*Original Paper*

# Assessment of the role of sulfasalazine in alteration of biological markers, sacro-iliac joint pathology and bath index of ankylosing spondylitis

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## Abstract

**To assess the role of sulfasalazine in alteration of biological markers, sacro-iliac joint pathology and BATH index of ankylosing spondylitis.**

**From February 2008 to July 2009.**

**Prospective randomised open level controlled trial.**

**Group 1- 16 patients received indomethacin and exercise.**

**Group 2- 16 patients received sulfasalazine in addition to above. Department of Physical Medicine & Rehabilitation, Institute of Post Graduate Medical Education &Research, Kolkata. ESR, CRP, Sacro-iliac test, radiological grading of SI joint, BATH index.**

**Data analysed by McNemar's chi-square test and Fisher's exact test showed no improvement in sacro-iliac test, SI joint involvement and CRP. But ESR was diminished significantly in group 2 according to Mann- Whitney test. Interestingly BASDAI and BASFI score was not improved according toWilcoxon's matched pairs signed rank test. Sulfasalazine is being used as disease modifiers in AS patient for long time. But this study showed that only ESR not CRP was improved with sulfasalzine. Interestingly sacro-iliac joint pathology, BATH indexes for disease activity and function (BASDI & BASFI) were not improved significantly with sulfasalzine. Sulfasalazine is effective to reduce ESR not CRP in patient with ankylosing spondylitis. It is not helpful to improve BATH index of disease activity and function.**


***key words*** **: Ankylosing spondylitis, sulfasalazine, CRP, ESR, BATH index.**


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Ankylosing spondylitis is an inflammatory disorder of unknown cause that primarily affects the axial skeleton; peripheral joints and extra-articular structures may also be involved. The disease usually occurs in the second or third decade with male preponderance. However, its prevalence in the young working group of people with the considerable contribution to socio-economic condition of country is one of important reasons of studying the disease.

It is well known that spinal and hip ankylosis often makes the patient completely disabled. This disability renders a threat to the economic condition of not only the patient and his or her family but also to the society in general[1,2]. The only hope to prevent this situation is early diagnosis, management and rehabilitation. The rational for the use of sulfasalazine in AS is the common

association between inflammatory bowel disease and spondylo-arthropathies, as well as the description of inflammatory lesion in the ileum of spondylo-arthropathy patient[3].

Sulfasalazine (dose 2-3 g/day) has been used in AS since 1984. A meta-analysis showed sulfasalazine to be superior to placebo for three clinical variables (duration of morning stiffness, severity of morning stiffness, severity of pain) and one laboratory parameter (IgG level)[4].

Since that publication however the new evidence for the effectiveness of this drug for AS is less convincing, at least for patients with axial involvement only. Sulfasalazine proved to be more effective than placebo in spondylo-arthropathy patient (including AS)[5]. Sulfasalazine is effective in reducing synovitis in peripheral arthritis but had no result in axial involvement[6].

## Material and Methods

The present study was conducted in the Department of Physical Medicine and Rehabilitation IPGME & R, Kolkata during the period from February 2008 to July 2009. The patient with Ankylosing spondylitis (fulfilling modified New York criteria 1984) attended PMR OPD, IPGMER and SSKM Hospital was included in this study with following exclusion criteria:

(1) Complication of AS like aortic incompetence, cardiac conduction defect, neurological involvement, renal amyloidosis

(2) Chronic hepatic disease and chronic renal disease

(3) Hypersensitivity to sulfasalazine.

Informed consent was obtained from all individuals and the study was carried out in accordance with the Institutional Human Clearance Committee. After randomised selection into two groups a detailed history was taken and clinical examination was done. The relevant clinical findings and history were recorded in the proforma. Routine blood examination like Hb %, TC, DC, ESR, CRP, and HLA B27 as well as radiological examination of SI joint, spine, peripheral joints were done. Disease activity and functional capacity were assessed by BATH index like BADAI, BASFI.

The management of patients was based on a regular approach to exercise, NSAIDs when necessary along with motivating the patients for active physical therapy and educating about the disease. Patients were encouraged to maintain a good posture, to avoid harmful activities and injuries. Indomethacin 75 mg sustained release capsule once daily was prescribed for all the patients as per individual‘s need along with antacids. Sulfasalazine was used in a 500 mg twice daily for 2 weeks followed by 1 g twice daily for next five and half months to group B patients. After initial visit all the patients were followed up at monthly interval and detail follow up results were recorded at 6 months.

## Results

At the end of the study period a thorough statistical analysis by different tests like Fisher’s exact test, Mann-Whitney U test, Wilcoxon’s matched pairs signed rank test, McNemar’s chi - square test were done. Fifty per cent of the patient of this study were in there third decade with male preponderance (male: female = 7: 1). During this one and half years study the youngest and the oldest patients were aged 18 and 53 years respectively; 43.75% of patients were in middle income (Rs 3000-6000 / month) group. Labour (31.25%) was the predominant group followed by service holder (18.75%), student (25%), businessman (12.5%), household (12.5%). In this present study 93.75% of the patients had insidious onset with predominant (87.50%) axial skeletal involvement. ESR, determined in first visit were up to 30 in 18.75%, between 31-60 in 43.75 %, more than 60 in 37.50% of cases; 62.5% of cases were CRP positive and 68.75% patients were with grade 2 radiological sacro-ilitis. Sacro-iliac test was positive in 78.12% of study group.

Comparative analysis of numerical variables between groups 1 and 2 by Mann-Whitney U test, it is noted that in visit 2, improvement of ESR in group 2 has become statistically significant (p value 0.022) indicating the positive effect of sulfasalazine. Comparative analysis of categorical variables between group 1&2 Fisher’s exact test failed to show any improvement of CRP in either group (p value 0.273 in group1 and 0.724 in group 2). No change in sacro-iliitis grading noticed in either group (p value 0 .336 in group1 and 0.131 in group 2). Peripheral joint involvement has come down to 4 from 9 in group

1 while in group 2 it has come down to 2 from 7 without any statistical significance (McNemar's chi-square test p value 0.063 in both the groups). Comparative analysis of different parameters including chest expansion and BATH index showed that only ESR was improved in group 2 (Table 1).

Comparative analysis different variables from visit 1 (v1) to visit 2 (v2) in group 1 and group 2 by McNemar's Chi - square test failed to show any improvement of sacro-iliac stress test due to sulfasalazine. Similarly no statistically significant improvement was noted in radiological grading of sacro-illitis (p value 0.500 in group1 and 1.000 in group 2).

Improvement of CRP was much better in group 2 than group 1 but this improvement was not statistically significant (p value 1.000 in group1 and 0.063 in group 2) (Table 2).

## Discussion

Three patients were dropped out from this study comprising 32 patients conducted over 18 months. Age of onset was most commonly in the 15-24 years with male preponderance (male to female ratio was 7:1)[7]. 10% develop symptoms before puberty.[8, 9]. In this study 87.5 % (n=28) patient's site of disease onset was in the axial skeleton and 24 of them presented with low back pain without radiation as the initial symptom. According to

**Table 1 — *Comparison of numerical variables between Group 1 and 2 – Mann-Whitney U test***

| Variable | Rank sum group 1 | Rank sum group 2 | U | Z | P value |
|---|---|---|---|---|---|
| Age | 289.5 | 238.5 | 102.5 | .961 | .336 |
| Chest v1 | 298.5 | 229.5 | 93.5 | 1.3 | .1935 |
| Chest v2 | 305.5 | 222.5 | 86.5 | 1.564 | .1177 |
| ESR V1 | 260.0 | 268.0 | 124.0 | -0.150 | 0.880 |
| ESR V2 | 324.5 | 203.5 | 67.5 | 2.28 | 0.0225 |
| BASMI V1 | 289.5 | 238.5 | 102.5 | 0.96 | 0.336 |
| BASMI V2 | 286.0 | 242.0 | 106.0 | .829 | 0.407 |
| BASFI V1 | 272.5 | 255.5 | 119.5 | 0.32 | 0.748 |
| BASFI V2 | 257.5 | 270.5 | 121.5 | -0.244 | 0.806 |
| BASDAI V1 | 304.5 | 223.5 | 87.5 | 1.526 | 0.126 |
| BASDAI V2 | 281.0 | 215.0 | 95.0 | 0.988 | 0.323 |

**Comparisons of numerical variables between group 1&2 by Mann-Whitney U Test**

**Under this heading it is noted that in visit 2, p value in respect to ESR has become statistically significant ,the value being 0.022.So it indicates that sulfasalazine has added advantage in reducing ESR though none of the other parameters has shown statistically significant change**

**Table 2 — *Distribution of Cases according to CRP Positivity***

| | Visit 1 | | | Visit 2 | | |
|---|---|---|---|---|---|---|
| Group | Negative | Positive | Total | Negative | Positive | Total |
| Group 1 | 8 | 8 | 16 | 7 | 9 | 16 |
| Group 2 | 4 | 12 | 16 | 9 | 7 | 16 |
| | 12 | 20 | 32 | 16 | 16 | 32 |

**Fisher's exact test 2 tailed p value 0.273 Fisher's exact test 2 tailed p value 0.724**

**Above table shows that in group 1, 8 patients were CRP positive in first visit that became 9 in second visit whereas in group 2 of the 12 positive patients 7 remained positive in second visit**

several evidences 15% of patient's first symptom is in one or more peripheral joint.[9] In this study 12.5% patients came with peripheral joint arthritis as the presenting symptom.

In this study the patients on sulfasalazine had shown clinical and functional improvement though all of them may not be statistically significant. On first visit 14 had ESR in the range of 31-60 mm, 12 had ESR more than 60 mm.On follow up it is being seen that there is statistically improvement in this parameter especially in the patients getting sulfasalazine. Comparison of value of ESR between group 1 and 2 by Mann-Whitney U test shows significant improvement (p value of 0.022). Change in value from visit 1 to visit 2 in group 2 receiving sulfasalazine by Wilcoxon's matched pairs signed rank test shows significant p value of .033. It is clearly seen that sulfasalazine has significant role in reduction of ESR. There are studies including one by Kirwan in 1993 and another by Clegg, *et al* in 1996[10] showing reduction of ESR with sulfasalazine in ankylosing spondylitis patients. CRP was positive in 20 patients that came down to 16 on follow up but the improvement pattern of CRP is not statistically significant.

Sacro-iliac test positivity came down to 15 from 25 patients. So there is improvement in this parameter but is not statistically significant. One interesting finding here is that, there is clinical improvement in the form of sacro-iliac stress test but it is not being supported radio logically.

According to various studies sulfasalazine is effective in reducing synovitis in peripheral arthritis of AS patients but had no result on axial involvement.[11] In our study also 5 patients out of 7 in group 2 on sulfasalazine improved without any statistical significance. Although BATH functional index (BASFI) was improved without any statistical significance, disease activity of BATH index (BASDAI) was unchanged.

## Conclusion

Although sulfasalazine is well known to control disease activity, this study showed that it is only good to improve ESR not CRP. Interestingly it is not altering sacroiliac joint involvement as evidenced by no statistical improvement in sacro-iliac test and radiological grading of sacro-illitis. Widely accepted BATH index of disease activity (BASDI) and functional capacity (BASFI) were also not improved by sulfasalazine.[12,13]

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