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A PROSPECTIVE MULTICENTRIC COHORT STUDY TO EVALUATE THE TOLERANCE OF COLCHICINE IN PATIENTS OF CRYSTAL ARTHRITIS

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ABSTRACT **Introduction:** Colchicine is approved therapy for management of acute crystal arthritis and secondary prevention of arthritis episodes. There is paucity of studies from India to establish tolerance colchicine for long term. Hence, this study was carried to study the tolerance of colchicine over 6 months or more. **Materials and Methods:** This study was conducted from 1 January 2016 to 31 December 2018 and in 5 centres across India. In this study, 174 patients were recruited who were on tablet colchicine 0.5mg twice daily for at least 6 months. Patients were observed for development of adverse effects and intolerance. **Results:** Out of the 174 recruited patients, the adverse effects were noted in 7.4% (n=13). Most common adverse effect was diarrhoea followed by abdominal pain, nausea, vomiting, constipation, and elevated creatine kinase levels. **Conclusion**: Our study shows that tablet colchicine is a well tolerated drug in the management of crystal arthritis for long term prophylaxis.

KEYWORDS : : Colchicine, Adverse effects, Diarrhea

INTRODUCTION:

Crystal arthritis is a common condition seen in clinical practice. Gout, calcium pyrophosphate deposition disease (CPPD/ pseudogout), calcium oxalate deposition disease and basic calcium phosphate deposition disease are among the common forms of crystal arthritis. Gout is most common crystal arthritis, the prevalence of gout worldwide ranges from 0.1% to 10% [1]. In the United States, it is the most common inflammatory arthritis [2].

The joint inflammation of gout or CPPD related crystal arthritis has either monosodium urate (MSU) or CPPD crystals in the joint cavity [3]. The deposition of these crystals triggers an immune response with release of inflammatory cytokines and neutrophil recruitment [4]. As time progresses, there is irreversible damage in the joint space which leads to chronic pain, disability, and deformed joints [2].

Colchicine has been used to treat various ailments for thousands of years. However, it was first described as a treatment of pain and swelling in 1550 BC by the Papyrus of Egypt [5]. It is an alkaloid extracted from plants of the genus Colchicum (autumn crocus) [3]. Today, colchicines is widely used for treatment and prophylaxis of acute gout flares and other crystal arthritis. In addition to its commonly

known uses colchicines have potential benefits in wide range of other conditions like periodic fever syndromes, osteoarthritis , pericarditis and non healing ulcers because of its anti-inflammatory effect.

It is a well known fact that, colchicine reduces adverse cardiovascular outcomes in patients with established cardiovascular disease[8] As gout patients have an increased risk of cardiovascular events because of the underlying hyperuricemia[9] and it is likely that geriatric patients with gout would also have cardiovascular comorbidities, colchicine may be doubly beneficial for them.

There are various ways in which colchicine exerts its actions. Primarily, colchicine binds to free tubulin dimers which can block subsequent microtubule polymerization [8]. Colchicine also inhibits neutrophil adhesion, extravasation and recruitment by altering neutrophil L-selectin expression and endothelial cell E-selectin distribution, thereby suppressing release of the chemotactic agent leukotriene B4 [9], as well as altering neutrophil deformability [10]. In addition, colchicine modulates leucocyte mediated inflammatory activities by inhibiting production of superoxides and release of various cytokines and pyrogens [10,11].

The absorption of Colchicine is variable. Peak plasma concentrations occur 0.5 to 2 hours after dosing, and in plasma 50% of colchicine is protein-bound [13]. Colchicine is partially deacetylated in the liver and large amounts of colchicine and of its metabolites undergo enterohepatic circulation [14]. After a single 2 mg intravenous dose the average plasma half life is 20 minutes; Plasma half-life is increased in severe renal disease (40 min) and decreased in severe hepatic disease (9 min) [14]. Colchicine is primarily eliminated from the body via transport by P-glycoprotein which is expressed in hepatocytes (biliary excretion), proximal renal tubules (renal excretion), enteric cells (gut excretion), monocytes and cells of the bloodbrain barrier [15].

Colchicine is considered as a toxic drug due to its narrow therapeutic window, with reported fatalities with single doses as low as 7 mg [16]C. Although generally well tolerated but, fatalities have been reported in patients with chronic renal insufficiency taking unadjusted doses of colchicine [17-18]. The commonest side-effects are gastrointestinal, including diarrhoea, vomiting and nausea, which may occur in > 20% of colchicine users. Gastrointestinal toxicity is dose dependent and may improve by lowering the colchicine dose. Rarer acute adverse effects include myopathy, rhabdomyolysis and myelosuppression [19]. In patients of renal disease, chronic daily use of unadjusted doses, may lead to colchicine neuromyopathy [20-21]. Symptoms of colchicine toxicity usually resolve within 1 week to several months of discontinuing the drug.

There is a paucity of literature from India, on adverse effect profile of colchicine when used for secondary prevention of crystal arthritis over long durations. Hence, we planned a multicentric cohort study to look for the same.

METHODOLOGY:

This was a prospective multi centric cohort study done in the Northern, Eastern, Western, and Southern parts of India. Patients were recruited from different medical institutions situated in Kolkata, New Delhi, Jaipur, Pune, and Kochi. The study was done over a period of 2 years, from 1st January 2016 to 31st December 2018. We included the adult patients with crystal arthritis receiving colchicine therapy for at least 6 months. Patients receiving colchicine for conditions other than crystal arthritis and those with previous history of colchicine intolerance were excluded from the study. Before starting the therapy, the patients were informed about the possible adverse effects of the drug, and were also asked to report in case of any adverse event. Informed consent was taken from all the study subjects. After a follow up of 6 months, inquiry was made about the patient's tolerability of colchicine and occurrence of any adverse drug reactions. A descriptive report was then made about the adverse events reported from the various study centres.

RESULTS:

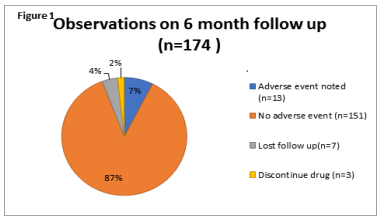
A total of 174 patients were recruited from five centres across India. Out of this, 129 patients were male and 45 patients were female. Patients recruited were between the ages of 20 and 80 years. The mean age was 53 years. The descriptive results of each centre are shown in Table-1.

Table 1– Study results

Location	Number of patients	Number of Adverse events	Descriptive report
Kolkata	90	7	7 patients had adverse event 3 developed diarrhea 1 had colicky abdominal pain 1 had vomiting 1 had constipation
New Delhi	15	1	1 patient had adverse event 1 patient developed nausea
Pune	25	1	1 patient had adverse event 1 patient developed diarrhea
Jaipur	15	1	1 patient had adverse event 1 patient developed nausea
Kochi	29	3	3 patients had adverse events 1 patient had abdominal pain 1 patient developed diarrhea 1 patient had creatine kinase elevation
Total	174	13	Total Loss of follow up = 7 patients

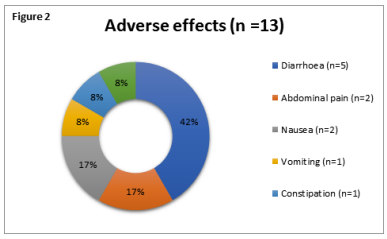
Out of the total 174patients recruited, only 7.4% (n=13) developed adverse events after starting the drug and only 1.74% (n=3) patients had to discontinue the medication due to intolerance. Also, 4.02% (n=7) of patients were lost to follow up and 2.29% (n=4) patients stopped the drug on their own (Figure 1).

Figure 1



The most common adverse events observed were gastrointestinal (figure 2). Diarrhea (n=5, 2.8%) was the most common adverse event followed by abdominal pain (n=2, 1.1%), nausea (n=2, 1.1%); vomiting (n=1, 0.5%); constipation (n=1, 0.5%); and raised creatine kinase level (n=1, 0.5%). Other side effects (neuromyopathy, rhabdomyolysis, and myelosuppression) were not reported and there was no mortality in our study.

Figure 2



DISCUSSION:

Our study was conducted at 5 centres in diverse geographical locations of India. We evaluated how well the crystal arthritis patients tolerated long term prophylaxis therapy with colchicine. Our study, included patients who had completed at least 6 months of treatment, hence it was possible to note both the short and long term side effects of the drug. Till date, no multi centric study in India has assessed the adverse effects of colchicines treatment over a long period of time in patients with crystal arthritis.

A total number of 174 patients were recruited for the study with an approximate gender ratio of 5:1 (male:female), which mirrors the natural preponderance of crystal arthritis in males. The results showed excellent tolerability of colchicine in most of our patients. Few patients developed adverse events (n=13,7.4%) of therapy and even fewer stopped the medications (n=3, 1.74%), due to these adverse events. The most common adverse events observed were gastrointestinal (figure 1)

In a study by Terkeltaub et al. of 575 patients showed that patients on low dose colchicine (n=74) therapy experienced very mild gastrointestinal adverse effects (36.5%) which was comparable to the placebo group. Whereas, amongst the high dose group (n=52) a larger

number (76.9%) of patients reported gastrointestinal adverse effects. Furthermore, the high dose group reported severe side effects (n=10, 19.2%) which were not reported in the low dose or placebo groups [22]. In an Indian study done in 186 patients of crystal arthritis, looking at adverse reactions of low dose colchicine therapy of 5 days to 3 months, it was found that adverse events were only mild gastrointestinal problems (n=7, 3.7%) [23]. Paulus et. al conducted a study of colchicines use in 64 patients of crystal arthritis and the adverse effects were mainly gastrointestinal and mild (n=5, 2.3%) [24].

Our study results are in concordance to the studies mentioned above. Only mild gastrointestinal symptoms were noted and diarrhoea followed by abdominal pain, nausea and vomiting were common manifestations. But, these studies were done in the subjects receiving colchicines for duration lesser than 6 months. Hence, long term tolerability was not established.

The effectiveness of low dose colchicine for 6 months in reducing gout flares is more than that taken for a 3 month period, according to the study conducted by Borstad et al. [25]

Analysis of the results from these studies along with other assessments helped to create guidelines for acute gout flares and prophylaxis. As the EULAR guidelines permit the use of colchicine in the first 12 hours of a gouty flare, colchicine should be used as the first line prophylaxis for the first 6 months of urate lowering therapy in dosage of 0.5-1mg per day [26]. The use of colchicine in elderly and in patients with cardiovascular risk has an added cardio-protective effect that mandates its use in crystal arthritis.

CONCLUSION:

Contrary to the common belief that colchicine is a very toxic drug, our study found that among patients with crystal arthritis, colchicine at a dose of 0.5 mg twice daily was well tolerated with few adverse effects mainly gastrointestinal. Hence, we conclude that colchicine therapy is well tolerated, and can be safely given for long term secondary prevention of crystal arthritis.

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