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The Impact of NSAIDs on Pain and Comorbidities in Ankylosing Spondylitis: A Gender-Specific Investigation

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ABSTRACT

Ankylosing spondylitis (AS) is an inflammatory arthritic disease that mostly affects the joints and ligaments of the spine. While research has improved our understanding of AS pathogenesis and its treatment, most of what is known about AS has been obtained from studies in men. The purpose of the study was to evaluate the efficacy and comorbidities associated with non-steroidal anti-inflammatory drugs (NSAIDs) in women with AS. A total of 67 adult women from an AS support group responded to a survey about their AS associated NSAID use. The survey included questions about demographics, time since diagnosis, NSAID use history and frequency, pain level and type, other medications used, and comorbidities diagnosed before and after diagnoses with AS. The most common NSAIDs used were Celecoxib, Naproxen, Meloxicam, and Diclofenac. A majority (91.9%) of participants used a combination treatment that included an additional biologic. While NSAIDs decreased pain in AS patients, no one NSAID was found to be more effective than another in this population. Of the NSAIDs examined, only Celecoxib correlated with a reduction in AS associated spinal pain (patients taking Celecoxib had a spinal pain level of 3.5/10 while those taking other NSAIDs had a pain level of 4.7/10). Hypertension and irritable bowel syndrome were the most common comorbidities among AS participants. One-third of AS patients taking Meloxicam reported hypertension, and Meloxicam correlated with incidence of hypertension ($p=0.037$). This study of female AS participants suggests that NSAIDs reduce AS pain but that individual NSAIDs vary in their specificity and association with comorbidities.

Keywords

Ankylosing Spondylitis, NSAIDs, Women, Inflammation, Pain Reduction, Comorbidities, Celecoxib, Meloxicam.

Introduction

Ankylosing Spondylitis (AS) is a chronic rheumatic inflammatory disease characterized by inflammation at osteotendinous and osteoligamentous junctions in the spine and sacroiliac joints [1-3]. AS presents in the second and third decades of life, and approximately 80% of patients with AS will experience symptoms before the age of 30 [3-5]. AS has historically been understood to be a disease that affects males (with a 10:1 male:female diagnosis ratio), but in the past several years, the diagnostic prevalence between men and women has almost equalized to a 1:1 ratio, due to a better understanding of how AS may manifest differently between genders [6]. The underrepresentation of women with AS in the literature is one explanation for why around 25% of female patients with AS are misdiagnosed, causing a delay in diagnosis and a longer period of disease burden [6]. Previous studies have shown that women have an average of an 8.8-year delay in diagnosis, and that this delay can increase to 11.4 years if they are missing the HLA-B27 genetic marker for AS [6]. The signs and symptoms of AS in a given patient differ because of individual immunological, genetic, and hormonal differences [6]. The inflammatory lesions and ossification typical of AS contain infiltrates with CD4+ and CD8+ lymphocytes, macrophages, and the inflammatory cytokines tumor necrosis factor (TNF-α) alpha and transforming factor beta (TGF-β) [3]. Males have a higher

TNF-α and interleukin-17 (IL-17) responses compared to females, while females have an increased IL-6 response [6]. Genomics studies show that men have a higher number of uniquely expressed genes in AS compared to women (1522 uniquely expressed genes compared to 251 in women) [6]. In particular, men uniquely express the tissue-nonspecific alkaline phosphatase (TNAP) along with the ANKH inorganic pyrophosphate transport regulator (ANKH) gene, both used for bone ossification, while women do not [6]. The ANKH gene encodes a protein connected to AS that causes structural damage in people with the disease [6]. Estrogen levels are lowered in AS females, exacerbating the disease, while testosterone in males has no known effect [6].

Treatment variations between men and women with AS exist. One study showed that tumor necrosis factor inhibitors (TNFi), a common treatment in men, have a significantly lowered efficacy in women with AS [6]. NSAIDs are commonly suggested for both male and female AS patients. Approximately 60% of female participants are treated with NSAIDs [1]. NSAIDs reduce pain and inflammation in AS and are often the first line of defense in this disease [4,7,8]. NSAIDs differ by their chemical structure and selectivity [9], but all work by inhibiting cyclooxygenases (COX, COX-1 and COX-2) and the conversion of arachidonic acid into pain molecules such as thromboxanes, prostaglandins, and prostacyclins and the subsequent inhibition of platelet adhesion, vasodilation, metabolic temperature, and nociception [9]. COX-1 is required for the correct function of the gastrointestinal mucosa lining, kidneys, and platelet aggregation while COX-2 is specific to inflammation [9]. NSAIDs are effective in reducing pain when compared to a placebo in AS [4] though specific studies examining NSAIDs in AS are overrepresented by male patients [10]. Previous studies examining the effect of NSAIDs on AS included Etoricoxib, Celecoxib, Meloxicam, Diclofenac, Naproxen and Indometacin [4,11]. Diclofenac, Naproxen, and Indometacin inhibit both COX-1 and COX-2, while Etoricoxib and Celecoxib work mainly on COX-2 [12]. Meloxicam inhibits COX-2 but partially inhibits COX-1 [12]. Multiple studies found that Etoricoxib is the most effective NSAID to reduce pain in patients with AS. While NSAIDs are generally effective in AS, many factors affect their degree of efficacy. Cinar et al. showed that people responded best to NSAIDs when they were younger, experienced a short symptom duration, and that their disease was present for less than 6.9 years. NSAID use history and frequency can also affect their effectiveness and secondary negative effects. For example, short-term NSAID use (<3 months) results in improvements in pain, morning stiffness, and fatigue with AS [10] while long-term use can cause hypertension and cardiac complications [7-9]. The effect of NSAIDs on comorbidities is difficult to establish and requires careful experimental planning. For example, one study excluded patients with cardiovascular disease before diagnosis with AS to be able to see if a particular NSAID reduced the likelihood of cardiovascular disease developing in patients with AS [7]. A previous study had multiple comorbidity exclusions that were used in evaluating the tolerability and efficacy of Etoricoxib against Naproxen. One of the comorbidities excluded from the study was if a participant had gastrointestinal surgery due to complications of clinical malabsorption, neoplastic disease, or bleeding disorders [5]. There were also more digestive concerns with peptic ulcers and inflammatory bowel disease when patients used NSAIDs [5]. The comorbidities connected to vascular health that were excluded involved heart disease, peripheral artery occlusive disease, and hypertension [5]. Gastrointestinal problems caused by NSAIDs are linked to the ones that stop COX-1 enzymes from working which then destroys the mucosal lining [9]. Another study conducted showed that a 12% increase in patients on continuous use of NSAIDs increased their chances of developing hypertension [8].

NSAIDs are an important first line of defense in AS, but their overall efficacy and association with comorbidities and secondary negative outcomes in women with AS is not fully clear. We found that NSAIDs are generally effective in decreasing pain in AS but that no one NSAID is particularly effective in decreasing pain in our patient group. Celecoxib decreases spinal pain and Meloxicam is correlated with an increase in hypertension. These studies should serve a platform in the development of individualized treatment plans for women with AS.

Methods

The Eastern Mennonite University IRB has exempted this study for review due to the exclusion of children and participant interaction was through a survey that posed no risk or harm in relation to finances, employment, education, and their identity could not be found through data collection. Data was collected through an electronic survey posted in an online Facebook support group for women with AS. The participants in the study included 67 females who were 18 years or older and living in the United States. The subjects self-reported that they had a definitive diagnosis of AS. Participants completed a 5-10 minute survey that included a consent form in which they agreed to participate in the study. Participants reported a minimum age of 18 years old in correspondence with being a female. The survey included questions about demographics regarding age and if they lived in the United States. The questions then confirmed that the participant had a diagnosis of AS and the length of time with diagnosis. In the survey, questions were asked about current and previous NSAIDs they were using to get a better idea of each medication's effectiveness. The participants ranked their pain level on a scale of 1-10 in overall pain before and after taking an NSAID, joint pain, nerve pain, spinal pain, and pain in everyday activities. This information was important to determine if one medication is correlated more with reducing pain in one area than another [11]. The participants were also asked to describe their pain. The frequency of NSAID use, the time of day that medication is taken, and the length of time taking NSAIDs were included in the survey to understand the response rate and the efficacy of the medication [10,11,13]. Outside factor questions were included that asked about other medications taken with NSAIDs and comorbidities diagnosed before and after their Ankylosing Spondylitis diagnosis. These questions helped consider outside factors that could contribute to pain levels and the effectiveness of NSAIDs [5,7,10,11]. The data from the survey was sorted demographically and by the type of NSAIDS used, their pain scores, and their comorbidities. Chi-square tests, repeated

measures ANOVA, Correlations, and ANOVA with an alpha of 0.05 were performed using JASP. The independent variable (different NSAIDs) was compared to the dependent variable (the different pain scores) produced by the pain-ranking questions in the survey.

Results

Demographic and NSAID History Information

After filtering through the data to only look at people within the United States, the total number of participants was 67. The average age of the women who participated was 43.8 years old, with the youngest participant being 22 and the oldest participant being 74 years old. The women in the study had an average of 6.14 years with an official diagnosis of AS, with one participant having a diagnosis of 52 years. The average amount of time a participant had been using an NSAID was 3.34 years, with the short time using an NSAID being 1 month and the longest being 20 years. The majority of participants were also taking a biologic with the NSAID, as 91.9% of the participants used a combination treatment of NSAIDs and biologics. The survey showed that Celecoxib, Meloxicam, Diclofenac, and Naproxen were the highest used NSAIDs among the participants. The breakdown for the usage was 28.36% Celecoxib, 20.90% Diclofenac, 26.87% Meloxicam, and 23.88% Naproxen among the participants.

Pain Rankings

The difference between pain levels before and after taking NSAIDs showed significance with a *p*-value below 0.001 shown in Table 1. However, there was no statistical difference between the changes in pain level when compared to the 4 major NSAIDs used with a *p*-value of 0.590 shown in Table 1. The pain level between the different medication groups before and after usage of NSAIDs showed a similar drop in pain scores observed in Figure 1.

Table 1: Repeated measures ANOVA significance test for overall pain level and type of NSAID.

Repeated Measures ANOVA

Within Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p
Pain Level	295.397	1	295.397	169.004	< .001
Pain Level ✻ Drug Data	3.377	3	1.126	0.644	0.590
Residuals	110.116	63	1.748		

Note. Type III Sum of Squares

Between Subjects Effects

Cases	Sum of Squares	df	Mean Square	F	p
Drug Data	9.331	3	3.110	0.776	0.512
Residuals	252.550	63	4.009		

Note. Type III Sum of Squares

Pain Levels and Principle NSAIDs Used

An ANOVA was run for each pain scale ranking compared to the four main drugs found in the survey. The results showed that there was not one drug that did significantly better in reducing pain involved in the joints, spine, nerves, and pain from everyday activities as shown in Table 2.

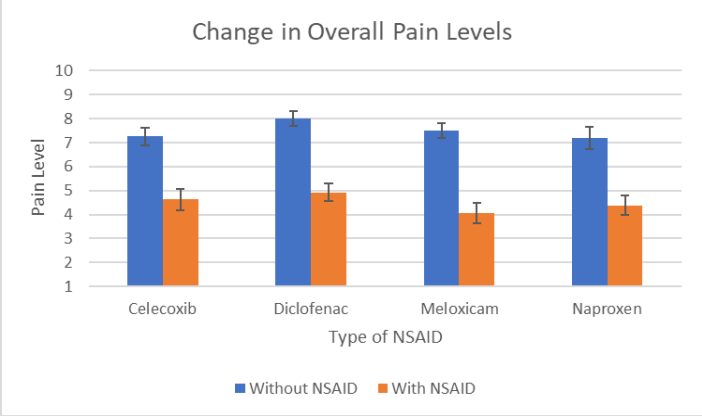


Figure 1: The change in pain level on a scale of 1-10 before and after using NSAIDs was analyzed. Overall drop in pain was found to be significant with a *p*-value of < 0.001. There was no significance in the difference between each NSAID as each dropped by an average of 3 points.

Table 2: ANOVA *p*-value comparison between the four main drugs and each pain scale.

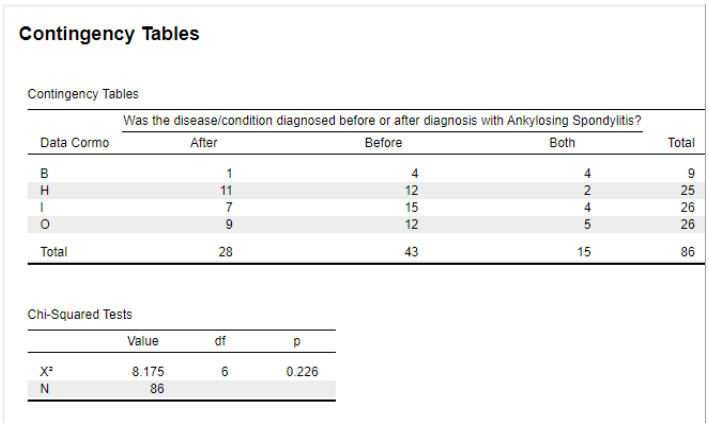
	Pain Level Rankings Compared to 4 Main Drugs			
	Joint Pain	Nerve Pain	Spinal Pain	Everyday Activities Pain
4 Main Drugs	0.587	0.462	0.236	0.65

Correlation of Pain Levels with Each NSAID

The next phase in analyzing the data from the surveys was to see if there was a correlation between each type of medication and pain scale ranking individually. A majority of the medications showed no significant correlation between the drug effectiveness and the different pain scales. However, Celecoxib showed significance with a *p*-value of 0.04 as shown in Table 3. Spearman's r for the Celecoxib correlation was -0.25 showing a weak correlation in decreasing the pain levels in the spine. Participants who did not use Celecoxib showed that their pain level decreased to 4.71 on a scale of 1-10 in terms of spinal pain. The participants that used Celecoxib for their NSAID use in pain control further decreased their spinal pain to a mean of 3.5 pain level on a scale of 1-10. These changes can be seen in Figure 2.

Table 3: *p*-values for each drug compared to the different pain levels individually (**: significant).

	Joint Pain	Nerve Pain	Spinal Pain	Everyday Activities Pain
Celecoxib	0.669	0.169	**0.04	-
Naproxen	0.8	0.986	0.601	0.815
Diclofenac	0.305	0.222	0.35	0.338
Meloxicam	0.257	0.79	0.507	0.978



Contingency Tables

Contingency Tables

Data Cormo	Was the disease/condition diagnosed before or after diagnosis with Ankylosing Spondylitis? After	Before	Both	Total
B	1	4	4	9
H	11	12	2	25
I	7	15	4	26
O	9	12	5	26
Total	28	43	15	86

Chi-Squared Tests

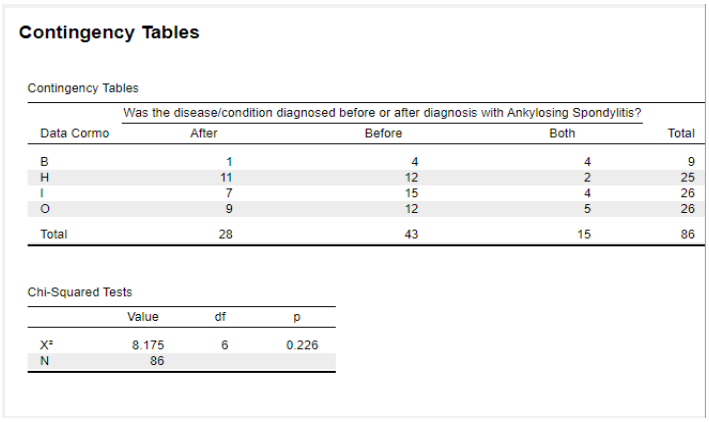
	Value	df	p
X^2	8.175	6	0.226
N	86		

Figure 2: Difference in pain levels in spinal pain with and without Celexocib. Celexocib showed a significant correlation with spinal pain with a *p*-value of 0.04 and a negative weak correlation. Participants taking Celexocib had a spinal pain level of 3.5 while those other NSAIDs had an average pain level of 4.71.

Comorbidities

The type of comorbidity diagnosis was compared to the timeframe of AS diagnosis. There was no significant difference between when a person was diagnosed with AS and the comorbidities as shown in Table 3. However, even though there was no significance at the time of diagnosis of comorbidity, hypertension and irritable bowel syndrome (IBS) showed to be the most common type of comorbidity among participants. The most common comorbidities were then compared to each of the four main drugs used in the survey. A majority of the drugs showed no significance when compared to the different types of NSAIDs. Meloxicam, however, showed significance when running a Chi-square test to see the breakdown of comorbidities for the participants who did and did not take the drug. There were a total of 67 participants in this breakdown and 18 of them had a comorbidity allowing significance to show with a *p*-value of 0.037 as seen in Table 4. The data also showed that out of the 18 people taking Meloxicam six people had hypertension.

Table 3: Chi-square test of comorbidities appearance to the time of AS diagnosis.



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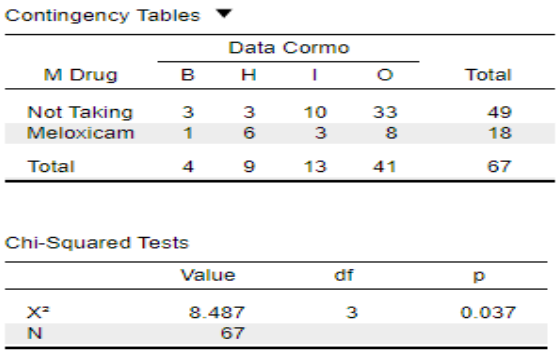

Contingency Tables

M Drug	Data Cormo B	H	I	O	Total
Not Taking	3	3	10	33	49
Meloxicam	1	6	3	8	18
Total	4	9	13	41	67

Chi-Squared Tests

	Value	df	p
X^2	8.487	3	0.037
N	67		

Table 4: Chi-square test for comparison of an individual drug to comorbidities (B: Both, H: Hypertension, I: Irritable Bowel Syndrome, O: Other)

Discussion

The main purpose of the study was to evaluate which NSAID would have the strongest correlation with pain reduction in women with AS. The survey showed that NSAIDs have been beneficial for women as there was a significant drop in pain levels when looking at the before and after use of the medication. However, in the results, there was no NSAID that did significantly better when compared against each other. These results counteracted previous studies, as one study done in 2020 performed a meta-analysis for indirect comparison of NSAIDs used to treat Ankylosing Spondylitis showed that Etoricoxib was the most effective in reducing pain overall [4]. The trials analyzed in the 2020 study had at least 69% of their participants being male [4]. Another study that analyzed MRI scans to look at inflammation in the spine, which had 86% of the participants being male, showed that a combined treatment of intercept, a type of tumor necrosis factor inhibitor, and Celecoxib was effective in inflammation reduction [14]. Even though the NSAIDs have helped in reducing the pain in women, the women with the disease are still struggling as pain is still present. This brings into question whether there are other NSAIDs that need to be looked at to further reduce women's pain levels. For example, looking into other selective COX-2 NSAIDs might be beneficial due to the effect they have in reducing bone ossification and lower adverse effects for smaller doses of COX-2 NSAIDs [15]. Another type of COX-2 NSAID outside of Celecoxib and Etoricoxib is Lumiracoxib. However, there has been a risk of complications relating to the liver with this NSAID [16].

The results of the study also found significance with Celecoxib as there was a small correlation for pain reduction when looking at spinal pain. There was an additional decrease of 1.21 points on a pain scale of 1-10 when compared to those not taking Celecoxib. The additional decrease in spinal pain is an important factor to know because medications can affect each person differently. With the increased suffering women feel from this disease, any additional help in reducing pain would be beneficial so they can try to gain back their lives as much as possible. An important note found from another research project was that Celecoxib alone did not show significant improvement in spinal pain until the patient reached 52 weeks in the study [14]. The additional time period it

takes for the medication to work is another factor to consider when prescribing Celecoxib so physicians do not switch to another NSAID quickly due to it needing more time for it to take effect in patients.

Through this study, a significant correlation between Meloxicam and comorbidities, specifically hypertension, was shown when comparing participants' NSAID usage. A third of the participants who were taking Meloxicam were shown to also have hypertension. In previous studies, Meloxicam was shown to have lower vascular problems than Naproxen [17]. Another showed that Meloxicam had lower vascular risks when comparing the different adverse events correlated with the medication [18]. The connection between Meloxicam and hypertension is important for physicians treating women with AS to know. If the patient has a family history of hypertension, it is not in their best interest to prescribe this NSAID to them.

There is a cost factor to consider as well when looking at which NSAID to prescribe for treatment for women with AS. Due to NSAIDs having a history of causing different adverse effects, it can cause a person's medical costs to increase. For example, patients taking NSAIDs are more likely to get prescribed a gastroprotective drug and increase their risk of having GI hemorrhage by 24% in older patients [19]. The additional problems the medication causes increase the financial costs due to needing to pay for more medications or other procedures to fix complications caused by NSAIDs. One study done in 2003 found that there was a cost of around $526 dollars for those on one or more NSAIDs who also had to use gastroprotective medicine [19]. Within today's economy, the price may differ. The GoodRx, which is a company that tries to help patients save money on medication, priced Celecoxib at $13 while Meloxicam was $5 [20]. Even though Meloxicam is the cheaper NSAID, Celecoxib has been shown to have lower gastrointestinal complications [21]. Spending additional money for a higher-priced NSAID, in the long run, might end up helping prevent higher medical costs in the end. Also, understanding the prices of the medication and the connection to adverse events can help a physician navigate treatment plans for patients of all different economic statuses.

The results of the experiment could have been impacted due to limitations made in the study design. For example, participants should have been given fewer free response options throughout the survey. The free-response questions made it harder to understand the generalized overall effects of NSAIDs and the overall treatment plan for participants. The free responses caused an abundance of other medications to be listed that were not used by other participants. This decreased the number of participants that were used in the pain level and NSAID comparison, which could have correlated to the number of results that showed insignificant. Also, keeping the survey questions to multiple choice only would allow an increase in participants outside the United States due to being able to control that the medications being looked at are approved in different countries. The experiment could have also been improved to help gather better data by giving descriptions for each type of pain looked at so the participant could give the most accurate answer. For example, a person may think that nerve and spinal pain have a similar meaning or that the pain location is the same. The results could have also been impacted by how honest a person was with completing the survey. A person could have selected random choices for any of the multiple-choice questions and put any type of response in the free response questions. Having to rely on people to answer honestly can reduce the chances of being able to find significant results within the sample population. The results of the experiment could have also been impacted by how effective the questions asked in the survey were to be able to accept the hypothesis. Since the survey was not one that has been effective in the past, it could have impacted how useful the questions were to get meaningful results.

The experiment leads to further discussion of whether the medications women are currently using to treat this disease are enough. The study talked about earlier in this section showed that Etorixocib was significant in helping reduce pain in a majority of men. Since the data did not show one type of NSAID being more effective than another, it could bring to question whether women need an additional medication analyzed to create an overall significant result as Etorocoxib does in men. The results showed that NSAIDs help reduce pain overall, but there was not a specific NSAID that was most effective in pain reduction. NSAIDs should not be eliminated from use in women with AS, but finding one medication that causes a positive majority effect in the reduction of pain for women could help streamline treatment plans. For example, tumor necrosis factor inhibitors with the use of NSAIDs are an effective treatment plan used in men [6]. However, it is not effective in women [6]. This is a good example of how more medications/treatment options need to be evaluated for women. One medication that could be next to be analyzed is Iguratimod [22]. This drug has similar effects to NSAIDs in helping reduce inflammation while also working towards other symptoms like protecting the bones [22]. The drug was also being looked at as a possible outlet for treatment as a way to try and reduce the adverse events and toxic effects that medications like NSAIDs cause [22]. The reduction in testing out different medications can help reduce the time that pain levels are out of control and help a person get back to as much of a normal life as possible.

Data Accessibility

Schmidt, Kristopher, 2024, "Data for Ankylosing Spondylitis Pain and NSAID Survey (Responses) - Form Responses 1", https://doi.org/10.17026/LS/KGUA93, DANS Data Life Sciences data base.

Consent

Each participant read and gave permission electronically to participate in the study at the beginning of the survey.

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