Original Research Article

Estimation of interleukin 1β levels in acute gout patients before and after colchicine

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Abstract

Gout is a debilitating condition that affects millions across the world. In gout, hyperuricemia results in the deposition of monosodium urate monohydrate crystals in joints and soft tissues. IL-1β, an interleukin has been shown to be the most prominent inflammatory marker in the pathogenesis of gout. This study was conducted to assess the IL-1β lowering effect of oral colchicine in gout patients. Forty gout patients were randomly divided into 2 groups and one group was treated with oral colchicine while the other group was treated with NSAIDs for a period of 2 months. Their serum IL-1β levels were estimated before and after treatment. Baseline demographics were similar between the groups. It was found that IL-1β levels in the colchicine group were significantly lower than the IL-1β levels of the NSAID group. They also had better symptomatic relief. This study concluded that serum IL-1β was elevated in gout patients and colchicine was effective in lowering it.

Key words

Gout, IL1-β, Colchicine, NSAIDS.

Introduction

Hyperuricemia may result in the deposition of monosodium urate monohydrate (MSU) crystals in joints and soft tissues. When shed from deposits or precipitated de novo, acute inflammation may result [1]. Although gouty arthritis was first recognized more than 4,500 years ago [2], the pathogenic mechanisms are still not fully characterized. For most patients, therapy with non-steroidal anti-inflammatory drugs (NSAIDs) or corticosteroids for acute episodes and prevention of recurrence with agents that lower the serum uric acid levels are highly effective. MSU crystals induce a variety of inflammatory cytokines and chemokines including Tumor Necrosis Factor-α (TNF α), Interleukin 1β (IL-1β), IL-6, CXCL8 (IL-8), and CXCL1 (growth-related oncogene) [3-6]. Recently reported observations identify IL-1β as the pivotal cytokine in gouty inflammation and provide new insights into the role of a molecular complex called the inflammasome in the release of IL-1β by MSU crystals [7-10]. An agent that decreases the levels of IL-1β can be expected to bring therapeutic relief to patients suffering from gout. Oral colchicine has been used for the treatment of gout. An assay of IL-1β levels before and after colchicine therapy will give us a mark of the efficacy of colchicine treatment and help benchmark it against other anti-gout medications.

Aim of the study

To study the effects of oral colchicine therapy on IL-1β levels in gout patients.

Materials and methods

The study was conducted in the Institute of Rheumatology, Madras Medical College in Chennai. It was a randomized prospective interventional study. Randomization was computer generated. The study was conducted for a period of six months from August 2018 to February 2019. The subjects for the study were selected from the gout patients attending the Rheumatology outpatient department (OPD) at the Institute.

Inclusion criteria

- All patients diagnosed under 2015 ACR-EULAR classification for acute gout were included in the study.

Exclusion criteria

- Patients with chronic gout / acute on chronic gout
- Patients aged <30 and >60 years
- Patients with active infections
- Critically ill patients
- Patients having neoplasms, chronic kidney disease and any other cause of secondary gout
- Patients with contraindications to NSAIDS.

After obtaining Institutional ethical committee approval, forty patients were selected after screening with the above mentioned criteria (**Figure - 1**). Written and informed consent was obtained from all the participants of the trial. Twenty healthy age and sex matched controls were recruited for the study. The forty patients were randomized into 2 groups (computer generated randomization). A detailed history was obtained and a meticulous clinical examination was done for all patients. Pertinent lab investigations like Complete blood count, fasting blood sugar, lipid profile, CRP, ESR, urea, creatinine, Serum uric acid, 24 hours urine uric acid, ultrasound abdomen were done in all cases. Serum IL-1β levels were assayed using ELISA for all the forty patients and twenty healthy controls to provide a baseline (**Table - 1**). Group 1 was treated with colchicines and group 2 was treated with NSAIDS. The dose of oral colchicine was 1g stat followed by 0.5mg after 6 hours and subsequently treated with 0.5 mg twice daily. Patients in group 1 received paracetamol for pain control. Patients in group 2 received indomethacin 50 mg thrice daily till the acute attack settled and were followed with 25mg twice daily. Both the treatments were continued for 2 months. The patients were monitored regularly once in 15 days during this time in the OPD and were thoroughly examined. After 2 months, all the patients had a repeat of their lab investigations including IL-1β. Details of

compliance, adverse events and symptomatic relief were recorded meticulously to be analyzed later. The results were analyzed with the help of SPSS 21 software. Unpaired Student 'T' test was used to test statistical significance between the two groups and controls. Paired Student 'T' test was used to test statistical significance between pre and post treatment values in each group. The *p* value of <0.05 was taken as significant.

Figure – 1: Flowchart showing study design.

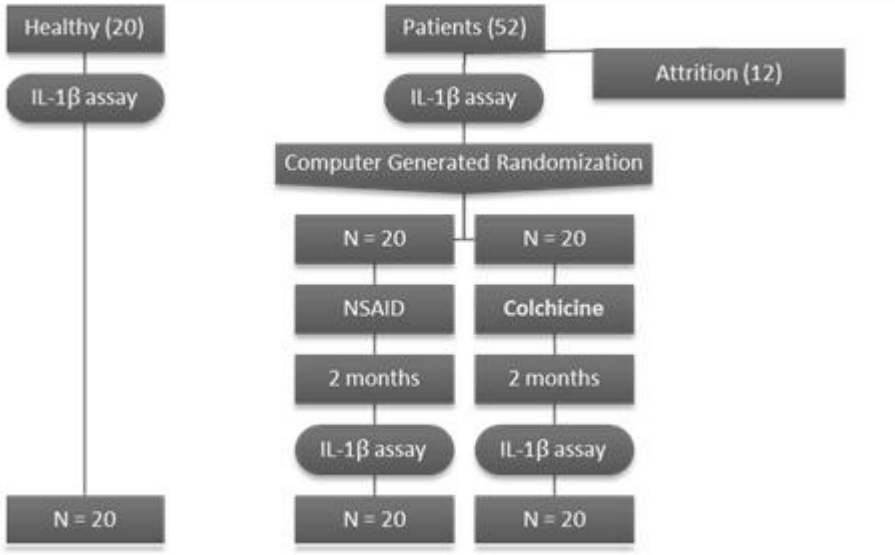


Table – 1: Baseline parameters.

Parameters	Healthy group (N=20)	Colchicine group (N=20)	NSAID group (N=20)	P value
Age (yrs)	49.85	42.35	40.91	NA
BMI (kg/m^2)	23.12	23.97	24.59	0.7439
FBS (mg/dL)	87.46	89.95	93.65	0.3250
Total cholesterol (mg/dL)	110.38	205.45	160.41	0.6320
HDL (mg/dL)	44.8	42.4	40.26	0.5395
TGL (mg/dL)	90.26	141.55	137.71	0.0917
CRP (mg/L)	**2.1**	**10.50**	**14.4**	**0.3922**
ESR (mm/hr)	**11.8**	**23.00**	**29**	**0.2280**
Urea (mg/dL)	32.34	29.45	33.51	0.5930
Creatinine (mg/dL)	0.9	0.912	1.214	0.3160
Serum uric acid (mg/dL)	**4.2**	**9.2**	**9.826**	**0.3324**
IL-1β (pg/mL)	**2.775± 0.7**	**132.75± 36.2**	**127.25± 32.8**	**0.8406**

Results

At the onset there were 52 patients who met the inclusion criteria. Before randomization, 12 patients were dropped due to various reasons. 20 gout patients were recruited in the colchicine group and 20 in the NSAID group. There was no statistically significant difference in the demographic parameters between cases and controls.

The mean serum IL-1β level in the healthy controls was 2.775± 0.7 pg/ml. The mean serum

IL-1β level in the colchicine group was 132.75± 36.2 pg/ml, before the commencement of the trial. The mean serum IL-1β level in the NSAID group was 127.25 ± 32.8 pg/ml, before the commencement of the trial. The mean serum IL-1β levels in colchicines group were significantly higher than that of healthy controls ($p < 0.001$). Similarly, there was a significantly higher IL-1β levels in NSAID group as compared to controls ($p < 0.01$) (**Figure – 2, 3**). At baseline, the serum IL-1β levels in both colchicines and NSAID groups were similar (p 0.846).

Table – 2: Comparison of parameters between colchicine group and NSAID group after treatment.

Parameters	Colchicine Group After Treatment (N=20)	NSAID Group After Treatment (N=20)	P value Paired Data
Age (yrs)	42.35	40.91	NA
CRP (mg/L)	5.4	10.21	**0.0123**
ESR (mm/hr)	12.8	24.2	**0.0030**
Serum uric acid (mg/dL)	8.9	9.71	0.0880
IL-1β (pg/mL)	**39.225±12.5**	**94.375± 22.5**	**0.0012**

Figure - 2: Serum IL-1β levels in healthy and NSAID groups.

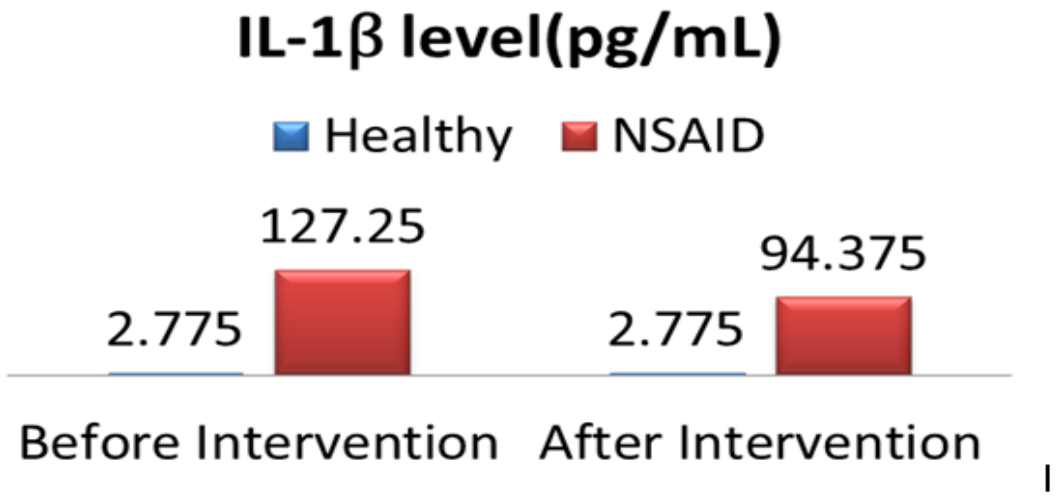


Figure – 3: Serum IL-1β levels in healthy and colchicine groups.

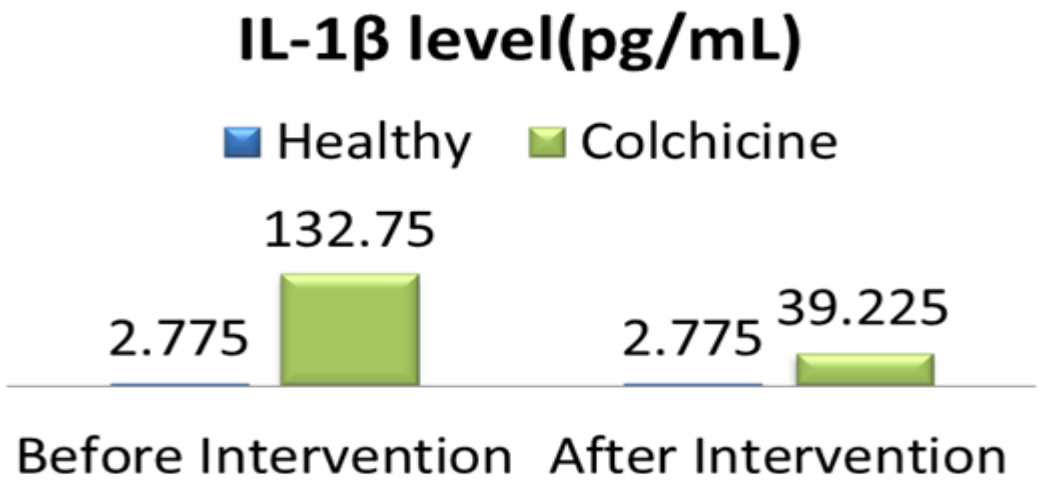
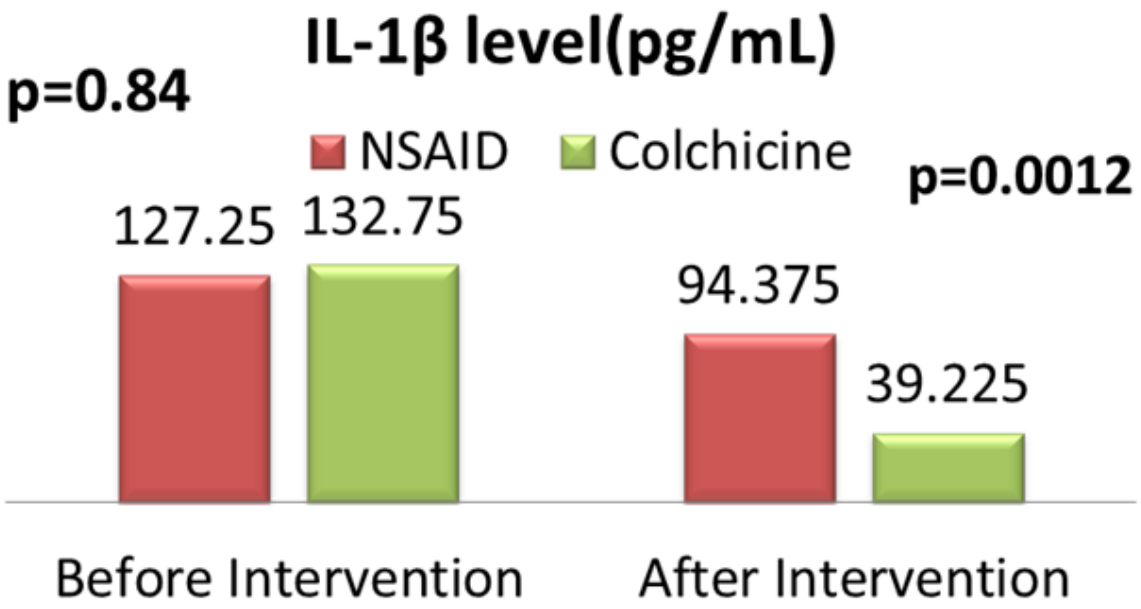


Figure – 4: Serum IL-1β levels in NSAID and colchicine groups.



The mean serum IL-1β level in the colchicine group dropped to 39.225±12.5 pg/ml, after the conclusion of the trial. The mean serum IL-1β level in the NSAID group dropped to 94.375 ± 22.5 pg/ml, after the conclusion of the trial (**Table - 2**). There was a significant difference in the post intervention serum IL-1β levels in both colchicine and NSAID groups (p 0.0012) with a greater fall in colchicine group.

Colchicine was able to significantly lower the serum IL-1β levels from 132.75± 36.2 pg/ml to 39.225±12.5 pg/ml (p 0.0003). Although this was still higher than the level in healthy controls, this represented a significant reduction. NSAIDs were able to lower the serum IL-1β levels from 127.25± 32.8pg/ml to 94.375± 22.5 pg/ml. The end point attained in the NSAID group was significantly higher than the end point achieved by oral colchicine (p 0.0012) (**Figure - 4**).

Both colchicine and NSAID were well tolerated by the patients with no reports of serious adverse events or inability to comply with the treatment regimen.

The patients in both the groups showed improvement in their symptoms (pain and swelling of joints) and this was subjectively more evident in the colchicine group.

Discussion

There are limited studies on the effects of colchicines on IL1β levels.

Role of IL-1β

IL-1β plays a pivotal role in the pathogenesis of gout. Monocytes that encounter MSU crystals express and release cytokines, including IL-1β, TNF α and IL-6, and the neutrophil chemokine CXCL8 [3-6]. Since TNF appears to be upstream of IL-1β in rheumatoid arthritis, studies were performed to determine whether TNF α was responsible for the crystal-induced release of IL-1β. Studies revealed that the effects of MSU crystals were independent of TNF α, since IL-1β was released prior to TNF α and inhibition of IL-1 with IL-1R antagonist suppressed the expression of TNF α [9]. Therefore, studies were performed to determine whether MSU crystals were capable of activating the NALP3 inflammasome. The initial studies, which used a monocytic cell line or peripheral blood monocytes from normal volunteers, demonstrated that MSU crystals cleaved proIL-1 beta and released the active 17-kd molecule from

the cells [9]. Further, an *in vivo* mouse model of gout, crystal-induced peritonitis, also demonstrated that caspase 1 and ASC were critical, since mice deficient in either of these molecules developed significantly reduced MSU crystal–induced inflammation. These observations demonstrate that each of the components of the NALP3 inflammasome is required for the processing of pro IL-1β and the induction of crystal-induced inflammation.

Role of colchicine

Since MSU crystals induced the processing of pro IL-1β, experiments were performed to examine the effect of colchicine on the NALP3 inflammasome. Colchicine was highly effective at preventing the MSU- or CPPD-induced processing of proIL-1β and the release of IL-1β [9]. Therefore, colchicine is capable of preventing the crystal-induced activation of the inflammasome and the release of IL-1β, although the concentration employed was greater than that which was effective prophylactically, suggesting an alternative mechanism for the effectiveness of colchicine at preventing an attack of gout. Low-dose colchicine has also been shown to decrease the adhesion of neutrophils to endothelial cells by altering the distribution of adhesion molecules on endothelial cells. The mechanism by which colchicine prevents crystal-induced activation of the inflammasome is not known. It is possible that the ability of colchicine to inhibit microtubules may somehow prevent the crystals from entering the cell, possibly by interfering with the complement membrane attack complex or CD14, or possibly by preventing the crystals from interacting with NALP3 through the LRR domain.

Future therapeutic possibilities

The possible effectiveness of IL-1 inhibition was recently evaluated in a mouse model of MSU-induced inflammation. Inhibition of IL-1 by anakinra prevented MSU-induced peritoneal neutrophil accumulation, while TNFα blockade was not effective. Together, these observations suggest that IL-1 and the inflammasome may be promising therapeutic targets in patients with gout, particularly in those patients with chronic polyarticular disease for whom NSAIDs or corticosteroids are contraindicated or too toxic. Our study proves that till the advent of novel agents, colchicine can be used safely in such patients.

Conclusion

Our study concludes unequivocally that IL-1β is elevated in gout patients. Oral colchicine was able to lower the levels of IL-1β in patients with gout, with much better efficacy than with NSAIDs alone. It was well tolerated. Hence, we suggest that colchicines may be considered as a poor man's IL1β antagonist.

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