Vitamin C as a Serum Uric Acid Lowering Agent in Hyperuricaemia

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ABSTRACT

Objective: To assess the impact of Vitamin C supplementation compared to Allopurinol therapy on the modulation of serum uric acid levels in individuals diagnosed with hyperuricaemia.

Study Design: A comparative analytical study.

Place and Duration of the Study: Department of Pharmacology and Therapeutics, Shaheed Zulfiqar Ali Bhutto Medical University, in collaboration with the Department of Medicine and Rheumatology, Pakistan Institute of Medical Sciences, Islamabad, Pakistan, from May to December, 2023.

Methodology: Eighty-six hyperuricaemic patients were enrolled and segregated equally into two groups. Group 1 received Allopurinol while Group 2 received Allopurinol plus Vitamin C. Serum uric acid levels at days 0, 30, and 60 were monitored for the serum uric acid-lowering effect of medicines. Frequency and percentages were presented for qualitative variables such as gender and age. An independent t-test was applied to compare the serum uric acid level at different intervals between both groups. A p-value equal to or less than <0.05 was considered statistically significant.

Results: The Allopurinol Group's baseline serum uric acid level was 8.321 ± 0.097 mg/dl, and the baseline value of serum uric acid of Allopurinol plus Vitamin C was 8.547 ± 0.101 mg/dl. At day 60th, the mean serum uric acid level in the Allopurinol group was 7.524 ± 0.097 with p <0.001. In the Vitamin C plus Allopurinol group, the mean serum uric acid level was 6.371 ± 0.161 with a p-value <0.001. In the Allopurinol plus vitamin C group, the percentage reduction in serum uric acid level was more than 25.44% as compared to the Allopurinol group of 9.51%.

Conclusion: Vitamin C used with Allopurinol as an adjunct therapy is a more potent pharmacological strategy for lowering blood uric acid levels in hyperuricaemic patients than alone.

Key Words: *Hyperuricaemia, Vitamin C, Allopurinol, Uric acid*.

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INTRODUCTION

Over the last four decades, a continual increase in hyperuricaemia has been observed globally. Recent data underscore an escalating prevalence of hyperuricaemia and gout on a worldwide level. Hyperuricaemia impacts 0.3% of the global population, with a substantial 90% of cases occurring in males. Additionally, 10-20% of individuals experience a family history of hyperuricaemia.[1] The prevalence of hyperuricaemia increases with age, with higher rates observed in older age groups.[2] Hyperuricaemia is a medical condition marked by elevated levels of uric acid in the bloodstream. This condition may arise from heightened production of uric acid within the body or hindered excretion through the kidneys and gastrointestinal tract. Uric acid, a by-product typically eliminated through urine, accumulates when its levels exceed normal thresholds.[3] Male adults have a plasma uric acid concentration of >416 µmol/L (7.0 mg/dl). In contrast, female adults have a value of >357 µmol/L (6.0 mg/dl).[4]

Hyperuricaemia may be associated with an increased risk of stroke, hypertension, coronary heart disease (CHD), and cardiovascular events. Additionally, there is a complex association between hyperuricaemia and dementia. Hyperuricaemia may potentially accelerate cerebrovascular disease, leading to the development of vascular dementia. However, it is worth noting that hyperuricaemia may exhibit a neuroprotective effect in the context of Alzheimer's or Parkinson's dementia, possibly due to its antioxidant properties.[5,6] Based on research findings, the consumption of purine-rich foods such as meat, seafood, pulses, green leafy vegetables, and alcohol could be crucial in the development of hyperuricaemia.[7] Uric acid is the final product of purine metabolism, synthesised in the liver through the enzymatic action of xanthine dehydrogenase/oxidase (XDH/XO). Its formation depends on substrate availability and

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XO activity, primarily occurring in liver and intestinal cells.[8] Chronic hyperuricaemia mainly results from impaired kidney excretion, which removes most uric acid, while the gut contributes to additional clearance. The kidney's filtration cycle involves reabsorption in S1, partial release in S1/S2, and final absorption in S3 before excretion.[9] Lifestyle and dietary recommendations for individuals with hyperuricaemia should prioritise overall health considerations. Additionally, considering coffee consumption and vitamin C supplementation as preventive measures can help reduce urate levels and the risk of gout and associated conditions.[10] Therefore, uric acid synthesis can be prevented by a urate-lowering medicine called Allopurinol.[11]

Allopurinol, a purine analogue, exerts its therapeutic effects by inhibiting the xanthine oxidase (XO) activity, a key enzyme in uric acid synthesis.[12,13] Allopurinol is used to treat high uric acid conditions such as gout and tumourlysis syndrome. However, it may cause serious side effects, including skin rashes, fever, kidney damage, hepatitis, and increased eosinophils.[14] Vitamin C (Ascorbic acid), as an additional treatment, is a water-soluble vitamin found abundantly in vegetables and citrus fruits.[15] The uricosuric effect of vitamin C involves two proposed mechanisms. Firstly, vitamin C competes with uric acid for reabsorption in the kidneys through an anion exchange transport system, thereby promoting the excretion of uric acid. Secondly, vitamin C supplementation can increase glomerular filtration rate, further aiding in the elimination of uric acid from the body, Additionally, vitamin C and uric acid share antioxidant properties.[16] Maintaining a daily intake of 100–200 mg of vitamin C ensures that blood levels remain adequately saturated, typically ranging between 50 and 75 µmol/L.[17]

This study aimed to assess the effectiveness of reducing hyperuricaemia by comparing the outcomes of Allopurinol 100 mg monotherapy with the combination therapy of Allopurinol 100 mg and Vitamin C 500 mg in hyperuricaemia patients. The study's rationale was to focus on administering a prescribed low dose of Allopurinol, supplemented with Vitamin C aimed to evaluate the benefits, and potential side effects associated with this combined approach.

METHODOLOGY

This comparative analytical study was conducted in the Department of Pharmacology and Therapeutics, Shaheed Zulfiqar Ali Bhutto Medical University, in collaboration with the Department of Medicine and Rheumatology, Pakistan Institute of Medical Sciences, Islamabad, Pakistan, after receiving clearance from the Ethical Review Board (No: F .1-1/2015/ERB/SZABMU/1111). It lasted from May to December, 2023. Patients for the study were initially enrolled using a simple randomisation lottery method. Those identified with hyperuricaemia were then successively enrolled through a non-probability consecutive sampling technique. Subsequently, these patients were randomly assigned to one of the two groups using computer-generated random numbers. Patients who met the inclusion criteria were distributed in a 1:1 ratio into one of the two groups, with 43 patients in each allocated group. The anticipated size of the sample was computed as 86 by utilising the WHO calculator for the sample size estimation. Each group in the study consisted of 43 patients. Written consent was obtained from the willing participants, their families, or authorised representatives that the data would be published. Data confidentiality was upheld. Inclusion criteria in the study were hyperuricaemic patients of either gender, aged between 20 and 75 years, and Serum Uric acid level: 7.0-10.0 mg per decilitre. The exclusion criteria were hypersensitivity / allergy to study medicine, pregnancy and lactating women, gout (as hyperuricaemia can cause acute and chronic gout, which is treatable by high and low doses of Allopurinol depending on the chronicity of gout), patients with end-stage renal disease and liver disease, pregnant and lactating women, and those who declined to take part.

The baseline data included demographic data, patients' history, baseline serum uric acid level, and the patients' weight. Enrolled patients were randomised to receive either combination-based therapy or single therapy. Multiplicity adjustment was made in terms of age, gender, and severity of symptoms. The patients with serum uric acid levels ≥7 mg/dl were successively enrolled at the Department of Medicine and Rheumatology.

A total of 86 patients, regardless of gender, were enrolled and divided into two groups, with 46 patients in each group. Group 1 had 43 hyperuricaemic patients of either gender who were administered the tablet Allopurinol 100 mg once daily orally for 60 days. Group 2 had 43 hyperuricemic patients of either gender who were treated with a tablet of Allopurinol 100 mg once, plus a tablet of Vitamin C 500 mg daily orally for 60 days. Follow-up blood samples of enrolled patients were collected to estimate the serum uric acid level. NSAIDS were given on an SOS (when needed) basis to relieve pain.

The data analysis used version 25.0 of the Statistical Package for Social Sciences (SPSS). The frequency and percentages of the qualitative factors were reported, and the paired t-test was used for quantitative variables. The paired samples t-test was used to assess whether a statistically significant difference existed between the means of the two groups. The p-value of Group A was 0.003 and for Group B, it was <0.001. Both values indicated significance; however, the results of Group B with combination therapy, were highly significant as compared to single therapy. A $p \leq 0.05$ was considered statistically significant.

RESULTS

Out of a total hyperuricaemic patients, two from each group discontinued the intervention and did not follow up. So, the results were calculated from 84 patients. Out of them, 60 (71.4%) patients were male and 40 (28.6%) were female. The gender distribution in Group 1 was is 29 (69%) males and 13 (31.0%) females, whereas in Group 2, 31 (73.8%) males and 11 (26.2%) females. The frequencies and percentages are listed in Table I.

Table I: Frequency and percentage of individual participants in Group 1 and Group 2.

Age group (years)	Allopurinol		Allopurinol + Vitamin C	
	Frequency	Percentage	Frequency	Percentage
30-40	17	40.5	13	31
41-50	12	28.6	14	33.3
51-60	9	21.4	10	23.8
61-70	1	2.4	5	11.9
71-75	3	7.1	0	0
Total	42	100	42	100

Table II: Comparing serum uric acid level Group 1 (Allopurinol) and Group 2 (Allopurinol plus Vitamin C).

Group	At 0 day	At 30th day	At 60th day	p-value			%
				0 to 30th	30th to 60th day	0 to 60th day	0 to 60th
1	8.321 ± 0.097 (n = 42)	7.962 ± 0.096 (n = 42)	7.524 ± 0.097 (n = 42)	0.002	0.003	>0.001	-9.51%
2	8.547 ± 0.101 (n = 42)	7.540 ± 0.124 (n = 42)	6.371 ± 0.161 (n = 42)	<0.001	<0.00	<0.001	-25.44%

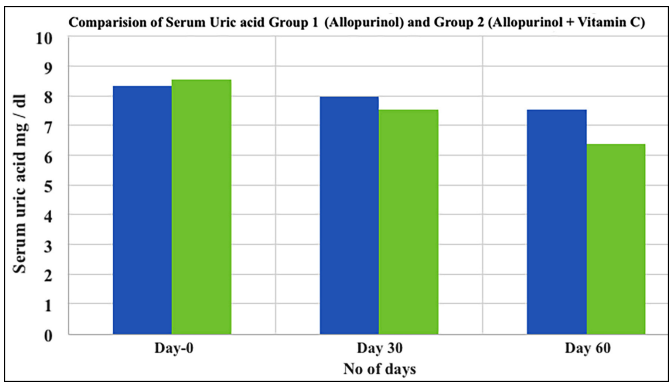

Figure *1*: Comparison of Serum uric acid level of both Groups.

In Table II Serum uric acid level of both groups is compared at day 0, 30th, and 60th day. Figure 1 shows the graphical representation of serum uric acid level.

DISCUSSION

In this study, serum uric acid level decreased more significantly when a combination of medicines, Vitamin C and Allopurinol, was introduced compared to Allopurinol alone. Combination therapy showed a marked percentage reduction of -25.44%, compared to -9.51% in single therapy. Globally, the incidence of hyperuricaemia is on the rise due to high-protein diets, increased cholesterol intake, lack of exercise, and medication adherence issues. Various strategies have been evaluated to improve treatment outcomes, including modifying treatments and adding Vitamin C to uric acid-lowering medications for enhanced effectiveness.

Brucato *et al*. conducted a study in Italy to indicate similar trends of Allopurinol effects on hyperuricaemia despite differences in study design and patient demographics. In an Italian study, Allopurinol treatment significantly reduced serum uric acid level from 9.75 ± 1.18 mg/dL to 5.88 ± 1.01 mg/dL (p <0.001) over 12 months.[18] This reduction aligns with this study Group 1, in which, there was a significant decrease in mean serum uric acid level from 8.321 ± 0.063 mg/dL to 7.524 ± 0.097 mg/dL (p <0.001) during 60 days of treatment. The reduction in mean serum uric acid level in the Brucato *et al*.'s study was greater, which may be due to the prolonged duration of therapy. Both studies demonstrate the efficacy of Allopurinol in lowering serum uric acid levels among patients with hyperuricaemia, distinct within different contexts and patient population.

The results of Group 1 show a significant reduction in mean serum uric acid level treated by Allopurinol, which was -9.5%. This aligns with the findings of Turab *et al*., who found a percentage reduction of Allopurinol in hyperuricaemic patients. They observed that the percentage reduction was 27%, which was more because the dose of Allopurinol was 300 mg for 3 months, whereas, in this study, the dose of Allopurinol was 100 mg for 60 days.[19] Therefore, Allopurinol emerges as a consistent and effective therapeutic option for clinicians managing hyperuricaemia to achieve urate-lowering effects. However, it is essential to consider individual patient characteristics, comorbidities, and potential side effects when prescribing Allopurinol, ensuring personalised treatment strategies for optimal patient outcomes.

Gao *et al*. investigated the impact of serum uric acid levels with varying doses of vitamin C. An inverse dose-response relationship was noted with vitamin C intake ranging from 400 to 500 mg/day, after which the effect plateaued. Different doses of Vitamin C, such as <90, 90–249, 250–499, 500–999, or ≥1000 mg/day, were administered. The adjusted mean serum uric acid concentrations for different levels were 6.4, 6.1, 6.0, 5.7, and 5.7 mg/dl, with a p <0.001. Whereas in Group 2 of this study, Vitamin C was given for 60 days with a dose of 500 mg daily. Serum uric acid level decreased from baseline 8.547 ± 0.101 to 6.371 ± 0.161 (n = 42).[20] The reduction in mean serum uric acid level in Gao *et al*.'s study was aligned with the present study. Both studies demonstrate the efficacy of ascorbic acid in lowering serum uric acid levels among patients with hyperuricaemia, distinct within different contexts and patient populations.

In a study conducted by Kensarah *et al*., the effect of 500 mg of Vitamin C taken for 2 months along with a purine-restricted

diet was observed on serum uric acid levels. At the start of the study, the serum uric acid level was 8.18 ± 1.70 mg/dL. After 30 days, the level decreased to 7.36 ± 1.52 mg/dL, representing an -11.14% reduction. By 60th day, the mean serum uric acid level was 7.89 ± 1.45 mg/dL, showing a further reduction of -3.67%. In contrast, the percentage reduction observed in Group 2 of this study was -25.44%, as compared to Kensarah's study, the percentage reduction in mean serum uric acid was higher. This may be due to the combination of medicine.[21]

The prevalence of hyperuricaemia is rising worldwide due to several causes, including high-protein diets, elevated cholesterol consumption, inactivity, and problems with medication adherence. Many tactics have been tested to increase eradication rates, such as altering treatment plans and perhaps increasing the efficacy of uric acid-lowering medicines by supplementing them with Vitamin C. The authors conducted a study on the addition of ascorbic acid to the medication Allopurinol in hyperuricaemic patients, taking into account the incidence of hyperuricaemia and associated consequences in the local community. The goal of adding Vitamin C was to assess how well it reduced blood uric acid levels when Allopurinol was taken in small doses.

CONCLUSION

Ascorbic acid, or Vitamin C, and Allopurinol together as adjunct therapy have been demonstrated to be more beneficial than either medication alone in hyperuricaemic individuals, who have increased blood uric acid levels. This combo strategy may result in more marked decreases in blood uric acid levels in hyperuricaemic individuals by using the synergistic effects of both medicines. With just a small sample size, this investigation was carried out at a single location. Small sample sizes can limit the generalisability of study findings. The follow-up durations were brief, and the observed indicators were limited in scope.

ETHICAL APPROVAL:

The Institutional Ethics Committee of the Shaheed Zulfiqar Ali Bhutto Medical University gave approval to the project.

PATIENTS' CONSENT:

Written consent was obtained from the willing participants, their families, or authorised representatives that the data would be published.

COMPETING INTEREST:

The authors declared no conflict of interest.

AUTHORS' CONTRIBUTION:

IS: Conception of the work, design, analysis, interpretation of data for the work, and drafting of the manuscript.
MK: Critical revision of the manuscript for important intellectual content.
FR, MA: Interpretation of data for the work and manuscript drafting.
SJ: Critical review.
All authors approved the final version of the manuscript to be published.

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