ECRONICON OPEN ACCESS

EC ORTHOPAEDICS
Research Article

Evaluation of Allopurinol (Xanthine Oxidase Inhibitor) in Management of Primary Gout (Niqras)

Hila Akhtarl[1]*, Misbahuddin Siddiqi[2], Mohammad Saad Ahmad Khan[3] and Syed Zeba Husain[4]

[1]*Assistant Professor, Department of Amraz-e-Jild Wa Tazeeniyaat, AIUMC and Hospital, Muzaffarnagar, Uttar Pradesh, India*

[2]*Professor, Department of Moalijat, Faculty of Unani Medicine, Aligarh Muslim University, Aligarh, Uttar Pradesh, India*

[3]*Assistant Professor, Department of Ilaj-bit-Tadbeer, Faculty of Unani Medicine, Aligarh Muslim University, Aligarh, Uttar Pradesh, India*

[4]*Private Unani Practitioner, Aligarh, Uttar Pradesh, India*

***Corresponding Author:** Hilal Akhtar, Assistant Professor, Department of Amraz-e-Jild Wa Tazeeniyaat, AIUMC and Hospital, Muzaffarnagar, Uttar Pradesh, India.

Received: May 16, 2020; **Published:** June 20, 2020

Abstract

Gout is the most prevalent crystals-induce arthropathy and is associated with impaired health-related quality of life. It is characterized by hyperuricemia and recurrent attacks of acute arthritis, often eventually associated with urate deposits in the tissues which may be manifest as tophi. Several studies suggest that its prevalence and incidence have risen in recent decades. The objective of present trial was to validate and to assess the efficacy and safety of Xanthine-oxidase inhibitor drug- Allopurinol on the patients of primary gout. The study was of 18 months and designed as a randomized open-label with a sample size of 30 patients. The progress in subjective parameters was evaluated weekly, and at the baseline, fifteen days and thirty days in objective parameter. On the basis of severity, the subjective parameters were ranked arbitrarily from 0- 3. There was observed a considerable improvement in subjective as well as objective parameters and no undesirable effect during and at the end of trial. Therefore, it can be deduced that Allopurinol was considerably capable in resolving the signs and symptoms of primary gouty patients and significantly reduced the serum urate level.

Keywords: *Arthropathy; Allopurinol; Gout; Hyperuricemia; Niqras; Urate*

Introduction

The term Gout is derived from the word "gutta" (meaning drop), as the physicians of the 13th believed that "noxa" (poison) falling in drops into the affected joint leads to gout [1-4]. Gout is one of the oldest known diseases, known as far back as 4,000 years ago and even now it is among the fastest growing disease in the United States and one of the most painful form of arthritis [5].

In Western countries, it affects up to 1 - 2% of men and result in disability and poorer quality of life [6]. The sex ratio being 20:1 and the mean age at onset 40 years; in women, the onset of gout is postmenopausal [7]. It is a purine metabolism disorder and typify by formation and deposition of monosodium urate (MSU) crystals around the diseased joints and in other tissues of body [8]. It is one of the most prevalent inflammatory arthritis in men and present as an acute or chronic/recurrent attack. The gouty arthritis symptoms are consequences of inflammatory responses due to deposition of monosodium urate crystals (MSU), which are derive from body fluids saturated with urate.

The essential prerequisites for the development of gout are [9-11]:

1. Advancement of hyperuricaemia leading to saturation of urate inside the body.
2. Precipitation of MSU crystals and
3. Monosodium Urate crystals and leucocytes Interactions.

Patients face recurrent episodes of acute gouty arthritis that passes through these above-mentioned steps. A few recurrent acute gouty patients with uncontrolled hyperuricaemia, develop chronic tophaceous gout characterised by formation of tophi around the soft tissues [12]. An excess of uric acid in blood is mainly based upon the urate solubility limit in serum. A concentration of more than 416 μmol/l is responsible for urate saturation and is taken as hyperuricaemia in both sexes. Risk of gout development augment gradually above this value, and a serum concentration of more than 535 μmol/l corresponds to a yearly incidence of about five percent [13].

During puberty, the serum urate levels augment sharply in men, and in women after the menopause. Approximate 95% female of pre-menopausal group, have serum urate level of less than 357 μmol/l, well below the solubility limit, because estrogens is protective against urate deposition by promoting urate clearance by renal system [10,11,14-16]. Hence, gout is uncommon in pre-menopausal group, and its frequency amplifies with age in men [17].

Hyperuricaemia is the results of urate overproduction as well as impaired uric acid excretion or from combination of two processes and a few hyperuricaemic patients have primary renal urate clearance impairment. Though, renal poor excretion in itself is not enough to leads gout, and some other factors are also necessary that include purine rich food, excessive alcohol intake, fatness and insulin resistance (insulin amplify renal tubular urate reabsorption) [1,2,7,8,18,19].

The factors involved in secondary causes of hyperuricaemia are chronic kidney weakness and certain drugs such as diuretics (loop and thiazide), low dose aspirin (1 - 2 g/d), or cyclosporine therapy. Patients with myeloproliferative and lymphoproliferative disorders, polycythemia vera, myeloid metaplasia, bronchogenic carcinoma, sickle cell anemia and psoriasis lead to hyperuricaemia through increased cellular turnover. There are many enzyme defects such as deficiency of fructose-one-phosphate aldolase, glucose-six-phosphatase, and hypoxanthine guanine phosphoribosyl transferase, phosphoribosyl pyrophosphate synthetase overactivity, may leads to constant hyperuricaemia and should be assumed in gouty patients under thirty years [1,18,20-27].

Nevertheless, foremost advancement in the management strategies, about ninety percent patients of gout arthritis are badly controlled or inappropriately managed and their hyperuricemia or episodic flares carry on. The introduction of latest imaging resources, pioneer urate-lowering remedies, and an intensive pathogenesis understanding of gouty arthritis lift up the chance of advanced gout care as well as better patient outcomes. The mainstay of treatment of the acute gouty attack is still colchicine, with ACTH and cortisone as additional effective agents. When there are indications of the development of chronic gouty arthritis uricosuric agents should be employed. The fundamental control of gout seeks the adjustment of the central underlying fault e.g. hyperuricemia. Normalizing the serum uric acid to less than 5.0 - 6.0 mg/d (300 - 360 mol/L), is the initial footstep to avoid recurrent attacks, and abolish deposition of tophi. Urate lowering therapy should be initiated in any patient who already has tophi or chronic gouty arthritis [2]. The xanthine oxidase inhibitors allopurinol is the usual drug of choice. It inhibits xanthine oxidase and reduces conversion of hypoxanthine, xanthine to uric acid [28].

Allopurinol has been widely used in clinical practice for over 20 years for the treatment of hyperuricemia and gout [29]. Allopurinol (4-hidroxypirazolol pyrimidine) is the first line therapy employed to treat hyperuricemia. It interrupts the uric acid production and also inhibits synthesis of purine. It is a well-tolerated drug [30]. Allopurinol has been used since the 1960s to prevent recurrent acute gouty arthritis. It is a structural isomer of hypoxanthine that is capable of inhibiting xanthine oxidase (the enzyme responsible for uric acid synthesis), resulting in decreased serum urate levels and improvement of gout [31,32]. Allopurinol is well absorbed from gut. Allopurinol is used in chronic gout (Niqris muzmin) and in prevention of acute exacerbations [33].

Materials and Methods

The present 18 months clinical study was carried out on thirty primary gouty patients in D/o Moalijat, Faculty of Unani Medicine, Aligarh Muslim University, Aligarh, India during the period of 2015 - 2016. The study was approved by Institutional Ethical Committee

and designed as a randomized open-label trial. Patients, who completed the inclusion criteria, were given the especially designed information sheet which contained complete information's about the drug to be used, treatment manner, and study nature and when patients was completely satisfied, he was included in the study and he was asked to sign the informed consent form. The patients were selected on the basis of history, investigations and physical examinations. An applicable history of all patients was noted down with regard to their principal complaints with duration, name, age, gender, marital status, religion, alcohol intake, and food habits. Other significant points such as family history, history of trauma, renal calculi, acute attack of monoarticular arthritis, history of diuretics and NSAIDs group medicine uses, were also strictly noted down of all the patients at the beginning of the study.

To assess the involvement of other body system, all patients were questioned about the presence of difficulty in breathing, diarrhea, nausea, vomiting of food, micturition problems such as burning, proteinuria, haematuria, frequency etc. at the beginning of the trial i.e. zero day and thereafter frequently during the entire follow-up. The general, systemic, and joints examination of all gouty patients were lettered regularly in the especially designed Performa of study. The diseased joints were also observed for the signs of inflammation, movements (active and passive), and presence of swelling at the starting of the trial i.e. zero day and subsequently frequently during the entire follow up duration i.e. seven day, fourteen day, twenty-one day, and finally at thirty day of trial and all patients were also inspected for the presence of tophi around the joints. During the entire course of study, the hematological evaluation of all patients was also done at steady period. To draw out the presence of rheumatoid disease, CRP (C - reactive protein) and RA-factor (Rheumatoid Arthritis Test) was carried out at the starting of the trial, and random blood sugar, Liver Function Test, Renal Function Test, and haemograme (ESR, Hb%, TLC, DLC) were carried out two times i.e. at the starting of the trial and at the end of trial to set up the safety and observe the adverse effect (if any) of trial drug on renal, liver function and blood glucose level as well.

During the course of study, the serum uric acid level estimated at the starting of the trial and then frequently during the entire follow up period i.e. at fifteen day and thirty day of trial. Patients temperament was judge on the ground of diverse parameters mentioned by renowned Unani physicians and duration of protocol therapy was fixed to thirty days and diagnosis of patients was made on the basis of American College of Rheumatology Criteria.

The whole conclusions were noted down on the especially designed case report form. At the baseline all patients were randomly allocated for the trial, by using lottery method. The whole findings of trial were statistically analyzed under the supervision of expert biostatisticians to establish the effectiveness of trial drug on signs and symptoms of gouty arthritis patients and in lowering serum uric acid level as well. Patients who could not complete the inclusion criteria were expelled from the trial.

Patient's selection principle

Inclusion principle:

- Hyperuricaemic patients possess the clinical features of primary gout.
- Patients with age group falling between thirty to sixty years.
- Patients of both genders i.e. male and female.
- Patients who were willing to discontinue NSAIDs for joint pain and sign the informed consent form.

Exclusion principle:

- Severe respiratory, kidney, liver and cardiac abnormality.

- Breastfeeding and pregnant females.
- Patients of Secondary gout.
- Patients beyond 60 years and under 30 years of age.

Withdrawal criteria:

- Patient's failure to consume the drug.
- Patient's letdown follows up.
- Unwanted reaction of trial drug.

Disease assessment methods

Subjective parameter:

- Tenderness.
- Swelling.
- Pain.
- Painful joints movement.
- Redness over the joints.
- Increased local temperature.

Objective parameters:

- High Serum uric acid level above the normal perimeter i.e. greater than 6 mg/100 ml in females patients and greater than 7 mg/100 ml in case of males patients.

Dosage schedule and mode of administration of test drug

Allopurinol (Brand name-Zyloric) is a well-known modern pharmacopoeia drug, manufactured by gsk Glaxo Smith Kline Pharmaceuticals Limited Andhra Pradesh India, taken from the market. This modern drug is registered in India for management of patients of gouty arthritis. It is selected on the basis of its mechanism of action e.g. uricostatic-decrease production of uric acid, mentioned in classical modern pharmacy textbook under the principles of treatment of gout. Allopurinol has been used by the doctors for many years to manage the gout devoid of any noteworthy adverse effects, Allopurinol is given to each patient in the dosage of 1 tablet (100 mg) thrice a day orally after meal irrespective of age, sex and severity of disease. During the course of study, adverse effects (if any) remarked by patients were note down in especially designed case Report Form (CRF) and severe cases were excluded from the trial. For the management of gout by

Allopurinol, skilled, licensed physicians, who had been practicing medicine for an average of ten years, were selected. Physicians attended continuing medical education (CME) speech on several evidence-based contemporary medicine interventions as well.

Follow up of patients

For investigation, follow up of all gouty patients is done at entry point, fifteen days, and thirty days and for symptomatic relief follow up is carried out at zero, seven, fourteen, twenty-one and thirty days.

Observation and Results

Demographic data

During the protocol of trial, it was noticed that the incidence of gout was equal in both communities i.e. Muslims and Hindu (50%) and higher in male gouty patients (67%) among the 40 - 50 age group (40%). highest numbers of patients were wedded (93%) and belong to middle income group (63%), housewives (27%) and servicemen (27%) groups, followed by businessmen 6 cases (20%), laborers cases (10%), farmer 3 cases (10%), and student 2 cases (7%) and had Balghami mizaj (53%) and mixed dietary habits (63%). History of alcohol addiction, monoarticular arthritis, and Family history was positive in seventeen percent, eighty percent, and thirty-three percent cases respectively. It was also observed that great toe or first metatarsophalangeal joint was involved in maximum number of cases (43%), while in 37% cases involvement of joints was polyarticular and knee joint and ankle joint were involved in 13% and 7% cases.

Effect of drug on subjective parameters

Painful joints movement

During the trial, it was observed that painful joints movements were present in 27 patients and 48.14% improvement was noticed at the end of trial. The entry point and thirty-day evaluation were found to be statically noteworthy i.e. $P < 0.01$. This finding exhibit that the effectiveness of trial drugs is noteworthy on painful joint movement (Table 1 and figure 1).

Swelling

During the course of trial, it was noticed that swelling was present in twenty-one patients (out of thirty) and 47.61% improvement was noticed at the end of trial. The entry point and thirty-day evaluation were found to be statically noteworthy i.e. $P < 0.01$. This findings exhibit that the effectiveness of trial drugs is remarkable on symptom of swelling (Table 1 and figure 1).

Tenderness

During the course of trial, it was noticed that out of thirty patients, twenty-one patients suffered from tenderness and 57.14% improvement in tenderness was noticed at the end of trial. The entry point and thirty-day evaluation were found to be statically noteworthy i.e. $P < 0.01$. These findings exhibit that the effectiveness of trial drugs is remarkable on resolving the symptom of tenderness (Table 1 and figure 1).

Increased local temperature

During the entire course of trial, it was noticed that out of thirty patients, only five patients suffered from complaint of increased local temperature and forty percent improvement in complaint of increased local temperature was noticed at the end of trial. The entry point

and thirty-day evaluation were found to be statically noteworthy i.e. P < 0.01. These findings exhibit that the effectiveness of trial drugs is remarkable on resolving the complaint of increased local temperature (Table 1 and figure 1).

Pain in joint

During the entire course of trial, it was noticed that complaint of pain in joint is positive in all patients of study group and 53.33% improvement in complaint of joint pain was noticed at the end of trial. The entry point and thirty-day evaluation was found to be statically noteworthy i.e. P < 0.01. These findings exhibit that the effectiveness of trial drugs is remarkable on resolving the complaint of pain in joints (Table 1 and figure 1).

Features	0 day	7 day	14 day	21 day	30 day
	No. of patients	No. of patients improved and %	No. of patients improved and %	No. of patients improved and %	No. of patients improved and %
	T	T	T	T	T
Painful joints movement	27	3 (11.11)	6 (22.22)	11 (40.74)	13 (48.14)
Swelling	21	1 (4.76)	5 (23.80)	9 (42.85)	10 (47.61)
Tenderness	21	2 (09.52)	6 (28.57)	7 (33.33)	12 (57.14)
Increased local temperature	5		1 (20)	2 (40)	2 (40)
Pain	30	3 (10)	7 (23.33)	11 (36.66)	16 (53.33)
p < 0.05 (Paired 't' test applied between zero and 30th day)					

Table 1: *Effect of drugs on subjective parameters.*
T = Test drug (Allopurinol).

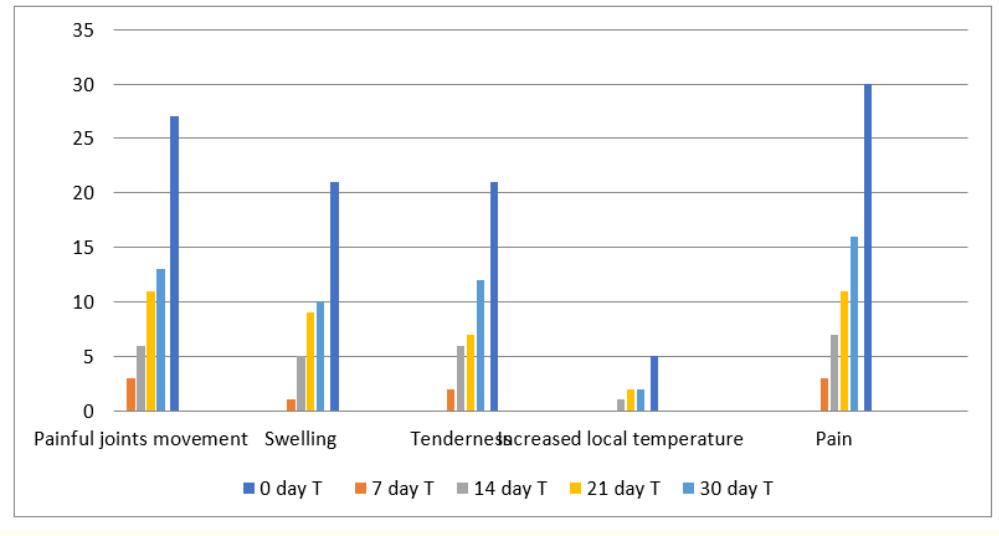

Figure 1: *Showing the effect of test drugs on subjective parameters.*

Effect of drug on objective parameter

The Mean ± SD of serum uric acid before starting the treatment was 8.40±1.08 and it got reduced to 7.58 ± 1.13 after treatment. Now paired 't' test is applying to all observations booked previous to and subsequent to thirty days of trial (t = 16.05, p = 0.01). The p value finding exhibit that the outcome of trial drug is noteworthy in dipping high serum uric acid (Table 1 and figure 2).

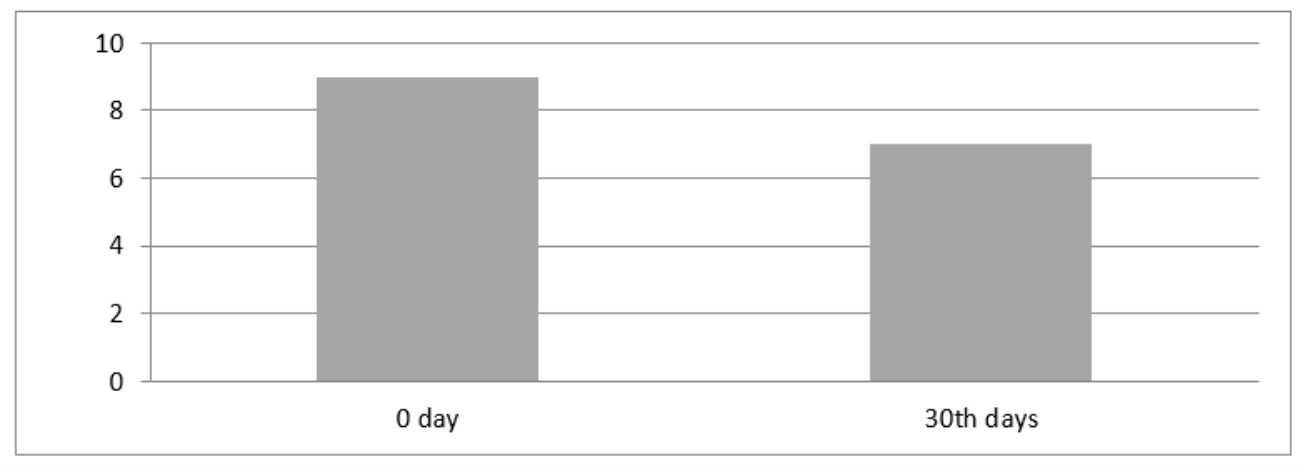

Figure 2: *Showing the effect of test drugs on serum uric acid.*

Discussion

This present trial was carried on thirty patients to assess the efficiency of Allopurinol in the treatment of Primary Gout. The disease is principally noticed in male patients i.e. 67% and between the 40 - 50 age group i.e. 40%. These findings exhibit that the gout has a alliance with a particular age group and gender. All these findings are in harmony with the previous explanation mentioned in Unani and modern medical text i.e. Gout is rare beneath thirty year of age and the frequency and commonness of gout enhance with age in both male and female [1,2,10,34-36]. The frequency of gout is higher in males comparatively to pre-menopausal female, as uricosuric effect of estrogen encourage uric acid excretion in premenopausal females [1,10].

In present study incidence of gout was found higher among the Muslims community patients and it is mainly due to association of gout with intake of purine rich food items such as meat products, which are commonly eaten by Muslim peoples. As per renowned Unani physicians and modern literature, mentioned in modern textbooks, purine-rich diet such as meat eaten by the non-vegetarian amplified the risk of gout development.

During the protocol period, it was noticed that 37% cases fall under the vegetarian's diet group and 63% cases fall under the non-vegetarian's diet group. This findings are parallel to classical Unani text books description and fresh literatures [1,2,18,34,37-40]. In present trial out of thirty patients, 93% patients were found wedded and seven percent patients were found unmarried. This is accordance with Buqrat's saying i.e. "A young man does not take gout unless he indulges in coitus" and excessive sexual activity, especially after a meal, is recognized as a high risk factor for gout in males [2,15,41-44]. More studies are required in this field.

Allama Qarshi Avicenna and Rhazes, renowned Unani physicians, have clearly mentioned that balgham is linked in the gout pathogenesis. In present trial, findings exhibit that patients with phlegmatic temperament were more in numbers (53%), that is parallel to classical Unani literature [38,45]. It is very clearly mentioned in the classical text book that the disease is related with leisure and rich peoples are commonly affected [1,35,37-40] and in our trial, it was observed that the middle income group peoples belonging to servicemen and housewife class were outnumbered i.e. 63% and in higher income group it was 17%. But it is important to clarify here that the patients of our hospital are generally belonging to middle and lower class, hence the conclusions are incoherent. But it may be due to shifting of disease trend involving more and more to middle class and higher middle class.

More than 2000 years ago, gout is recognized as a familial disorder by Hippocrates. This statement is uniformly significant at present time too. Present study covers 33% patients, who had a positive family history. These findings are similar to descriptions given in Oxford Textbook of Rheumatology and Boyd's Pathology.

During the protocol of study only 17% cases give the positive history of alcohol intake, while the residual 83% patients did not give any such history. This finding does not correspond with the findings of Choi and colleagues who founded that alcohol intake is a key cause for gout development. This difference may be credited mainly to 2 components. Firstly, most of the patients included in the study were belong to Muslim community, and secondly, small sample size of our trial. It was also noticed that 43% patients had the classical presentation of first metatarsophalangeal joint which is parallel to the explanation mentioned in standard medical literature [1,2,10,18]. This observation of our trial is a justification for the Unani nomenclature (Niqras: derivative from Naqaroos meaning first metatarsophalangeal joint) of this disease [38].

To evaluate the outcome of trial drug on subjective parameters the patients were assessed for diverse sign and symptoms of disease e.g. pain, swelling, redness, painful joints movement, tenderness, and increased local temperature. The severity of symptoms of disease, based on arbitrary grading system, was rated as severe, moderate, mild, and absent and graded as 3, 2, 1 and 0 respectively. There was significant but steady development noticed on every visit of the patient and approximate 48.14% of patients felt the reformation in painful joint movement complaint on the thirty day of trial. Likewise, 57.14% patients felt progress in tenderness, while 47.61% patients felt progress in swelling, 40% patients felt improvement in increased in local temperature, and 53.33% patients felt improvement in pain in joints at the end of trial.

Trial drugs was observed to be remarkable in resolving the symptoms of tenderness, painful joints movement, increased local temperature, swelling, and pain (applying paired 't' test, $p < 0.01$).

Table 2 exhibiting the objective parameter which is serum uric acid level and it was estimated at fifteen day gap, the entry point serum uric acid level was 9.34 ± 1.06 and on the thirty day it was 7.58 ± 1.13 ($t = 16.05$ $p < 0.005$), demonstrating that trial drugs had a very significant action on dipping serum uric acid level.

	Test drug		
	Before Treatment	**After Treatment**	
Follow up in days	**0 day**	**15th days**	**30th days**
Mean Serum uric acid ± S.D. (mg/dl)	9.34 ± 1.06	8.40 ± 1.08	7.58 ± 1.13
	t = 16.05 p = 0.01		

Table 2: *Effect of drugs on serum uric acid.*

It is due to well-known action of allopurinol i.e. uricostatic- decrease serum uric acid concentration in both under excretory and over-producers. Allopurinol itself is a short-acting (t½ 2 hrs) competitive inhibitor of xanthine oxidase, but its major metabolite alloxanthin (oxypurine) is a long acting ((t½ 24 hrs) and noncompetitive inhibitor- primarily responsible for uric acid synthesis inhibition *in vivo.* At high concentrations, allopurinol also becomes noncompetitive inhibitor. During allopurinol administration, plasma concentration of uric acid is reduced and that of hypoxanthine and xanthine is increased. In place of uric acid alone, all 3 oxypurines are excreted in urine. Since hypoxanthine and xanthine are more soluble, so their precipitation and crystallization in tissues and urine does not occur [46]. Our findings are parallel to modern literature and suggesting that the drug is very much effective in the reducing of serum uric acid level. During the course of study, it is instructed to all patients that they must avoid purine rich diets intake and take profuse water along with trial drug.

It was also noticed that trial drug has no noteworthy unfavorable effect on biochemical parameters and hematological parameters during the entire course of the study (Figure 3).

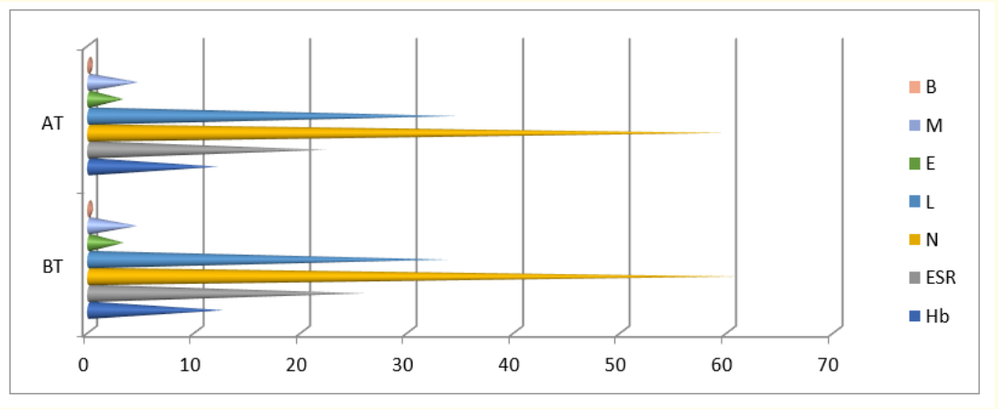

Figure 3a: *Showing the effect of test drugs on safety parameters (Hematological Parameters). (BT: Before Treatment; AT: After Treatment; B: Basophil; M: Monocyte; E: Eosinophil; L: Lymphocyte; N: Neutrophil; ESR: Erythrocyte Sedimentation Rate; Hb: Hemoglobin).*

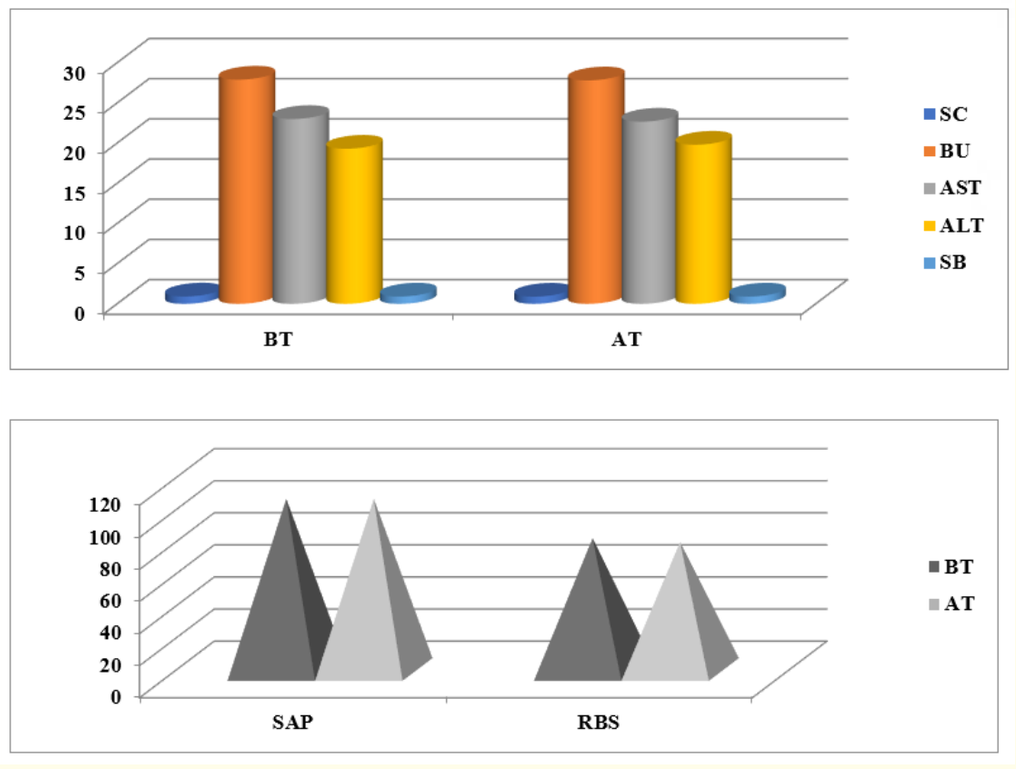

Figure 3b: *Showing the effect of test drugs on biochemical parameters. (SC: Serum Creatinine; BU: Blood Urea; AST: Aspartate Aminotransferase; ALT: Alanine Aminotransferase; SB: Serum Bilirubin; BT: Before Treatment; AT: After Treatment; SAP: Serum Alkaline Phosphatase; RBS: Random Blood Sugar).*

Conclusion

It was concluded that Allopurinol is extensively valuable in relieving the signs and symptoms of gouty arthritis and has significant result on dropping serum uric acid concentration as well as has no any remarkable unfavorable effects on safety parameters. Hence, trial drug is secure to employ in gouty arthritis cases.

Acknowledgement

We owe a deep debt of appreciation to our gentle teacher Prof. Misbahuddin Siddiqi Department of Moalijat, Faculty of Unani Medicine, Aligarh Muslim University, Aligarh-202002, for providing precious supervision during the entire work. We are also thankful to the Ministry of AYUSH, New Delhi, for providing financial support and to the volunteers who participated in the study for their humble cooperation.

Bibliography

1. Syngle Ashit and Deodhar SD. "Rheumatology Principles and Practice 1st edition". New Delhi: Jaypee Brothers Medical Publisher (P) Ltd (2010): 190-206.
2. Longo Dan L., *et al*. "Harrison's Principles of Internal Medicine 18th edition". Volume-II. Mc Graw Hill Companies, Inc (2012): 2837-2838.
3. Anonymous. "Dorland's Illustrated Medical Dictionary 28th edition". Bangalore: Easter Press Ltd., (1999): 713.
4. Venes Donald. "Taber's Cyclopedic Medical Dictionary 21st edition". Philadelphia: FA Davis Company (2009): 976-977.
5. Internet. "Gout and Uric Acid Education Society". www.gouteducation.org 3.
6. Sivera F., *et al*. "Multinational evidence-based recommendations for the diagnosis and management of gout: integrating systemic literature review and expert opinion of a broad panel of rheumatologists in the 3e initiative". *Annals of the Rheumatic Diseases* 73 (2014): 328-335.
7. Roubenoff R. "Gout and Hyperuricemia". *Rheumatic Disease Clinics of North America* 16 (1990): 539-550.
8. March LM., *et al*. "Epidemiology of gout: An update". *Best Practice and Research Clinical Rheumatology* 24 (2010): 811-827.
9. Annemans L., *et al*. "Gout in the UK and Germany: prevalence, comorbidities and Management in general practice 2000-2005". *Annals of the Rheumatic Diseases* 67 (2008): 960-966.
10. Goldman Lee and Ausiello Denis. "Cecil Textbook of Medicine 23rd edition". Volume II. Philadelphia: Saunders Elsevier (2007): 2069-2075.
11. Nasimul H., *et al*. "An Overview of Niqris (Gout) and its interpretation with hyperuricemia". *International Journal of Advanced Ayurveda, Yoga, Unani, Siddha and Homeopathy* 2 (2013): 137-142.
12. McGill NW. "Gout and other crystal-associated arthropathies". *Best Practice and Research: Clinical Rheumatology* 14 (2000): 445-460.
13. Campion EW., *et al*. "Asymptomatic hyperuricaemia. Risks and consequences in the normative aging study". *The American Journal of Medicine* 82 (1987): 421-426.
14. Nicholls A., *et al*. "Effect of oestrogen therapy on plasma and urinary levels of uric acid". *British Medical Journal* (1973): 449-451.

15. Wortmann Rober L and Kelley William N. "Kelly's Textbook of Rheumatology 7th edition". Volume II. Pennsylvania: Elsevier Saunders (2005): 1402-1426.

16. Jason D Wright MD and Anil B Pinto MD. "Clinical manifestation and treatment of gout". *Primary Care Up-date Ob/Gyns* 10 (2013): 9-23.

17. Lawrence RC., *et al*. "Estimates of the prevalence of arthritis and selected musculoskeletal disorders in the United States". *Arthritis and Rheumatology* 41 (1998): 778-799.

18. Schmitz Paul G and Martin Kewin J. "Internal Medicine just the facts". Mc Graw Hill Medical Library of congress cataloging in Data (2008): 733-738.

19. Ledingham JGG and Warrell DA. "Concise oxford textbook of medicine". Oxford University Press, (1985): 970-975.

20. Henry John Bernard. "Clinical Diagnosis and Management by Laboratory Methods". 17th edition. Philadelphia: W.B. Saunders Company (2003): 136-139.

21. Luk Andrew J and Simkin Peter A. "Epidemiology of hyperuricemia and Gout (Reports)". *The American Journal of Managed Care* (2005): 435-442.

22. Agarwal AK. "Medicine Update. part II". A Publication of the Association of Physician of India (2009). 984-991.

23. Saag Kenneth G and Choi Hyon. "Review Epidemiology, risk factors, and lifestyle modification for gout". *Arthritis Research and Therapy* 8.1 (2006): S2:1-7.

24. David Carol., *et al*. "Rheumatological Physiotherapy". Philadelphia: Mosby International Ltd 24 (1999): 161-163.

25. Dadig Bonnie., *et al*. "Gout A Clinical Overview". *Clinician Reviews* 21 (2011): 7-29.

26. Souhami RL and Moxham J. "Textbook of Medicine 3rd edition". Churchill: Livingstone Library of Congress Cataloguing in Publication Data (1997): 949-953.

27. Golwalla Aspi F and Golwalla Sharukh A. "Medicine for Students 22nd edition". *Neel Graphics* (2008): 1048-1054.

28. Chilvers Edwin R., *et al*. "Davidson's Principles and Practice of Medicine 19th edition". Churchill Livingstone (2002): 1013-1016.

29. Arellano Felix and Sacristan Jose A. "Allopurinol Hypersensitivity Syndrome: A Review". *The Annals of Pharmacotherapy* 27 (1993): 337-343.

30. Gomes., *et al*. "Desensitization to Allopurinol in localized and Systemic Hypersensitivity Reactions". *Journal of Allergy Disorders and Therapy* 4 (2013): 138.

31. A Kopke A and Greeff OBW. "Hyperuricaemia and Gout: Review". *South African Family Practice* 57.1 (2015): 6-12.

32. Min HK., *et al*. "Allopurinol hypersensitivity syndrome in patients with hematological malignancies: characteristics and clinical outcomes". *The Korean Journal of Internal Medicine* 30.4 (2015): 521-530.

33. Akram Mohd., *et al*. "Comprehensive review on therapeutic strategies of gouty arthritis". *Pakistan Journal of Pharmaceutical Sciences* 27.5 (2014): 1575-1582.

34. Warner EC. "Savill's system of Clinical Medicine" 14th edition: India (1964): 417.

35. Majusi Ali Bin Abbas. "Kamilus Sana (Urdu Translation by Hakeem Ghulam Hussain Kintoori) Vol- II. New Delhi: Idara Kitabu sh Shifa (2010): 507-514.

36. Maddison PJ., *et al*. "Oxford Textbook of Rheumatology Vol- II". London: Oxford University Press (1993): 983-988.

37. Khan Hakim Waliullah. "Ghina Muna Ma Tarjuma-e-Minhajul Ilaj" (Original author Abu Mansoor-ul-Hasan Bin Nooh Qamri). YNM. 276-284.

38. Rhazi Abu Bakr Mohd Bin Zakariya. Kitabul Hawi (Urdu Translation) Volume XI. New Delhi: CCRUM, Ministry of Health and Family Welfare (2004): 75-171.

39. Rhazi Abu Bakr Mohd Bin Zakariya. "Kitabul al Mansoori (Urdu Translation). New Delhi: CCRUM Ministry of Health and Family Welfare, Government of India (1991): 136.

40. Looqa, Qusta bin. "Risala Fi Auja Al-Niqris (Urdu Translation by prof Hkm Syed Zillur Rehman)". Aligarh: Ibn Sin Academy, Dodhpur (2007): 68-137.

41. Nuki George and Simkin Peter A. "Review A Concise History of Gout and Hyperuricemia and Their Treatment". *Arthritis Research and Therapy* 8.1 (2006).

42. Pillinger MH., *et al*. "Hyperuricemia and gout: new insights into pathogenesis and treatment". *Bulletin of the Hospital for Joint Diseases* 65.3 (2007): 215-221.

43. Omole OB and Ogunbanjo GA. "The evolution of gout (an old lifestyle disease)". *South African Family Practice* 51.5 (2009): 396-398.

44. Fourtunas Costas. "Perceptions of gout (podagra) during the Byzantine era, with a special focus on a poem by Michael Psellus". *Journal of Nephrology* 26.22 (2013): S110-S112.

45. Sina Ibn. Alqanoon fit Tibb (Urdu Translation by Hakeem Ghulam Husain Kintoori) New Delhi: Idara kitab us shifa, YNM 3: 1121-1123.

46. Tripathi KD. "Essentials of Medical Pharmacology 7th edition (Reprint)". JP Brothers Medical Publishers (2014): 214-217.

Volume 6 Issue 7 July 2020