Journal of Cardiovascular Disease Research

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

ANALYZING RISK FACTORS AND RENAL ADVERSE EFFECTS IN SPONDYLOARTHRITIS SUBJECTS ON NON STEROIDAL ANTI INFLAMMATORY DRUGS

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Type of study: Original Research Paper

Conflicts of interest: nil

ABSTRACT

Background: For diagnosis and management of spondyloarthritis, assessing radiologically, lab parameters, symptoms, and history is vital, and is principally managed with NSAIDs. However, they can cause subclinical renal injury which is not detected on tests like creatinine.

Aim: To study the correlation between NSAID use duration and subclinical kidney injury incidence in Spondyloarthritis subjects by comparing serum cystatin-c with serum creatinine.

Methods: The present prospective hospital-based observational study was done on 36 subjects having spondyloarthritis. The levels of cystatin-c and serum creatinine were assessed at baseline, 4 weeks, and 12 weeks. The data collected were assessed for results formulation.

Results: In subjects with spondyloarthritis, the use of different NSAIDs showed no significant difference concerning serum creatinine with $p=0.548$ at 12 weeks, whereas, serum cystatin c levels showed significant results with $p<0.001$ after 12 weeks.

Conclusion: Following intake of NSAIDs, no significant change was seen in the values of serum creatinine. However, a significant increase by 2 or 3-folds was seen in levels of serum cystatin-c compared to the initial value, and hence, cystatin-c can be used as an early biomarker for subclinical renal injury compared to serum creatinine.

Keywords: Ankylosing spondylitis, NSAIDs, Subclinical renal injury, Spondyloarthritis

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

INTRODUCTION

Inflammation in the enthesis and axial skeleton is characteristic of Spondyloarthritis which is a diverse group of arthritis. Spondyloarthritis comprise spondylitis related to inflammatory bowel diseases, arthritis, psoriasis, arthritis, reactive arthritis, and/or ankylosing spondylitis.[1] Spondyloarthritis can present itself with vague symptoms with no definitive identification signs or symptoms. Spondyloarthritis can present with stiffness and back pain. Ankylosing spondyloarthritis is the main prototype of the spondyloarthritis.[2]

In young adult males, ankylosing spondylitis is one of the most prevalent diseases reported in the Outpatient Department of Medicine. The subjects with ankylosing spondylitis present most commonly with the back pain as presenting symptom and the most commonly associated etiologic factor being genetic predilection with HLA B-27.[3] The recent literature data shows an association of ankylosing spondylitis to Interleukins (IL-37, IL-23, IL-17, and IL-6) and TNF-α (tumor necrosis factor). It is usually diagnosed by genetic analysis, radiographic changes, and clinical features.[4]

The primary management strategy of spondyloarthritis includes NSAIDs like Etoricoxib, Naproxen, Indomethacin, and/or Aceclofenac, and biologicals. Other management strategies are glucocorticoids and anti-rheumatic drugs that can act as disease-modifying agents. Biological treatment is commonly employed in western countries. In developing countries including India, NSAIDs are the first line of treatment owing to the high cost of the biologicals. However, many side effects are associated with NSAIDs use including gastrointestinal, cardiac, and renal causes.[5]

Subclinical renal injuries are usually seen associated with the NSAIDs which are usually not seen in the routine laboratory tests and renal function tests. Clinical or overt renal side effects of NSAIDs (non-steroidal anti-inflammatory drugs) like increased levels of serum creatinine are reported in a few subjects having spondyloarthritis.[6] Hence, the present study was done to study the correlation between NSAID use duration and subclinical kidney injury incidence in Spondyloarthritis subjects by comparing serum cystatin-c with serum creatinine.

MATERIALS AND METHODS

The present prospective hospital-based observational study was conducted to study the correlation between NSAID use duration and subclinical kidney injury incidence in Spondyloarthritis subjects by comparing serum cystatin-c with serum creatinine. The study population was comprised of the subjects visiting the Outpatient Department of Medicine of the Institute.

The study included a total of 36 subjects from the male gender within the age range of 19-56 years and the mean age of 26.4±4.2 years. Based on the radiological investigations and different criteria, a diagnosis was made for spondyloarthroplasty (axial+ peripheral spondyloarthroplasty, peripheral spondyloarthroplasty, or axial spondyloarthroplasty). Based on the Armor criteria, for each clinical feature, a score of 1 was assigned, and scores of 6 or more were taken as spondyloarthroplasty. The classic clinical feature considered were acute

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

diarrhea within 1 month of onset, cervicitis within 1 month of onset, non-gonococcal urethritis within 1 month of onset, lumbar morning stiffness, and lumbar night stiffness.

The score of 1 was allotted to the Buttock score. Other clinical features considered were inflammatory bowel disease (Crohn's or ulcerative colitis), balanitis, Psoriasis, Iritis, well-defined enthesitis, Iritis, Heel pain, Sausage-like toe or digit(s), Asymmetric oligoarthritic, bilateral alternating buttock pain, sacroiliitis (unilateral grade 3 and bilateral grade 2), family history of a spondyloarthropathy, human leukocyte antigen HLA-B27, and NSAIDs having a score of 2. Other criteria used were based on the international society for Axial spondyloarthropathies including sacroiliitis on radiographs with one HLA-B27 or spondyloarthropathy feature which included Eye (uveitis), human leukocyte antigen (HLA-B27), Crohn's/colitis disease-elevated *C-Reactive Protein (*CRP), Arthritis, enthesitis (heel), NSAID good response, inflammatory back pain, psoriasis-positive family history of spondyloarthropathy, and sausage digit (dactylitis).

Sacroiliitis as diagnosed on radiographs bilaterally and given grades of 2-4 or unilaterally 3-4 based on the new modified criteria acute inflammation active on MRI. All the subjects included in the study had spondyloarthritis except subjects having inflammatory bowel disease and psoriasis, subjects with NSAID use for other causes, existing renal disease, hypothyroidism, hypertension, or diabetes mellitus, and subject with biologicals like corticosteroid, methotrexate, and sulfasalazine. After explaining the detailed study design, informed consent was taken from all the subjects in both written and verbal form.

After the final inclusion of the study subjects, detailed history was recorded for all the study subjects followed by a clinical examination. Depending on the criteria, in all 36 subjects, the blood sample was collected for all the subjects under aseptic and sterile conditions at baseline, 4 weeks, and 12 weeks for assessment of serum cystatin-c levels and serum creatinine levels.

The collected data were subjected to statistical evaluation using SPSS version 20, Chicago Inc., USA, ANOVA test, Fischer's extract test, and Chi-square tests. The data were expressed in percentage and number, and mean and standard deviation. The level of significance was kept at $p<0.05$.

RESULTS

The present prospective hospital-based observational study was conducted to study the correlation between NSAID use duration and subclinical kidney injury incidence in Spondyloarthritis subjects by comparing serum cystatin-c with serum creatinine. The study included a total of 36 subjects from the male gender within the age range of 19-56 years and the mean age of 26.4±4.2 years. All study subjects were males. 58.33% (n=21) subjects were HLA positive and 41.66% (n=15) subjects were HLA-B27 negative. The most common diagnosis was axial spondyloarthritis in 66.6% (n=24) subjects followed by Axial+ peripheral spondyloarthritis in 19.44% (n=7) subjects, and peripheral spondyloarthritis in 13.8% (n=5) study subjects respectively. NSAIDs used were etoricoxib being most common in 52.7%

ISSN: 0975-3583,0976-2833 VOL13, ISSUE 05, 2022

(n=19) subjects followed by Indomethacin in 19.4% (n=7) subjects, aceclofenac in 16.6% (n=6) subjects, and naproxen in 11.1% (n=4) study subjects respectively (Table 1).

Concerning the levels of serum creatinine, they were non-significant between 4 NSAIDs used at all time intervals at baseline, 4 weeks, and 12 weeks with respective p-values of 0.406, 0.623, and 0.548 respectively. The level of Etoricoxib increased from baseline, 0.75±0.14 to 4 weeks and 12 weeks (0.81±0.15). For aceclofenac, levels at baseline were 0.71±0.15, which decreased at 4 weeks to 0.70±0.14, and at 12 weeks, it increased to 0.73±0.07. For indomethacin, levels slightly decreased from baseline 0.77±0.13 to 0.76±0.08 at 4 weeks which remained consistent at 12 weeks. For Naproxen, serum creatinine levels decreased from baseline, 0.86±0.14 to 0.81±0.08 at 4 weeks, and further 0.79±0.13 at 12 weeks (Table 2).

On assessing the changes in serum levels of cystatin c, for etoricoxib, levels increased from baseline to 4 weeks, and 12 weeks from 0.85±0.13 to 0.93±0.07 and 1.08±0.13 respectively. At baseline and 4 weeks, there was no significant difference in levels of serum cystatin c with 4 NSAIDs used with p=0.953. Similar results were seen at 4 weeks having a p-value of 0.509. However, at 12 weeks, serum cystatin c levels were significantly higher for Naproxen (1.14±0.16) followed by Etoricoxib, 1.08±0.13, Indomethacin, 1.06±0.09, and aceclofenac with least value of 0.84±0.12 with p=0.01.

For serum eGFR cystatin c levels, at baseline, the levels were highest for aceclofenac followed by etoricoxib, naproxen, and indomethacin had the least value. This was statistically non-significant with p=0.984. At 4 weeks, similar results were seen with p=0.224. At 12 weeks, the serum eGFR cystatin c levels were highest for aceclofenac, 115.22±14.84 followed by indomethacin, 83.02±11.73, etoricoxib, 81.86±19.54, and the least value was for naproxen, 74.69±22.79. This difference was statistically significant with p=0.006 as shown in Table 4.

DISCUSSION

The present prospective hospital-based observational study was conducted to study the correlation between NSAID use duration and subclinical kidney injury incidence in Spondyloarthritis subjects by comparing serum cystatin-c with serum creatinine. The study included a total of 36 subjects from the male gender within the age range of 19-56 years and the mean age of 26.4±4.2 years. All study subjects were males. 58.33% (n=21) subjects were HLA positive and 41.66% (n=15) subjects were HLA-B27 negative. The most common diagnosis was axial spondyloarthritis in 66.6% (n=24) subjects followed by Axial+ peripheral spondyloarthritis in 19.44% (n=7) subjects, and peripheral spondyloarthritis in 13.8% (n=5) study subjects respectively. NSAIDs used were etoricoxib being most common in 52.7% (n=19) subjects followed by Indomethacin in 19.4% (n=7) subjects, aceclofenac in 16.6% (n=6) subjects, and naproxen in 11.1% (n=4) study subjects respectively. These demographics and disease characteristics were comparable to the studies of Hoek FJ et al[7] in 2003 and Hasse-Fielitz A et al[8] in 2009 where authors assessed subjects with demographic and disease characteristics similar to the present study.

For the assessment of the levels of serum creatinine, they were non-significant between 4 NSAIDs used at all time intervals at baseline, 4 weeks, and 12 weeks with respective p-

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values of 0.406, 0.623, and 0.548 respectively. The level of Etoricoxib increased from baseline, 0.75±0.14 to 4 weeks and 12 weeks (0.81±0.15). For aceclofenac, levels at baseline were 0.71±0.15, which decreased at 4 weeks to 0.70±0.14, and at 12 weeks, it increased to 0.73±0.07. For indomethacin, levels slightly decreased from baseline 0.77±0.13 to 0.76±0.08 at 4 weeks which remained consistent at 12 weeks. For Naproxen, serum creatinine levels decreased from baseline, 0.86±0.14 to 0.81±0.08 at 4 weeks, and further 0.79±0.13 at 12 weeks. These results were consistent with the results of Briguori C et al[9] in 2010 and Lafrance JP et al[10] in 2009 where authors reported similar alterations in serum creatinine levels following NSAIDs for spondyloarthritis as in the present study.

Concerning the changes in serum levels of cystatin c, for etoricoxib, levels increased from baseline to 4 weeks, and 12 weeks from 0.85±0.13 to 0.93±0.07 and 1.08±0.13 respectively. At baseline and 4 weeks, there was no significant difference in levels of serum cystatin c with 4 NSAIDs used with p=0.953. Similar results were seen at 4 weeks having a p-value of 0.509. However, at 12 weeks, serum cystatin c levels were significantly higher for Naproxen (1.14±0.16) followed by Etoricoxib, 1.08±0.13, Indomethacin, 1.06±0.09, and aceclofenac with least value of 0.84±0.12 with p=0.01. These findings were in agreement with the findings of Akgul O et al in 2011 and Chen B et al in 2015 where authors reported significantly higher cystatin c levels for naproxen use in spondyloarthritis. These results were similar to the studies of Shukla A et al[11] in 2017 and Terenzi R et al[12] in 2018 where authors suggested the highest serum cystatin c levels with naproxen as in the present study.

On assessing the serum eGFR cystatin c levels, at baseline, the levels were highest for aceclofenac followed by etoricoxib, naproxen, and indomethacin had the least value. This was statistically non-significant with p=0.984. At 4 weeks, similar results were seen with p=0.224. At 12 weeks, the serum eGFR cystatin c levels were highest for aceclofenac, 115.22±14.84 followed by indomethacin, 83.02±11.73, etoricoxib, 81.86±19.54, and the least value was for naproxen, 74.69±22.79. This difference was statistically significant with p=0.006. These results were in line with the results of Lipton S[13] in 2012 and Malakar A et al[14] in 2020 where authors reported serum eGFR cystatin c levels similar to the present study.

CONCLUSION

Considering its limitations, the present study concludes that following intake of NSAIDs, no significant change was seen in the values of serum creatinine. However, a significant increase by 2 or 3-folds was seen in levels of serum cystatin-c compared to the initial value, and hence, cystatin-c can be used as an early biomarker for subclinical renal injury compared to serum creatinine. However, the present study had a few limitations including a small sample size, short monitoring time, and geographical area biases. Hence, more longitudinal studies with larger sample size and longer monitoring period will help reach a definitive conclusion.

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TABLES

Characteristics	**%**	**n=36**
Mean age (years)	26.4±4.2	
Gender		
Females	0	0
Males	100	36
HLA-B27		

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Negative	41.66	15
Positive	58.33	21
Diagnosis		
Axial+ peripheral spondyloarthritis	19.44	7
Peripheral spondyloarthritis	13.8	5
Axial spondyloarthritis	66.6	24
NSAIDs used		
Etoricoxib	52.7	19
Naproxen	11.1	4
Indomethacin	19.4	7
Aceclofenac	16.6	6

Table 1: Demographic and disease characteristics of the study subjects

Time	Etoricoxib (Mean± S.D)	Naproxen (Mean± S.D)	Indomethacin (Mean± S.D)	Aceclofenac (Mean± S.D)	p-value
Baseline	0.75±0.14	0.86±0.14	0.77±0.13	0.71±0.15	0.406
4 weeks	0.79±0.19	0.81±0.08	0.76±0.08	0.70±0.14	0.623
12 weeks	0.81±0.15	0.79±0.13	0.76±0.06	0.73±0.07	0.548

Table 2: Change in serum creatinine levels with different NSAIDs in the study subjects

Time	Etoricoxib (Mean± S.D)	Naproxen (Mean± S.D)	Indomethacin (Mean± S.D)	Aceclofenac (Mean± S.D)	p-value
Baseline	0.85±0.13	0.84±0.12	0.88±0.15	0.88±0.23	0.953
4 weeks	0.93±0.07	0.94±0.07	0.91±0.05	0.86±0.13	0.509
12 weeks	1.08±0.13	1.14±0.16	1.06±0.09	0.84±0.12	**0.01**

Table 3: Change in serum cystatin c levels with different NSAIDs in the study subjects

S. No	Time	Etoricoxib (Mean± S.D)	Naproxen (Mean± S.D)	Indomethacin (Mean± S.D)	Aceclofenac (Mean± S.D)	p-value
1.	**Baseline**	108.02±15.07	107.35±18.21	107.02±19.25	111.82±24.37	0.984
2.	**4 weeks**	97.73±14.28	95.35±19.64	101.85±9.56	113.22±19.25	0.224
3.	**12 weeks**	81.86±19.54	74.69±22.79	83.02±11.73	115.22±14.84	**0.006**

Table 4: Change in serum eGFR cystatin c levels with different NSAIDs in the study subjects