTION

Essential hypertension affects 25% of the world's population and is a major cause of stroke, congestive heart failure, end-stage renal disease, and myocardial infarction. Hypertension is a common disease, affecting 30% to 35% of adults, and is especially common in groups at high risk of cardiovascular disease. Hypertension is commonly associated with hyperuricemia. It has been noted that 20%-40% of patients with essential hypertension have hyperuricemia, and may represent an additional risk factor for the development of cardiovascular disease.

Hyperuricemia is present in 25% of untreated hypertensive subjects, in 50% of subjects taking diuretics, and in 75% of subjects with malignant hypertension. Elevation of uric acid in hypertension could be a consequence of reduced renal function, the use of diuretics, the presence of hyperinsulinemia and oxidative stress, or elevated renal vascular resistance, which are commonly present in this condition. Urate level is routinely elevated in metabolic syndrome, because of high insulin levels, which decrease urate excretion, and it is unclear whether lowering urate levels will ameliorate any of the clinical features of this syndrome.

Despite a large number of safe and effective antihypertensive agents and useful lifestyle modification measures, optimal blood pressure (BP) control is attained in less than 40% of patients receiving therapy. Interestingly, raising uric acid levels in rats resulted in increased BP and the development of microvascular disease. The mechanism of hypertension uric acid–mediated reduction in endothelial nitric oxide levels and stimulation of renin expression. Studies in humans have also correlated uric acid levels with both endothelial dysfunction and elevated plasma renin activity. Furthermore, several controlled clinical trials have reported that lowering uric acid with xanthine oxidase (XO) inhibitors improves endothelial function under a variety of conditions.

Aim of the study: To evaluate the adjuvant effect of allopurinol with valsartan on blood pressure control in patients with essential hypertension.

SUBJECTS AND METHODS

The study had been approved from College of Medicine, university of Mosul. Administration and ethical approval was obtained from Nineveh Directorate of Health. Newly diagnosed cases of grade 2 hypertension defined as systolic BP ≥ 160 mmHg and diastolic Bp ≥ 100 mmHg, with serum uric acid level of ≥ 7 mg/dL, with no evidence of target organ damage, had never been treated with antihypertensive medication for any indication were enrolled in this double-blind randomized control trial study during the period from June 2012 to July 2013. Patients with renal, cardiovascular and hepatic disease were excluded. Formal consent was obtained from all participants after discussing the purpose of the research with them and they were divided after gender stratification by simple random technique into two groups: each group consisted of 30 patients, group 1 received 80 mg valsartan daily (using Diovan manufactured by Novartis), and allopurinol 100 mg (using Zyloric manufactured by Glasgow, Smith, Klin) for 4 weeks, and group 2 received valsartan 100 mg and placebo for 4 weeks duration. Both allopurinol and placebo were arranged in the form of unmarked capsules. Blood pressure and serum uric acid were measured before starting therapy and at the end of 4 weeks in both groups. Fasting serum glucose, lipid profile, serum urea, serum creatinine were measured in all patients in addition to general urine examination, electrocardiography and echocardiography.

Measurement of blood pressure: It was vital that the blood pressure readings were as accurate as possible, measurements were made to the nearest 2mmHg, in the sitting position with the arm supported, after 5 minutes' rest; the cuff contained a bladder that encompasses at least two-thirds of the circumference of the arm.

Uric acid measurement was done, using standard kit manufactured by Randox Company following the instructions.

Independent t-test for two means was used in comparing between the two groups. Also paired t-test was used to analyze the difference of various parameters in each group. All values were expressed as mean ± standard deviation (SD).
RESULTS
Sixty patients were enrolled in this study, they were 44 males and 16 females as in Table 1.

Table 2 shows the patients characteristics of the studied groups before therapies. There were no differences between the groups regarding mean age and pretreatment systolic and diastolic blood pressure.

Table 3 shows the results of the comparison of the studied parameters of group 1 before and after therapy. There were a highly significant reduction in both systolic, diastolic BP, and uric acid (P = 0.001).

Table 4 demonstrates the results of the comparison of the studied parameters of group 2 before and after therapy. There were a highly significant reduction in both systolic and diastolic BP, and uric acid (P = 0.001).

Table 5 shows that the reduction in systolic and diastolic BP in group 1 was significantly superior to systolic and diastolic BP in group 2 with a mean differences of -24.20±2.00 systolic blood pressure and -16.93±4.73 for diastolic blood pressure in group 1 versus -20.33±2.33 for systolic BP, and -9.84±0.84 for diastolic BP in group 2.

Table 1. Sex distribution of the studied groups.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Group 1 (Hypertensive patient on Valsartan plus Allopurinol)</th>
<th>Group 2 (Hypertensive patient on Valsartan plus placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Male</td>
<td>23</td>
<td>70%</td>
</tr>
<tr>
<td>Female</td>
<td>7</td>
<td>30%</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 2. Patient’s characteristics of the studied groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group 1 Mean ± SD</th>
<th>Group 2 Mean ± SD</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>51.47 ± 6.51</td>
<td>52.3 ± 6.8</td>
<td>0.631</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>162.83 ± 6.25</td>
<td>167.3 ± 9.41</td>
<td>0.034</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>102.83 ± 10.06</td>
<td>102.67 ± 9.71</td>
<td>0.950</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>7.43 ± 0.84</td>
<td>7.25 ± 0.68</td>
<td>0.365</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Mean ± SD</th>
<th>After Mean ± SD</th>
<th>Mean difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>162.83 ± 6.25</td>
<td>138.5 ± 7.78</td>
<td>-24.20 ±2.00</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>102.83 ± 10.06</td>
<td>85.90 ± 5.33</td>
<td>-16.93 ±4.73</td>
<td>0.001</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>7.93 ± 0.84</td>
<td>4.70 ± 0.61</td>
<td>-3.25±0.18</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*independent t-test for two means was used.

DISCUSSION
Hypertension is associated with endothelial dysfunction. One major factor responsible for the impaired regulation of vascular tone is the increase in oxidative stress, leading to a premature breakdown of endothelium derived vasoactive nitric oxide.20

An important source for oxygen free radical production within the endothelium is the enzyme xanthine oxidoreductase. In its oxidase form this enzyme generates superoxide anion and hydrogen peroxide as byproducts.21

Table 3. The comparison of the studied parameters of the group 1 before and after the therapy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Mean ± SD</th>
<th>After Mean ± SD</th>
<th>Mean difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>167.3 ± 9.41</td>
<td>146.77 ± 11.04</td>
<td>-20.33 ±2.33</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>102.67 ± 9.71</td>
<td>90.83 ± 8.82</td>
<td>-11.84 ±0.84</td>
<td>0.001</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>7.25 ± 0.68</td>
<td>6.52 ± 0.52</td>
<td>-0.73 ±0.16</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*paired t-test for two means was used.

Table 4. The comparison of the studied parameters of group 2 before and after therapy.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before Mean ± SD</th>
<th>After Mean ± SD</th>
<th>Mean difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>162.83 ± 6.25</td>
<td>138.5 ± 7.78</td>
<td>-24.20 ±2.00</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>102.83 ± 10.06</td>
<td>85.90 ± 5.33</td>
<td>-16.93 ±4.73</td>
<td>0.001</td>
</tr>
<tr>
<td>Uric acid (mg/dL)</td>
<td>7.93 ± 0.84</td>
<td>4.70 ± 0.61</td>
<td>-3.25±0.18</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*paired t-test for two means was used.

Table 5. The comparison of the mean difference of the systolic and diastolic BP of group 1 versus group 2 after therapies.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>valsartan and allopurinol</th>
<th>valsartan and placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>-24.20±2.00</td>
<td>-20.33±2.33</td>
<td>0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>-16.93±4.73</td>
<td>9.84±0.84</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*paired t-test for two means was used.
The present study was performed to evaluate the effect of allopurinol on a sample of hypertensive patients in Mosul population treated by valsartan. The study involved 60 patients were randomly allocated into two equal groups to rule out the effect of different variables as potential confounders.

The study clearly showed an amarked improvement in the systolic and diastolic blood pressures in the group who were taken valsartan (80 mg) and allopurinol (100 mg) daily for four weeks compared to the group who were put on valsartan (80 mg) alone.

A study done by Feig et al in 2004,2 in which adolescents with newly diagnosed essential hypertension were treated with allopurinol for one month, a reduction of serum uric acid level from a mean of 6.9 mg/dL to 3.3 mg/dL with 200 mg of allopurinol twice daily significantly reduced casual blood pressure measurements, and led to normalization of blood pressure in 4 of 5 subjects.

A study done by Feig et al in 2008,6 using allopurinol 200 mg twice daily for 4 weeks resulted in a mean change in systolic BP for group who were on allopurinol of −6.9 mm Hg (95% confidence interval [CI], −4.5 to −9.3 mmHg) vs −2.0 mm Hg (95% CI, 0.3 to −4.3 mm Hg; P=.009) for placebo, and the mean change in diastolic BP for allopurinol group was −5.1 mm Hg (95% CI, −2.5 to −7.8 mm Hg) vs −2.4 (95% CI, 0.2 to −4.1; P=.05) for placebo group, and allopurinol treatment resulted in normal BP in 20 of 30 participants, including 19 of the 22 (86%) whose uric acid levels were lowered to less than 5.0 mg/ dL. In contrast, only 1 of 30 participants became normotensive while receiving placebo during the study.

It has been shown that allopurinol treatment can improve forearm blood flow and endothelial dysfunction in patients with hypertension.22 In the context of reperfusion injury, it is understood that xanthine oxide derived oxygen free radicals are a major contributor to impaired flow and tissue damage and that allopurinol may exert protective effects against these reperfusion injuries.23

Theoretically, inhibiting xanthine oxide with reducing serum uric acid may improve endothelial function and vasodilator capacity. A potent way to prevent xanthine oxide-generated free radicals in the clinical setting is to use the orally allopurinol. There is evidence to suggest that allopurinol may prevent free radical–induced tissue damage; for example, allopurinol decreases reperfusion injury during coronary artery bypass graft surgery24,25 and improves cardiorespiratory function in an animal transplantation model 26 and in humans.27 Allopurinol may even speed up the repletion of high-energy phosphates during ischemia.28 More recently, data have emerged to suggest that the acute intra-arterial infusion of oxypurinol, the active metabolite of allopurinol, may improve endothelial function in hypercholesterolemic humans.29 It is possible that part of the beneficial effect exerted by allopurinol may be attributed to its antioxidant properties. Allopurinol, by blocking xanthine oxide, will reduce superoxide anion and uric acid production by this enzymatic pathway.30

In experimental animals intrarenal renin expression has been shown to be mediated by uric acid,a clue to the mechanism by which allopurinol lowers BP, and this was the observation that systemic vascular resistance and plasma renin activity both decreased significantly with this drug.9

Toma et al31 reported that uric acid stimulates renin release via a macula densa dependent mechanism using an in vitro microperfused afferent arterioglomerular preparation. Those studies showed that lowering uric acid may act at least in part, through reducing plasma renin activity.

In conclusion the study represent a potentially new therapeutic approach, that of control of a biochemical cause of hypertension, rather than nonspecifically lowering elevated BP. Although not representing a fully developed therapeutic strategy the study raises an alternative strategy that may prove to be more effective than currently available options.

REFERENCES


