Allopurinol in Inflammatory Arthritis (probably Gout): Indian Perspective in Light of EULAR Recommendations

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Abstract: Introduction-Hyperuricemia (solubility point of Mono Sodium Urate Crystal i.e. 7.1 mg/dl) is associated with gout and present in 0.2 to 2% of Indian population. EULAR has published the guidelines for the diagnosis of gout based on evidences. In this study, we tried to evaluate clinical correlation of arthralgia with serum uric acid level in Indian patients and benefit from Allopurinol treatment. Material and Methods-Study design - Prospective, open labeled single arm Study carried out in Hospital attached to Medical University. Exclusion Criteria were Patients having definitive diagnosis for the etiology of arthralgia or Definitive Gout by clinical diagnosis as per EULAR recommendation. Inclusion criteria were Patients having the history of use of analgesic with persistent symptoms, having less than 4 EULAR criteria for gout and willing to be enrolled in the study. Intervention - Allopurinol 100 mg twice a day was given to patients and clinically assessed on day 1, day 10 and at 4 week. Results – In elderly age group incidence is same in both sexes. Purine rich diet increases the risk five times with more risk of precipitation of symptoms at lower level of uric acid. Most common site of presentation was knee pain i.e. 50%. Serum Uric acid at enrollment was 6.76±0.99 that reduced to 3.74±0.63 at four week with dissolving of symptoms. Conclusion–There is a subset of Gout in elderly Indians, which is more prone to precipitation of symptoms at lower level of serum uric acid and equal gender distribution. Hyperuricemia in patients may be defined on 5.0 mg\% and target level should be kept less than 4.0 mg in Indians. Key words: Gout, Indian, EULAR, Allopurinol.

Introduction
Theoretically hyperuricemia is defined as solubility point of Mono Sodium Urate Crystal i.e. 7.1 mg/dl however practically it is defined as more than 2 SD of mean level in population. Although hyperuricemia is not an indication of therapy it is associated with gout and nephrolithitis and present in 0.2 to 2% of Indian population. Level of uric acid more than 6.5 mg/dL is associated with obesity, diabetes, and increased cardiovascular risk.

19% of the people who have increased serum uric acid are suffering from gout. Risk factors associated with gout are purine rich food, alcohol, and over weight. Incidence of gout is correlated positively with serum uric concentration especially with uric acid more than 8.0 mg/dL. In general practice gouty arthritis is more common than rheumatoid arthritis. Man has up to 9 times more risk than woman due to protective effect of estrogen in women. EULAR has published the guidelines for the diagnosis of gout based on evidences.

For diagnosis of gout the best time to do serum uric acid level is 2 weeks after the attacks when acute symptoms subside. In this study, we tried to evaluate clinical correlation of arthralgia with serum uric acid level in Indian patients and benefit from Allopurinol treatment.

Material and Methods-
Study design - This Prospective, open labeled single arm Study was carried out during 1st July 2007 to 30 May 2012 in Department of Orthopedic in Hospital attached to medical University, Kolhapur.

Exclusion Criteria were
1. Patients having definitive diagnosis for the etiology of arthralgia
2. Definitive Gout by clinical diagnosis as per EULAR recommendation i.e. 4 out 7 criteria were present

Inclusion criteria were
1. Patients having the history of use of analgesic with persistent symptoms
2. Having less than 4 EULAR criteria for gout
3. Willing to be enrolled in the study.

Intervention - Allopurinol 100 mg twice a day was given to patients and clinically assessed on day 1, day 10 and at 4 week.
at 4 week to record the pain score with the help of 5-point Linkert scale by patient. Joint swelling, tenderness and Erythema were assessed by physicians on the same scale. Serum uric acid level was repeated at 4 week.

**Sample size:** 28 patients were included in the study and followed up.

**Results-** Their demographic data were as follows:

**Gender ratio** –Male were slightly more than female but difference were non-significant. (Refer Figure 1) (p >0.05)

**Age (years)**
Age of all patients were 45.89±14.00 years while Male were 46.6±16.32 years and Female were of 45.08±11.38 years. (Refer Figure 2)

**Dietary habits**
Nonvegetarian i.e. purine rich diet were present in 82% of patients with frequency of 2 to 5 times per week. (Refer Figure 3)

**Presenting symptoms:**
Lower extremities involvement was the commonest presentation, accounted for 68% of patients. 50% of patients were having knee pain either unilateral or bilateral. Upper extremities was involved in 7% while 18% patients were presented with multiple joint pain i.e. more than 5 joints were involved. (Refer Figure 4)

**Serum uric acid:**
Serum uric acid was 6.76±0.99 at enrollment in all patients but male have higher level of SUA (7.23±0.78) as compare to female (6.22±0.95). Difference in mean SUA was also seen in Non-vegetarian (6.62±0.96) as well as vegetarians (7.4±0.97). SUA was classified into different subclass i.e. 5–, 6–, 7– 8-mg%. There representation was as follows: (Refer Figure 5)

It is seen that 75% patients were having hyperuricemia (uric acid 6.0 mg% or more) as per newer cut off point.

**Presence of EULAR criteria’s for clinical diagnosis**–
EULAR has recommended the criteria’s for clinical diagnosis of Gout as per the diagnostic ladder. They are as follows in increasing order –
1. Rapid pain and swelling
2. Erythema
3. Podegra
4. Hyperuricemia more than 6 mg%
5. Definitive tophi
6. X-ray
7. MSU crystals in joint fluid aspirate

For clinical diagnosis probability is 82.29% if first 3 criteria are fulfilled which increases to 99% if hyperuricemia is also present.

In this study, Pain, swelling and erythema was present in all the patients while podygra was present in none. On the basis of above presenting symptoms and taking cut off point of 6.0 mg%, only 75% patients were fulfilling 3 out of 7 criteria while remaining 25% were having 2 criteria’s with uric acid between 5.0 to 6.0 mg%. An MSU crystal in joint aspiration fluid was not done due to non feasibility in given set up. (Refer Figure 6)

### Table 1: Improvement in Pain score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>On enrollment (Day 1)</th>
<th>1st follow up (Day 10)</th>
<th>2nd follow up (4 week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain as per Linkert Scale (score)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (0)</td>
<td>0 (0.00%)</td>
<td>19 (67.86%)</td>
<td>28 (100%)</td>
</tr>
<tr>
<td>Mild (1)</td>
<td>1 (3.57%)</td>
<td>8 (28.57%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>Moderate (2)</td>
<td>25 (89.29%)</td>
<td>1 (3.57%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>Severe (3)</td>
<td>2 (7.14%)</td>
<td>0 (0%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>Extreme (4)</td>
<td>0 (0.00%)</td>
<td>0 (0%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>Total score</td>
<td>57</td>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>Value of paired t test at t27 on the respective follow up as compared to previous visit</td>
<td>18.68, P&lt;0.001</td>
<td>3.38, P&lt;0.01</td>
<td></td>
</tr>
</tbody>
</table>

### Improvement in pain – It was the patient accessed criteria. Pain score was recorded on 5 point scale by the patient on day 1, day 10 and at 4 weeks. Pain score was 57 on day 1 that reduced to 10 on day 10 and 0 on 4 week. (Refer Table 1)

### Table 2: Improvement in tenderness

<table>
<thead>
<tr>
<th>Parameter</th>
<th>On enrollment (Day 1)</th>
<th>1st follow up (Day 10)</th>
<th>2nd follow up (4 week)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenderness as per Linkert Scale (score)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None 'no pain' (0)</td>
<td>0 (0.00%)</td>
<td>16 (57.14%)</td>
<td>27 (96.43%)</td>
</tr>
<tr>
<td>Mild 'pain' (1)</td>
<td>9 (32.14%)</td>
<td>4 (14.29%)</td>
<td>1 (3.57%)</td>
</tr>
<tr>
<td>Moderate 'pain and winces' (2)</td>
<td>17 (60.71%)</td>
<td>8 (28.57%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>Severe 'pain; winces and withdraws' (3)</td>
<td>2 (7.14%)</td>
<td>0 (0.00%)</td>
<td>0 (0.00%)</td>
</tr>
<tr>
<td>Total score</td>
<td>49</td>
<td>20</td>
<td>1</td>
</tr>
<tr>
<td>Value of paired t test at t27 on the respective follow up as compared to previous visit</td>
<td>7.91, P&lt;0.001</td>
<td>4.16, P&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

### Improvement in swelling:

Swelling was accessed by the doctor on 4 point scale as follows and scores were given. On day one score was 37 that reduced to 7 on first follow up and to 0 at 4 week. (Refer Table 3)
Uric acid was established in 1812 in patients having the pain in knee joint, while small joint were involved in only 18% of the patient. In contrast to pain in small joint, in this study half of the patients were having the pain in knee joint, while small joint were involved in only 18% of the patient.

In addition symptoms are seen at lower level of uric acid retention of uric acid is one of the important measure in reduction of joint pain. Improvement in serum uric acid has reduced significantly in all patients and was between 3.5 to 4.0 mg% on average at the end of four week.

Improvement in erythema – Presence of erythema was scored 28 on presentation which reduced to 23 on first follow up and to 4 on four week. (Refer Table 4)

Improvement in serum uric acid: serum uric acid has reduced significantly in all patients and was between 3.5 to 4.0 mg% on average at the end of four week. (Refer Table 5)

Discussion
In this study male and female were in equal ratio in contrast to male predominance in Gout. It may be due to loss of protective effect of estrogen in female because the patient age group was similar in both male and female and female were of postmenopausal group. In this age group, there is age related increase in other metabolic disease like diabetes, hyperlipidemia and hypertension which independently increase the retention of uric acid.

5 times more incidence in non vegetarian points to importance of purine rich diet as important associated factor in joint pain and reduction in purine intake may be one of the important measure in reduction of joint pain. In addition symptoms are seen at lower level of uric acid in non vegetarian as compare to vegetarian. It again may be correlate the increase sensitivity to precipitation of symptoms in non vegetarians.

In contrast to pain in small joint, in this study half of the patients were having the pain in knee joint, while small joint were involved in only 18% of the patient.

Only 75% patients were having the hyperuricemia i.e. SUA more than 6.0 mg% while remaining have the uric acid between 5.0 to 6.0 mg%. Concentration of serum uric acid becomes more important in light of EULAR recommendation for diagnosis of gout. In our study group, Patients were not fulfilling the EULAR criteria for gout. 75% patients were satisfying 3 criteria while 25% were satisfying only 2 i.e. pain, swelling and erythema.

In our case, if cut off point be made at 5.0 mg% than all patient may satisfy at least 3 criteria of EULAR recommendation and goal of treatment may be kept at around 4.0 mg%. Shrivastava and Gaur also has recommended the treatment of hyperuricemia if more than 5.0 mg% and found most of the symptomatic patients had SUA between 5.0 to 6.0 mg%.

In one study association between MSU crystals in synovial fluid and serum uric acid was established concluding median SUA acid level less than 5.85 for absence of MSU in synovial fluid. Many authors recommend keeping the uric acid level below 6.0 mg% in symptomatic patients.
than 6 have 6 times less risk of acute attack and have better prognosis\textsuperscript{32}.

Patients were treated empirically with Allopurinol and benefited which may point out the separate entity of gout in Indian perspective. Indians are different genetically in predisposition and prognosis of many diseases including diabetes. That leads to different diagnostic criteria’s in Indian population.

As SUA is positively correlated with cardiovascular risk factors, it needs to be addressed with special care. Urate Lowering Therapy is associated with improved clinical outcome\textsuperscript{34} and reduced frequency of attacks\textsuperscript{35} and improvement in renal function\textsuperscript{36}.

Although EULAR has recommended the threshold to less than 6 mg\%\textsuperscript{14}, it is an arbitrary level. There are studies with evidences that lower the SU better the outcome\textsuperscript{32, 37}. Tophi are also dissolved with greater velocity and completely when SU was less than 4 mg\%\textsuperscript{37-38}. There was suggestion to reduce SU less than 5 mg\% to deplete urate stores and to prevent further attack\textsuperscript{39}. There is a question to determine which one to be followed static cutoff level (predefined level of Uric acid in mg \%) or continuous cut off level (lower the better) as is the case with lipid levels in blood\textsuperscript{40}.

Conclusion

Indian patients are more prone to inflammatory arthritis probably gout if 3 out of 7 criteria of EULAR recommendation is used for diagnosis with cut off level of serum uric acid 5.0 mg\% in inter critical period. These criteria are more important in elderly patients (including post menopausal women), where the incidence of gout is similar in both male and female.

References

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Running title – EULAR guidelines in Indian scenario.