Effects of ACE Inhibitor (Lisinopril) with Folic Acid Supplementation in the Management of Hypertension Associated with Hyperuricemia

Asif Aziz, Sarwat Ashraf, Ali Akber Nangraj, Ali Raza Memon, Madiha Shah, Razia Bano and Salman Shams*

* Corresponding author: E-mail: salman_omfs@hotmail.com

ABSTRACT

Background: Hypertension is one of the leading cause of morbidity and mortality in all over the world as in developed and under developing countries. Hypertension mostly associated with other clinical chronic disorders like diabetes mellitus, hyperuricemia, dyslipidemia etc. The ACE inhibitors are a kind of antihypertensive drug that is widely using all over the world. ACE inhibitors lowers blood pressure, but also lower uric acid levels as well.

Aims & Objectives: To evaluate the efficacy of ACE inhibitors alone and along with the folic acid on systolic & diastolic blood pressure & on serum uric acid level.

Methodology: This case-control research was carried out at the Medicine Department with the help of the Department of Biochemistry at LUMHS Jamshoro and the PAQSJ Medical Institute in Gambat. A total of 200 mild to moderate hypertension individuals with hyperuricemia were chosen. They were divided into two groups: the control group was taken 10 mg of lisinopril, while the case study group received 10 mg of lisinopril with 0.8 mg of folic acid for 10 to 12 weeks.
**Results:** The mean value of systolic B.P in control group after treatment was 126 ± 4.9 (P<0.05) while in case study group after treatment was 118 ± 6.12 mmHg (P<0.05). Diastolic B.P in control group after treatment was 90 ± 4.76 mmHg while in case study group was 82.3 ± 3.66 mmHg (P<0.05). The serum uric acid level after treatment in control group was 6.7 ± 4.78 mg/dl while in case study group, it was 5.5 ± 5.11 mg/dl (P<0.001). Serum Folic acid levels after the treatment in control group was 12.31 ± 2.89 while in case study group it was 27.09 ± 3.47 nmol/L (P<0.001).

**Conclusion:** Folic acid enhances the effectiveness of an ACE inhibitor (lisinopril) and has a substantial influence in the lowering of serum uric acid as therapeutic agent in the cases of mild to moderate hypertension associated with hyperuricemia.

**Keywords:** Hyperuricemia; ACE inhibitors; hypertension; folic acid; serum uric acid.

## 1. INTRODUCTION

In humans, uric acid is the last catabolic byproduct of purine metabolism [1]. The incidence of Hyperuricemia (HUA) has been steadily increasing over the last three to four decades [2]. HUA is also the major cause of gout [3]. HUA has also been linked to established systemic clinical illnesses such as hypertension, diabetes, and myocardial infarction, among others [4]. An increase in uric acid levels might lead to a stroke or coronary heart disease [5].

Hypertension is linked to elevated uric acid levels as well as coronary heart disease [4,6]. Uric acid levels can be raised by diuretics and aspirin, which are commonly used by hypertensive patients [7]. According to several research findings, HUA is an independent risk factor for hypertension [8]. There are a variety of therapeutic treatments for HUA, including allopurinol, which inhibits the enzyme xanthine oxidase, benzene bromide, and probenecid, which increases the renal excretion rate of uric acid [9]. These medications merely lower serum uric acid levels and have no effect on blood pressure. These anti-HUA medications have a variety of adverse effects, including allergic reactions, changes in liver function enzymes, gastrointestinal issues such as vomiting and diarrhoea, decreased renal function, and bone marrow suppression [10,11]. As a result, a treatment regimen that controls blood pressure and lowers uric acid levels is required.

Angiotensin-converting enzyme (ACE) inhibitors are a kind of antihypertensive medication that protects the kidneys while simultaneously lowering uric acid levels [12]. Some experts believe that folic acid is also helpful in the treatment of HUA [13]. One phenomenon is that reduced uric acid excretion in the urine might cause homo cysteine and methylene tetra hydro folate reductase levels to rise [14]. Folic acid lowers the levels of these two compounds, making it useful in the treatment of HUA.

The goal of our study was to see if ACE inhibitors combined with folic acid had a long-term effect on lowering blood uric acid levels, which might be useful in the treatment of hypertension caused by HUA.

## 2. METHODOLOGY

This randomized control trial (CRT) study was conducted at Civil Hospital Liaquat University of Medical & Health Sciences (LUMHS) Hyderabad/Jamshoro and the Hospital of Pir Abdul Qadir Shah Jeelani Medical Institute Gambat Sindh. Total 200 diagnosed patients of mild to moderate hypertension associated with HUA (serum Uric acid no more than 7.5mg/dl) were recruited from medical and cardiology OPDs of LUMH Hyderabad, Jamshoro, and Gambat Sindh hospitals. Both males & females aged between 31 – 60 years with systolic blood pressure between 130 to 150 mmHg and diastolic blood pressure range from 90-110mmHg taking lisinopril 10mg with no any other vitamin B complex therapy during study period were included in this study. Patients aged 30 to 60 years old with a systolic blood pressure of more than 150mmHg and a diastolic blood pressure of more than 110 mmHg who were taking antihypertensive drugs other than ACE inhibitors and had a history of vitamin B therapy and anti HUA agents were excluded from the study. Pregnant women and those with known liver or renal diseases were also excluded.

A total of 5 mL of blood was obtained from each individual at two points: before the start of trial of treatment, level known as the zero level, and after the experiment was completed, the level
known as level –I. The serum uric acid level was estimated by uricase method by calorimeter technique, and the Vitamin B9 level was determined by kit method by an auto analyzer for the kit approach.

Total subjects were divided into two groups, each with an equal number of participants: group A received only ACE inhibitors; lisinopril group (Tb. Zestril 10 mg) once a day for 10 months was considered the control group, while group B received ACE inhibitors; lisinopril group (Tb. Zestril 10 mg once a day along tablet folic acid 0.4 mg twice a day) was considered the case study group.

The mean SD and statistical analysis was done by SPSS version 21 by applying the independent Student t test to know the significance value (P. value).

3. RESULTS

For this study, 200 hypertension individuals were selected and divided into two groups. The control group included 59 males and 41 females, whereas the case study group included 64 males and 36 females. The comparison of all variables in the control group before and after treatment associated with folic acid is provided in Table 1. Only a significant drop in systolic and diastolic blood pressure levels was detected in this group, whereas there was no significant reduction in serum uric acid levels or an increase in folic acid levels.

The comparison of variables in the case study group before and after the treatment period is given in Table 2. After therapy with lisinopril and folic acid, substantial reductions in systolic and diastolic blood pressure, serum uric acid level, and increased folic acid level were found in his group. After the therapy phase, the blood uric acid levels in the control and case study groups were compared graphically. In compared to the control group that did not get folic acid with the lisinopril medicine, there is a substantial decrease in blood uric acid levels in the case study group.

Table 1. Variables of control group (Group A) before & after treatment

| Variable          | At Zero Level | At Level-I | P. Value  |
|-------------------|--------------|------------|-----------|
| Age               | 45 ± 6.1     | 45 ± 6.2   | Not Significant |
| BMI (kg/m²)       | 22 ± 2.2     | 22 ± 2.0   | Not Significant |
| Systolic B.P (mmHg) | 142 ± 5.76  | 126 ± 4.9* | <0.05   |
| Diastolic B.P (mmHg) | 105 ± 5.23  | 90 ± 4.76* | <0.05   |
| Serum Uric Acid (mg/dl) | 6.9 ± 5.1  | 6.7 ± 4.78 | 0.12    |
| Serum Folic Acid (nmol/L) | 10.31 ± 4.67 | 12.31 ± 2.89 | 0.223 |

Table 2. Variables of case study group (Group B) before & after treatment

| Variable          | At Zero Level | At Level-I | P. Value  |
|-------------------|--------------|------------|-----------|
| Age               | 44 ± 7.13    | 44.12 ± 7.11| Not Significant |
| BMI (kg/m²)       | 22.4 ± 3.10  | 22.56 ± 2.87| Not Significant |
| Systolic B.P (mmHg) | 145 ± 4.76  | 118 ± 6.12* | <0.05   |
| Diastolic B.P (mmHg) | 103 ± 3.88  | 82.3 ± 3.66**| <0.001  |
| Serum Uric Acid (mg/dl) | 7.1 ± 3.89  | 5.5 ± 5.11* | <0.05   |
| Serum Folic Acid (nmol/L) | 12.31 ± 2.88 | 27.09 ± 3.47**| <0.001  |

Table 3. Variables after study period in control & case study groups

| Variable          | Control Group  | Case Study Group | P. Value |
|-------------------|----------------|------------------|----------|
| Systolic B.P (mmHg) | 126 ± 4.9     | 118 ± 6.12*     | <0.05    |
| Diastolic B.P (mmHg) | 90 ± 4.76    | 82.3 ± 3.66*    | <0.05    |
| Serum Uric Acid (mg/dl) | 6.7 ± 4.78   | 5.5 ± 5.11**    | <0.001   |
| Serum Folic Acid (nmol/L) | 12.31 ± 2.89 | 27.09 ± 3.47**  | <0.001   |
4. DISCUSSION

According to our knowledge, this is the first blinded randomized control study on the effects of folic acid in combination with lisinopril (ACE inhibitor) on blood uric acid levels in patients with HUA who had hypertension. Haibo Li et al. [15] conducted a study in China on the effects of Enalapril and folic acid on the same criteria and found substantial findings similar to ours. All across the globe, ACE inhibitors are often used to treat hypertension. Because ACE inhibitors limit uric acid reabsorption in the proximal tubules and increase the rate of urate and uric acid excretion via the kidney, they have an influence on blood pressure and serum uric acid levels [16,17]. As a result, ACE inhibitors may be beneficial in lowering uric acid levels in hypertensive individuals with HUA. There are other ideas on how folic acid affects uric acid in HUA, but two processes support our findings. Folic acid and its metabolites may inhibit xanthene oxide (XO), which reduces the breakdown of purines and so reduces the generation of uric acid. Folic acid may also enhance the breakdown of uric acid, increasing the rate of excretion and lowering serum uric acid [18]. The second crucial factor that supports our results is that folic acid lowers homo cysteine levels, which reduces the development of HUA [19].

Folic acid is particularly beneficial in painful gout since one of the functions of folic acid and its metabolite is to break down proteins, which increases the breakdown of uric acid and lowers the blood uric acid level [20]. Several investigations on the effects of folic acid HUA in gout patients have been conducted. Lyu LC et al. [21] in Taiwan conducted a case control research to examine the effects of vitamin B supplementation, folic acid, and ascorbic acid in gout patients and found that they were effective in reducing HUA. Zhang Y et al. [22] investigated the effects of folic acid, vitamin B6, and vitamin 12 on HUA and found that folic acid has a beneficial impact on blood uric acid. Although no studies on the combined effects of folic acid and antihypertensive medicines have been identified in the past, Forman JP et al. [23] claimed that folic acid may lower the incidence of hypertension. The use of folic acid can improve the efficiency of antihypertensive medications, according to Van Dijk RA et al. [24]. However, some further investigations, such as Boss Gr et al. [25], do not confirm our findings. They claimed that more than 1,000 mg of folic acid was administered but no favorable results were found.

Thus, the idea that this study subject is fresh necessitates several studies with different groups of ACE inhibitors, experiments on different races, different locations of the nation, correct dietary history, and maybe a proper dietary pattern throughout the experiment or research time.

5. CONCLUSION

It was concluded as per findings of this study that folic acid boosts the effectiveness of an ACE inhibitor (lisinopril) and has a substantial influence in the lowering of serum uric acid in the therapy of mild to moderate hypertension associated with hyperuricemia.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

As per international standard or university standard, Participants' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Visternichan O, Jalali SF, Taizhanova D, Muravlyova L, Igimbayeva G. Dynamic changes in purine catabolism in patients with acute coronary syndrome that underwent percutaneous coronary intervention. Caspian Journal of Internal Medicine. 2019;10(1):86.
2. Liu XY, Wu QY, Chen ZH, Yan GY, Lu Y, Dai HJ, et al. Elevated triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio increased risk of hyperuricemia: A 4-year cohort study in China. Endocrine. 2020 Jan 15;1:1-0.

3. Liu CW, Chang WC, Lee CC, Shau WY, Hsu FS, Wang ML, et al. The net clinical benefits of febuxostat versus allopurinol in patients with gout or asymptomatic hyperuricemia—a systematic review and meta-analysis. Nutrition, Metabolism and Cardiovascular Diseases. 2019 Oct 1;29(10):1011-22.

4. Ma W, Gao S, Huang S, Yuan J, Yu M. Hyperuricemia as a prognostic marker for long-term outcomes in patients with myocardial infarction with nonobstructive coronary arteries. Nutrition & Metabolism. 2021 Dec;18(1):1-9.

5. Patil SB, Belli B, Biradar S, Patil A. Study of serum uric acid and homocysteine levels in acute ischemic stroke. APIK Journal of Internal Medicine. 2021 Jan 1;9(1):10.

6. Ali N, Mahmood S, Islam F, Rahman S, Haque T, Islam S, et al. Relationship between serum uric acid and hypertension: a cross-sectional study in Bangladeshi adults. Scientific Reports. 2019 Jun 21;9(1):1-7.

7. Liu J, Chen L, Yuan H, Huang K, Li G, Sun N, Huo Y. Survey on uric acid in Chinese subjects with essential hypertension (SUCCESS): A nationwide cross-sectional study. Annals of Translational Medicine. 2021 Jan;9(1).

8. Dong J, Yang H, Zhang Y, Hu Q. Triglyceride-glucose index is a predictive index of hyperuricemia events in elderly patients with hypertension: A cross-sectional study. Clinical and Experimental Hypertension. 2022 Jan 2;44(1):34-9.

9. Singh Y, Samuel VP, Dahiya S, Gupta G, Gillhotra R, Mishra A, et al. Combinational effect of angiotensin receptor blocker and folic acid therapy on uric acid and creatinine level in hyperhomocysteinemia-associated hypertension. Biotechnology and Applied Biochemistry. 2019 Sep;66(5):715-9.

10. Goldstein LH. Pharmacokinetics of Anti-Rheumatic Drugs in a Geriatric Patient. InRheumatic Disease in Geriatrics. Springer, Cham. 2020;39-60.

11. Sahai R, Sharma PK, Misra A, Dutta S. Pharmacology of the Therapeutic Approaches of Gout. InRecent Advances in Gout Intech Open; 2019 Apr 5.

12. Pongpanich P, Pitakpaiboonkul P, Takkovatakarn K, Praditpornsilpa K, Eiam-Ong S, Susantitaphong P. The benefits of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers combined with calcium channel blockers on metabolic, renal, and cardiovascular outcomes in hypertensive patients: A meta-analysis. International Urology and Nephrology. 2018;50(12):2261-2278.

13. Singh Y, Samuel VP, Dahiya S, Gupta G, Gillhotra R, Mishra A, et al. Combinational effect of angiotensin receptor blocker and folic acid therapy on uric acid and creatinine level in hyperhomocysteinemia-associated hypertension. Biotechnology and Applied Biochemistry. 2019 Sep;66(5):715-9.

14. Kim J, Kim H, Roh H, Kwon Y. Causes of hyperhomocysteinemia and its pathological significance. Archives of Pharmacal Research. 2018 Apr;41(4):372-83.

15. Haibo Li , Xianhui Qin , Di Xie, Genfu Tang, Yan Zhang , Jianping Li, et al. Effects of Combined Enalapril and Folic Acid Therapy on the Serum Uric Acid Levels in Hypertensive Patients: A Multicenter, Randomized, Double-blind, Parallel-controlled Clinical Trial. Intern Med. 2015;54:17-24.

16. Reyes AJ. Cardiovascular drugs and serum uric acid. Cardiovascular Drugs Ther. 2003;17:397-414.

17. Lant AF, McNabb RW, Noormohamed FH. Kinetic and metabolic aspects of enalapril action. J Hypertens Suppl. 1984;2:S37-S42.

18. Lewis AS, Murphy L, McCalla C, Fleary M, Purcell S. Inhibition of mammalian xanthine oxidase by folate compounds and amethopterin. J Biol Chem. 1984;259:12-15.

19. Lwin H, Yoshiike N, Yokoyama T, Saito K, Date C, Tanaka H. The relationships between plasma total homocysteine and selected atherosclerotic risk factors according to the C677T methylenetetrahydrofolate reductase gene in Japanese. Eur J Cardiovasc Prev Rehabil. 2005;12:182-184.

20. Parvez GM, Akanda KM. Foods and arthritis: An overview. Bioactive Food as Dietary Interventions for Arthritis and Related Inflammatory Diseases. 2019 Jan 1;3-22.
21. Lyu LC, Hsu CY, Yeh CY, Lee MS, Huang SH, Chen CL. A case control study of the association of diet and obesity with gout in Taiwan. Am J Clin Nutr. 2003;78:690-701.
22. Zhang Y, Qiu H. Folate, Vitamin B6 and vitamin B12 intake in relation to hyperuricemia. Journal of Clinical Medicine. 2018 Aug;7(8):210.
23. Forman JP, Rimm EB, Stampfer MJ, Curhan GC. Folate intake and the risk of incident hypertension among US women. JAMA. 2005;293:320-329.
24. Van Dijk RA, Rauwerda JA, Steyn M, Twisk JW, Stehouwer CD. Long-term homocysteine-lowering treatment with folic acid plus pyridoxine is associated with decreased blood pressure but not with improved brachial artery endothelium-dependent vasodilation or carotid artery stiffness: A 2-year, randomized, placebo controlled trial. Arterioscler Thromb Vasc Biol. 2001;21:2072-2079.
25. Boss GR, Ragsdale RA, Zettner A, Seegmiller JE. Failure of folic acid (pteroylglutamic acid) to affect hyperuricemia. J Lab Clin Med. 1980;96:783-789.