TO ASSESS THE EFFICACY OF NAPROXEN AND SULFASALAZINE IN SUBJECTS WITH JUVENILE ONSET ANKYLOSING SPONDYLITIS (10-17 YEARS): A PROSPECTIVE STUDY

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Abstract

Background – Juvenile onset Ankylosing Spondylitis(JoAS) damages joints, inflames the spine, breaks bones, and causes back pain. Our study's objective was to evaluate the development of JoAS symptoms utilizing sophisticated inflammatory indicators.

Materials and methods: For this prospective study, three groups of 21 JOAS participants were created. Three men and two women made up Group A. There were four males and four females in each of the two groups, Group B and Group C. A placebo was given to Group A, 1000 mg of naproxen was given to Group B each day, and 2000 mg of sulfasalazine was given to Group C each day. BASFI, BASDAI, and BASGI scores of four were accepted by the study. JoAS was also connected to MMP-3, ICAM-1, IL-6, IL-17, TNF **α**, and IL-6. JoAS biomarker measures were taken at baseline and at six weeks in Groups A, B, and C. The levels of CRP, TNF **α**, IL-6, and MMP-3 in groups A, B, and C were compared.

Results - For TNF **α** -, IL-6, and MMP-3, the medication response was significantly greater in group C than in group B. IL-6 levels declined threefold in group C from baseline ($p = 0.01$) to the 6th week ($p = 0.001$). TNF **α** levels in groups B and C were lower than in group A. (p 0.01, p 0.001).

Conclusion IL-6 and TNF **α** are cytokines that may have a role in the immunopathogenesis of JoAS. We also believe that these cytokines can be utilized to make diagnoses and gauge the success of treatments. Sulfasalazine treats JoAS better than naproxen.

Keywords :- Juvenile onset of Ankylosing spondylitis, inflammatory markers , Sulfasalazine, Naproxen

Introduction:-

A person has juvenile onset ankylosing spondylitis (JoAS), symptoms first appear around the age of 16 and subsequently advance to include sacroiliitis and spine involvement(Burgos-Vargas, 2009). Among white populations, the prevalence rates for juvenile-onset AS range from 9% to 21%(Jadon et al., 2013;). Ankylosing spondylitis with juvenile onset (JoAS) is a chronic inflammatory illness that damages joints and produces inflammatory back pain(Zochling, 2011). Together with new bone development, it contains spinal inflammation (Jadon et al., 2013). Peripheral arthritis and enthesitis are present in the early years of JoAS in children and adolescents, followed by axial symptoms 5 to 10 years later(Burgos-Vargas, 2009).

The BASF (Bath ankylosing spondylitis functional index), the BASDAI (Bath ankylosing spondylitis disease activity index), and the BASG (Bath ankylosing spondylitis global index) are three functional indicators that can be used to assess JoAS symptoms and self-assessment questionnaires(Taylor & Harrison, 2004; Zochling, 2011). Since more children than adults need hip replacements, are in functional classes III and IV, and have higher mean Bath AS Functional Index (BASFI) scores, children have a more severe form of AS than adults(Heuft-Dorenbosch et al., 2004; Rudwaleit et al., 2004). There aren't many therapy options for JoAS. The cornerstone of therapy, nonsteroidal anti-inflammatory drugs (NSAIDs) alleviate symptomsClick or tap here to enter text.. Methotrexate and other disease-modifying anti-rheumatic medications (DMARDs) that suppress the immune system have not been found to be

effective in the treatment of JoAS(Chen et al., 2013; Colebatch et al., 2011). As a result, medications like Naproxen, an NSAID and delayed-release tablet, reduce prostaglandin E2 by inhibiting cyclooxygenase I and II and promote osteoclast activity(HILL & HILL, 1975). By stopping the production of new diseased bones, NSAIDs halt the progression of JOA.

For more than 20 years, the prodrug sulfasalazine has been used to treat JoASClick or tap here to enter text..
By causing caspase-8-induced apoptosis, it blocks the nuclear factor kappa-B (NF-kB) signaling pathway and reduces TNF **α** expression in macrophages. By decreasing the expression of the receptor NF-kB ligand, sulfasalazine prevents the development of osteoclasts.

Several cytokines are generated during inflammation and used as biomarkers to assess the prognosis of an inflammatory condition. Similarly, studies on TNF **α** and IL-6, IL-17, ICAM-1, and MMP-3 in patients have been linked to AS, and alterations in cytokine levels have been seen in biopsies(Bal et al., 2007a; De Vries et al., 2009a, 2009b; Du et al., Maksymowych et al., 2007). It has been discovered that the BASDI (back pain score) and CRP levels, respectively, are associated to the disease through MMP-3 and IL-6 levels(Maksymowych et al., 2007). ADC, or apparent diffusion coefficient, is a measure of diffusivity that has recently been discovered by researchers to have a positive link with C-reactive protein and to reveal details regarding the severity of inflammation in AS. Our study's objective was to assess the development of JoAS symptoms using more advanced inflammatory markers.

Material and methods

The current study was designed to evaluate the relationship between JoAS and inflammatory markers. The Rajshree Medical Research Institute in Bareilly, Uttar Pradesh, India, undertook the study. The study's protocol was explained to the department of orthopedics and the institutional board committee before being approved by the college's ethics committee (RMRI/eth/pg/2014-0223).

Population under study:
The Rajshree Medical Research Institute in Bareilly, Uttar Pradesh, India, provided the participants. Only participants who agreed to sign the written consent form and met the modified New York criteria for 3 months as well as the European League Against Rheumatism (ACR)/EULAR criteria for Rheumatoid arthritis were selected.
Three groups were formed from the study's 21 participants (10 to 17 years old) with JOAS: Group A (3 males and 2 females), Group B (4 males and 4 females), and Group C. (4 males and 4 females). A placebo was given to Group A, 1000 mg of naproxen was given to Group B, and 2000 mg of sulfasalazine was given to Group C. Following the participants for three months, hospital visits were required every week until the 12th week, during which time any negative effects of the chosen medications were carefully monitored.

Study Drugs
Because Naproxen inhibits Cox isozymes by binding to arachidonate in a competitive manner as an anti-inflammatory medication, the study was carried out on a subset of patients who received a daily dose of Naproxen of 1000 mg for a period of 12 weeks(HILL & HILL, 1975). Similarly , other participants received 2000 mg/day of sulfasalazine (Saaz, IPCA Laboratories, India) for 12 weeks because it inhibits the NF-kB signaling pathway and acts as a TNF **α** inhibitor.

NSAID-resistant participants were permitted to participate in the trial, but those who took NSAIDs every day for three months were unable to do so because the medications were too toxic and had unfavorable side effects(Colebatch et al., 2011). The trial was not open to participants who had a history of tuberculosis skin testing that was positive. Anti-TNF **α** medication, steroids, or participants receiving DMARDs (disease-modifying anti-rheumatoid medicines) were not allowed in the study population.

The chosen individuals also consented to prepare the questionnaire (pertaining to BASFI, BASDAI, and BASGI) in accordance with the 1996 recommendations(Zochling, 2011). Participants in the study had to have BASFI, BASDAI, and BASGI scores of 4 to be eligible. BASDAI questions were used to analyze the prespecified primary end goal, and BASFI questions were used to evaluate the prespecified co-primary end point for efficacy analysis(El Miedany et al., 2008; Rudwaleit et al., 2004; Song et al., 2009a, 2009b). The BASDAI and BASFI used questions on

fatigue, spinal pain, peripheral arthritis, enthesis and morning stiffness, Schober's test, and chest expansion before and after the 12th week to assess the major end points of improvement in physical function and spinal mobility.

Estimation of various parameters (Bal et al., 2007a; Brandt et al., 2004; De Vries et al., 2009a, 2009b; Maksymowych et al., 2007):

Blood concentrations of CRP, TNF **α**, IL-6, IL-17, ICAM-1, and MMP-3 were assessed in triplicate by skilled technicians and under the direction of central laboratory faculty members. Patients in all three groups had their serum drawn for analysis at the beginning and conclusion of the twelfth week of treatment. R & D Systems sold ELISA (enzyme-linked immunosorbent assay) kits for measuring TNF **α**, IL-6, and MMP-3 (Minneapolis, MN, USA). A kit from Indianapolis, IN, USA was used to assess CRP levels. The findings of the laboratory tests and the levels of ESR, CRP, TNF **α**, IL-6, and MMP-3 were not known to the surgeons.

Also, the prognosis of the therapy was noted under the supervision of surgeons at the beginning of the treatment, that is, in the first week and on the 12th week of the visit, on a questionnaire based on the BASFI, BASDAI, and BASGI scores.

Results

The goal of the study was to compare the levels of diagnostic biomarkers in people with active JoAS before and after the first and sixth weeks of treatment with a particular medication. Table 1 lists the demographic characteristics of the chosen individuals by age and disease status. The demographics and laboratory characteristics of the subjects separated into groups A (placebo), B (naproxyn), and C at the baseline characteristic showed no discernible difference (sulfasalazine). No significant differences were seen between any of the groups in terms of the sex ratio or clinical characteristics. Participants in the current study were evaluated utilizing questionnaires created by BASFI, BASDAI, and VAS. Following the participant's evaluation at the end of the sixth week, it was discovered that groups B and C's BASDAI and BASFI scores were statistically lower than those of group A. Group C had a statistically significant lower BADAI and BASFI score than group B following the participant assessment in the sixth week. In addition, when compared to group B participants, members in group C saw a 50% increase in their BASDAI score. Also, there was no discernible difference between groups B and C in the BASFI score, occiput-to-wall distance, or chest expansion (as shown in table 2).

The clinical response of individuals in the various groups with well-established AS is significantly correlated with the concentration of biomarkers, as shown in Table 2. At the baseline and sixth week, the levels of AS biomarkers in groups A, B, and C were assessed. Across groups A, B, and C, biomarker concentrations including CRP, TNF **α**, IL-6, and MMP-3 were compared. In comparison to group A, the CRP levels were statistically lower in groups B and C. Moreover, statistical analysis revealed that levels of ESR in all the groups did not vary significantly (as shown in Table 2).

TNF **α**, IL-6, and MMP-3 levels in group C were observed to respond to medicines in their respective groups much better than those in group B. Participants in group C experienced a three-fold drop in IL-6 levels from the beginning of treatment through the sixth week (p 0.001). Similar to group A, groups B and C showed statistically significant reductions in TNF **α** levels (p 0.01, p 0.001) (as shown in table 2).

Table 1- Baseline characteristics or Demographic profile of patients' understudy: -

	Descriptive characteristics of patients understudy	Placebo	Naproxyen	Sulfasalazine	*p- value*
1	**Age**	13.9	16.8	15.6	0.001*
2	**Men/Women**	3/2	4/4	4/4	--
3	**BMI**	22.5±2.31	24.6±3.22	26.1±5.76	≤0.05
4	**History of Uveitis +/-**	(2/0)	(1/0)	(0/1)	--
5	**History of Inflammatory bowel Disease +/-**	0/1	(2/2)	(1/1)	---
6	**History of Psoriasis +/-**	0/0	(1/0)	(2/0)	--
7	**History of Dactylitis +/-**	(1/1)	(0/1)	(0/0)	---
8	**History of Peripheral arthritis +/-**	(1/2)	(1/2)	(0/1)	---
9	**Disease Duration/Year**	2.3	5.4	4.2	0.001

Note – Data are in range or mean ± SD, BMI- Basal mass index, HLA- Human leukocyte antigen. *- Mann-Whitney test group with group as compared to placebo.

Table 2- JoAS assessments via various parameters and outcome of the variables after 12th week:-

		Placebo (Group A)			Naproxen (Group B)			Sulfasalazine (Group C)		
		1st week	12thWeek	*P* value b/w baseline and 6th week	1st week	12thWeek	#*P* value participants Placebo vs group B at 6th week	1st week	12thWeek	**P* value participants Placebo vs Group C at 6th week
1	**CRP m/L**	24.5 ±5.1	27.8±2.6	NS	27.2±4.3	12.3± 2.1 $^{\alpha}$	≤0.05	26.8±6.5	15.8±1.1 $^{\beta}$	≤0.05
2	**Morning Stiffness (Min)**	29.3±8.2	28.7 ± 16.3	NS	38.1±14.2	19.9±7.9 $^{\alpha}$	≤0.05	38.1±9.5	15.5± 4.1 $^{\beta}$	≤0.05
3	**Occiput to wall distance**	9.6±0.8	9.9 ± 0.6	NS	6.2±0.4	6.1± 0.9 $^{\alpha}$	NS	11.0±0.9	8.4±1.5	NS
4	**Back pain (0-10) (VAS)**	8.1±4.6	8.7±3.6	NS	9.7±1.8	5.7±2.9 $^{\alpha}$	≤0.05	8.7±1.9	4.9±1.7 $^{\beta}$	≤0.05
5	**Chest Expansion**	4.6 ±0.3	4.5±0.4	NS	4.8±0.8	4.9±0.5	NS	4.4±0.8	4.5±0.6	NS
6	**ESR (mm/Ist)**	38 ±5.6	34±3.9	NS	59 ± 8.3	44 ± 9.4	NS	39 ± 6.1	37 ±9.4	NS
7	**BASFI SCORE (0-10)**	6.7± 1.8	6.9±1.9	NS	6.9± 4.1	2.1± 2.2 $^{\alpha}$	≤0.05	6..4± 5.1	1.8± 1.4 $^{\beta}$	≤0.05
8	**BASDAI (0-10)**	6.4 ±1.9	6.8 ±2.7	NS	6.8±1.9	4.9 ±2.1 $^{\alpha}$	≤0.05	6.3±1.9	2.1±1.1 $^{\beta}$	≤0.05
9	**BASGI (0-10)**	4.3± 1.9	7.5± 2.9	NS	6.4±2.8	2.9± 0.3 $^{\alpha}$	≤0.05	4.5±2.9	2.1±1.0 $^{\beta}$	≤0.05
10	**MMP-3 ng/µL**	232.16±56.7	261±86.7	NS	256.250 ±59.7	84.54±15.2 $^{\alpha}$	≤0.01	279.45±63.5	64.5±19.5 $^{\beta}$	≤0.001
11	**IL-6 pg/ µL**	78.51 ± 32.58	87.94± 43.71	NS	58.96±21.29	25.9±7.82 $^{\alpha}$	≤0.01	89.56±23.54	16.56±.5.94 $^{\beta}$	≤0.001
12	**TNF α**	46.21±31.14	49.52± 54.26	NS	43.81±12.58	9.98±4.18 $^{\alpha}$	≤0.01	43.51±6.44	7.5±3.52 $^{\beta}$	≤0.001

Note- Data are in range or mean ± SD and values that are in median (range), BASFI- Bath ankylosing spondylitis functional index, BASDAI- Bath ankylosing spondylitis disease activity index (score ranges from 0-10), CRP – C reactive protein VAS Visual analogous scale ESR- Erythrocytes sedimentation rate, MMP- Matrix metallo proteinases, IL- Interleukin, TNF **α** tumor necrosis factor.

$^{\alpha}$ = $p\leq$-0.001- Statistically significant values for comparison within Naproxen (group B) between baseline via (paired *t* test (1st week & 6th week).

$^{\beta}$ =$p\leq$-0.001- Statistically significant values for comparison within suphasalazine (group C) between baseline via paired *t* test (1st week & 6th week).

$^{\#}$ =Statistically significant values for comparison between placebo and Group B at 6 week (unpaired *t* test)

* =Statistically significant values for comparison between placebo and Group C at 6 week (unpaired *t* test)

Discussion: -

The majority of the JoAS patients in this prospective trial (72% to 89%) exhibited high inflammatory markers prior to the administration of two medications. It is generally established that in JOAS, inflammatory indicators do not always accurately reflect disease activity(Bal et al., 2007b). Because of this, inflammatory markers were not employed to evaluate the severity of the condition or the effectiveness of treatment. This study demonstrated that elevated inflammatory markers were a sign of ongoing illness. Among JoAS patients who had baseline increased inflammatory markers, it seems advantageous to include the decline of inflammatory markers in the response criteria for continuing sulfasalazine treatment. There is currently no other well-established alternate therapy option for people with axial JoAS than non-steroidal anti-inflammatory medications. Sulfasalazine has shown some promise in the treatment of AS, particularly in the case of arthritis caused by the HLA-B27 gene. The impact on joint discomfort, joint edema, joint score, and laboratory markers in a clinical trial on polyarticular JOAS was only barely significant. Placebo-controlled double-blind research on individuals with juvenile spondylarthritis showed that sulfasalazine was superior to the placebo in terms of peripheral joint involvement. Although sulfasalazine has not been studied in pediatric patients who have been diagnosed with ankylosing spondylitis, research in adults with AS suggest that it likely has no effect on axial involvement.

Our findings concur with those of recent research in that sulfasalazine may be a useful therapy for axial types of JoAS. In this study, we discovered that patients with ankylosing spondylitis had considerably higher serum levels of MMP-3, IL-6, and TNF α compared to placebo, and we also found a strong association between CRP and IL-6 levels. Also, we discovered a connection between ESR and the levels of IL-6, MMP-3, and TNF α. They also found no link between ESR levels and BASMI

or BASDAI scores in AS patients when they were compared to placebo controls.

Etanercept was used in a limited open study to treat JoAS(Peloso et al., 2011). Eight patients (seven men) with a mean age of 15.9 years (range, 12 to 25 years) and a mean duration of 4.5 years (range, 1.2 to 17.5 years) of juvenile ankylosing spondylitis were included. There were six HLA-B27-positive patients. The suggested dose of etanercept for the treatment of polyarticular JoAS has been used in clinical trials at an average dose of 0.4 mg/kg body weight. More than 24 months later, the therapeutic results were still noticeable. Improvement with anti-TNF **α** medication has been shown in separate open research on 10 patients with juvenile spondylarthritis, using either infliximab (n = 8) or etanercept (n = 2).

We showed that in several groups, the levels of IL-6 were linked with ESR but not with CRP levels. There was a favorable correlation between IL-6 levels and the clinical indices measuring bodily mobility (BASMI), functional status (BASFI), and weariness scores. Chest enlargement was negatively correlated with ESR. A link between IL-6 levels and ESR was discovered by Conti et al. (2007) when they analyzed the blood levels of IL-6 in patients with JoAS. Similar to the outcomes of our investigation, (Conti et al., 2007; De Vries et al., 2009a) discovered a favorable association between CRP, ESR, and IL-6 levels. In line with the findings of Park et al., we did not observe a connection between pain and IL-6 levels (2007). The ongoing medical care may be the cause of the link between IL-6, CRP, and ESR levels but not with clinical activity indices.

In our study, all of the JoAS patients were taking naproxen, sulfasalazine, or a placebo. In the study by Bal et al. (2007), levels of IL-6 and CRP revealed a substantial link with cytokine levels despite their treatment, raising the question of whether medicine has an impact on cytokine levels. On the other side, Rudwaleit et al. (2007) and 2008 discovered a drop in IL-6 levels in individuals taking anti-TNF A-α therapy. In our investigation, we found that IL-6 levels were considerably greater in the group that got sulfasalazine compared to other groups, suggesting that IL-6 may possibly indicate disease activity characteristics in JoAS patients.

These investigations all revealed elevated serum TNF **α** levels in JOAS, as did ours. On the other hand, Kiltz U et al. (2012) found no variations in TNF **α** levels between JoAS patients and controls. TNF **α** levels, pain ratings, and ESR levels were all correlated in our study across all groups. We believe that TNF **α** in JoAS patients represents the disease activity, and because sulfasalazine considerably reduced the levels of inflammatory markers and cytokines in that group, sulfasalazine is more effective in treating JoAS patients. Therefore, more research and clinical trials are needed to evaluate the efficacy of anti-TNF **α** therapy utilizing clinical (BASFI, BASDAI, etc.) and laboratory disease activity markers (CRP, ESR, etc.). As a result, we believe that cytokines and inflammatory markers like IL-6 and TNF α are crucial in the immunopathogenesis of JoAS.

Furthermore, we think that these cytokines can be utilized as diagnostic and pharmacological effectiveness testing methods. In this case, we discovered that sulfasalazine is superior to naproxen for treating JoAS.

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Conflict of Interest: NO

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