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Research Article

Short-Term Efficacy of Hydroxychloroquine Versus Sulfasalazine in the Treatment of Undifferentiated Arthritis

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Abstract

Background: Early undifferentiated arthritis (UA) is an inflammatory joint disorder lasting under three months that does not meet criteria for specific rheumatic diseases. Some cases resolve spontaneously, while others progress to rheumatoid arthritis (RA) or related conditions. Early treatment may improve prognosis, but optimal therapy is uncertain. Methotrexate (MTX) is often first-line; however, sulfasalazine and hydroxychloroquine are alternatives when contraindications exist. Concerns about combination therapy toxicity and lack of direct comparisons prompted this study.

Objectives: The present study aimed to compare the clinical efficacy of sulfasalazine and hydroxychloroquine in patients with early UA.

Methods: This retrospective study evaluated 70 patients presenting with pain, swelling, or limited movement in one or both knees at Shahid Sadoughi Hospital. Patients were assigned to either sulfasalazine 1000 mg/day (n = 35) or hydroxychloroquine 400 mg/day (n = 35) for 12 weeks. Outcomes included pain scores, knee swelling, and range of joint motion. Complete clinical response rates were also assessed.

Results: The groups were similar in age and gender ($P > 0.05$). Baseline pain scores were 6.08 ± 1.14 (hydroxychloroquine) and 6.80 ± 1.30 (sulfasalazine). After treatment, pain decreased to 3.02 ± 1.97 and 1.77 ± 1.91, respectively ($P < 0.05$ for both), with greater reduction in the sulfasalazine group. No significant between-group differences were found in swelling or range of motion ($P > 0.05$). Complete clinical response occurred in 14.2% (hydroxychloroquine) versus 37.1% (sulfasalazine) ($P < 0.05$).

Conclusions: Both treatments significantly reduced pain in early UA, but sulfasalazine provided greater pain relief and higher rates of complete clinical response, suggesting it may be more effective for this patient population in the short-term.

Keywords: Hydroxychloroquine, Sulfasalazine, Undifferentiated Arthritis, Conventional Disease-Modifying Anti-rheumatic Drugs (cDMRds)

1. Background

Early undifferentiated arthritis (UA) encompasses a group of inflammatory joint diseases that last for less than three months and do not meet the criteria for established rheumatic diseases, such as rheumatoid arthritis (RA) (1, 2).

To be classified as early UA, patients must exhibit at least one swollen or tender joint. Individuals experiencing only stiffness, arthralgia, or discomfort during movement without the presence of swelling or tenderness do not fall under the category of UA (1). In its early stages, early UA may resemble conditions like early RA, scleroderma, or lupus. However, a definitive diagnosis typically emerges in the following months or even a year. Approximately one-third of patients with early UA progresses to RA or another rheumatic disease (3). Many patients with develop a different definitive rheumatic disease, while some experience spontaneous remission (4).

Recent research emphasizes the crucial role of early and effective treatment for individuals at risk of developing persistent and/or erosive arthritis during the initial stages of UA. This underscores the significance of proactive medical intervention in managing the condition and potentially altering its

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course (1). However, there is limited data available on the optimal choice of therapeutic agents for cases of early UA.

According to studies, using glucocorticoids in the early stages of the disease in low or moderate doses is recommended (5-7). Once disease activity is under control, it is advised to gradually reduce steroid usage. Additionally, the use of glucocorticoids should be temporary and limited to less than six months to minimize potential adverse effects (1).

If one or more high-risk features are present, patients should be started on disease-modifying antirheumatic drugs (DMARDs), preferably methotrexate (MTX), unless contraindicated (e.g., due to liver dysfunction or pregnancy planning) (8-10).

If MTX is contraindicated, sulfasalazine or leflunomide can be regarded as primary medications (1). In addition, MTX can be combined with either sulfasalazine and hydroxychloroquine or leflunomide, depending on factors such as patient tolerance, cost-effectiveness, and side effect profiles (1). The classical combination strategy of MTX plus hydroxychloroquine and sulfasalazine has shown good response and safety. It has been reported that 77% of refractory RA patients experienced a 50% improvement at nine months without major drug toxicity when using the MTX + hydroxychloroquine + sulfasalazine triple therapy (4). Nevertheless, determining the treatment that yields optimal results or potentially modifies the course of the disease is yet to be accomplished.

2. Objectives

Given suggestions by some authors that the combination of drugs may result in a higher toxicity profile (11, 12) and considering the absence of a comprehensive study comparing these drugs in terms of pain relief, reduction in knee swelling, and overall clinical response, the present study aims to assess and compare the efficacy of early (short-term) treatment with hydroxychloroquine and sulfasalazine over a 12-week period in patients with UA.

3. Methods

3.1. Design of the Study and Sample Selection

This retrospective study included 70 patients who experienced pain, swelling, or restricted movement in one or both knees at Shahid Sadoughi Hospital from 2018 to 2019. In this study, the diagnosis of UA was based on both clinical presentation and objective evidence of joint inflammation — such as swelling, warmth, and restricted motion — along with elevated inflammatory markers, all confirmed by a rheumatologist. According to decision physician, one group (n = 35) was prescribed 1000 mg/day of sulfasalazine and another group received 400 mg/day of hydroxychloroquine for 12 weeks. These patients in two groups were assessed before and after treatment with regard to the range of joint motion, pain, and knee swelling. The data were obtained through a comprehensive review of patients' medical records during the specified period.

3.2. Inclusion and Exclusion Criteria

Inclusion criteria encompassed individuals aged 35 to 65 years, with no history of rheumatic disease, arthritis graded between 1 and 3, and the presence of pain, swelling, and limited movement in one or both knees.

Exclusion criteria included a history of knee joint trauma, the use of arthritis medications, and grade 4 arthritis based on knee X-rays. Furthermore, the aspiration of bloody fluid, septic knee arthritis, or the identification of crystallopathy resulted to exclude patients from the study.

3.3. Swelling of the Knee Joint

Swelling of the knee joint based on the ballottement test was classified into 4 groups, including 0 (no swelling), +1, and +2 (moderate swelling), and +3 (severe swelling).

3.4. Range of Joint Motion

Range of joint motion is classified as unrestricted knee movement (0), movement between 0 - 25% of maximum rate (+1), 25 - 50% of maximum rate (+2), 50 - 75% of maximum rate (+3), and 75% - 100% of maximum rate (+4); Furthermore, 0 - 25% is equal to a 0 - 45° range of motion reduction; 25 - 50% is equal to a 45 - 90° range of motion reduction; 50 - 75% is equal to a 90 - 135° range of motion reduction; 75 - 100% is equal to a 135 - 180° range of motion reduction.

3.5. The Pain of Knee Joint

The knee joint pain, as assessed using the visual analogue scale, was measured on a scale of 0 to 10.

3.6. Complete Clinical Response to Treatment

The reduction of pain and swelling, coupled with the restoration of unrestricted knee movement by the end of the treatment period, was considered a complete clinical response to treatment.

Table 1. The Comparison of the Two Groups in Terms of Demographic Characteristics [a, b]

Variables	Hydroxychloroquine	Sulfasalazine	P-Value
Age			0.467
35 - 50	16 (45.7)	13 (37.1)	
51 - 60	19 (54.3)	22 (62.9)	
Total	35 (100)	35 (100)	
Gender			0.526
Men	7 (20)	5 (14.3)	
Women	28 (80)	30 (85.7)	
Total	35 (100)	35 (100)	

[a] Values are expressed as No. (%).

[b] Chi-square test.

3.7. Analysis of Data

Data were entered into SPSS, version 23. The Mann-Whitney test was used for comparing variables. For comparing variables before and after treatment, the Wilcoxon test was employed. Chi-square test was used for comparison of frequency of patients in terms of variables between two groups and a P-value less than 0.05 was considered significant.

4. Results

This study was conducted on 70 patients with UA in Rheumatology Department of Shahid Sadoughi Hospital. The comparison of the two groups in terms of demographic characteristics is shown in Table 1.

As shown in Table 1, no notable distinction was seen between the two groups in terms of age, and gender ($P > 0.05$). The comparison of the two groups regarding the knee injury, and duration of arthritis is shown in Table 2. As shown in Table 2, no notable distinction was observed between the two groups in terms of knee injury, and duration of arthritis ($P > 0.05$), indicating that the two groups were the same before treatment.

The frequency comparison of patients between the two groups with respect to knee swelling, and range of and joint motion is shown in Table 3. Although knee swelling and range of joint motion improved significantly after treatment in both groups, no remarkable difference was observed between the two groups before treatment ($P > 0.05$) and after treatment ($P > 0.05$) (Table 3).

The comparison of pain between the two groups is shown in Table 4. According to Table 4, although pain significantly decreased after intervention in both groups, the reduction was more pronounced in the sulfasalazine group compared to the hydroxychloroquine group ($P < 0.05$).

Table 5 displays a comparison of the frequency of patients with a complete clinical response between the two groups.

Table 5 indicates a notable distinction between the two groups in terms of the frequency of patients achieving a complete clinical response ($P < 0.05$). Specifically, the frequency of patients with a complete clinical response in the sulfasalazine group was significantly higher than in the hydroxychloroquine group. Additionally, no complications were observed in either of the two treatment groups at the end of the treatment period.

5. Discussion

This study is the first to compare the use of hydroxychloroquine and sulfasalazine in patients with UA. These components, including hydroxychloroquine and sulfasalazine, share a similar mechanism in inhibiting cytokine production. Hydroxychloroquine disrupts lysosomal activity and autophagy, destabilizes cell membranes, and modifies signaling pathways and transcriptional activity. These actions lead to the inhibition of cytokine production and the modulation of specific co-stimulatory molecules (13). The exact mechanism of action of sulfasalazine remains unclear, but it is known to inhibit cytokine release, including interleukins (IL-1, IL-2, IL-6, IL-12), and tumor necrosis factor-α, as well as immunoglobulin M (IgM) and IgG production, as observed in studies (14). Although treatment allocation in this study was non-randomized, the two groups were matched for baseline characteristics (age, gender, duration of arthritis, and symptom severity), ensuring a homogeneous study population and minimizing potential confounding.

Table 2. The Comparison of the Two Groups Regarding Variables [a, b]

Variables	Hydroxychloroquine	Sulfasalazine	P-Value
Knee injury			0.937
Right	5 (14.3)	4 (11.4)	
Left	4 (11.4)	4 (11.4)	
Both	26 (74.3)	27 (77.1)	
Total	35 (100)	35 (100)	
Duration of arthritis (wk)			0.759
< 6	6 (17.1)	7 (20)	
≥ 6	29 (82.9)	28 (80)	
Total	35 (100)	35 (100)	

[a] Values are expressed as No. (%).

[b] Chi-square test.

Table 3. The Comparison of the Frequency of Patients in Two Groups Considering Knee Swelling, and Range of Joint Motion [a]

Variables and Grades	Hydroxychloroquine	Sulfasalazine	P-Value [b]
Knee swelling (before)			0.190
0	2 (5.7)	3 (8.6)	
+1	30 (85.7)	23 (65.7)	
+2	3 (8.6)	7 (20)	
+3	0 (12)	2 (5.7)	
Knee swelling (after)			0.057
0	12 (34.3)	20 (57.1)	
+1	23 (65.7)	15 (42.9)	
+2	0 (0)	0(0)	
+3	0(0)	0(0)	
Comparison (before and after)	P < 0.001 [c]	P < 0.001 [c]	
Range of joint motion (before)			0.089
0	4 (11.4)	5 (14.3)	
+1	27 (77.2)	17 (48.6)	
+2	4 (11.4)	13 (37.1)	
+3	0 (0)	0 (0)	
Range of joint motion (after)			0.094
0	16 (45.7)	23 (65.7)	
+1	19 (54.3)	12 (34.3)	
+2	0 (0)	0 (0)	
+3	0 (0)	0 (0)	
Comparison (before and after)	P < 0.001 [c]	P < 0.001 [c]	

[a] Values are expressed as No. (%).

[b] Mann-Whitney test.

[c] Wilcoxon test.

The findings of this study showed that knee swelling and range of joint motion improved significantly after treatment in both groups, but there was no significant difference between the two groups after treatments. Additionally, although pain decreased significantly after intervention in both groups, the reduction of pain in the sulfasalazine group was greater than in the hydroxychloroquine group. Moreover, after treatment, the frequency of patients who responded to treatment in the sulfasalazine group was significantly higher than

Table 4 . The Comparison of Pain Between the Two Groups [a]

Variables	Hydroxychloroquine		Sulfasalazine		P-Value [b]
Pain (before)	6.080 ± 1.140	6 (1.5)	6.80 ± 1.30	7 (1.8)	0.031
Pain (after)	3.020 ± 1.970	4 (2.7)	1.77 ± 1.91	1 (2.6)	0.012
Comparison of before and after	P < 0.001 [c]		P < 0.001 [c]		-

[a] Values are expressed as mean ± SD or median (IQR).

[b] Mann-Whitney test.

[c] Wilcoxon test.

Table 5. A Comparison of the Frequency of Patients with a Complete Clinical Response Between the Two Groups [a]

Variable	Hydroxychloroquine	Sulfasalazine	P-Value [b]
Complete clinical response			0.029
Yes	5 (14.2)	13 (37.1)	
No	30 (85.8)	22 (62.9)	
Total	35 (100)	35 (100)	

[a] Values are expressed as No. (%).

[b] Chi-square test.

in the hydroxychloroquine group, indicating a higher efficacy of sulfasalazine in the treatment of patients with UA. Limited studies have explored the effects of hydroxychloroquine and sulfasalazine, either as monotherapy or in combination in UA therapy.

Muilu et al. (15), conducted a nationwide register-based study in Finland in 2020, evaluating the use of various anti-rheumatic drugs by the end of the first year following arthritis diagnosis in 2433 patients with UA. The study observed that 1121 patients (46.1%) utilized sulfasalazine, while 472 patients (19.4%) were prescribed hydroxychloroquine (15), suggesting a higher utilization of sulfasalazine in UA therapy in Finland. However, it is noteworthy that the study did not include a comparison of the efficacy between these two components.

Mahmoud et al., examined the efficacy of hydroxychloroquine as monotherapy for early UA. The study involved thirty patients diagnosed with early UA, all of whom received hydroxychloroquine after the UA diagnosis was established. The results showed a positive response in 96% of the patients, and 10% experienced a favorable response after doubling the treatment duration Additionally, the study observed a higher incidence of early UA in female patients compared to males, particularly among those in middle age, as indicated in the study results (16).

Wevers-De Boer et al., investigated the impact of drug therapy on UA, revealing that combination DMARD therapy, including MTX, sulfasalazine, and hydroxychloroquine is superior to MTX alone, particularly after a minimum of 4 months. This combination therapy demonstrated greater effectiveness in suppressing disease activity in patients with UA at a high risk of developing persistent arthritis. Therefore, it seems that initiating treatment early may lead to rapid suppression of inflammation (17). Mashayekhi et al. also assessed the outcomes of patients with undifferentiated peripheral inflammatory arthritis treated with DMARDs. Their findings revealed that although the majority of cases treated with combination therapy (DMARDs) do not progress to RA, most still require ongoing therapy, and only a few achieve medication-free remissions (18).

Heimans et al. conducted a study on UA patients and early RA, evaluating remission after a one-year follow-up. In this study, all patients initiated MTX, accompanied by prednisone. Patients who achieved early remission had their prednisone gradually tapered to zero. If they remained in remission at the 8-month MTX was also tapered to zero. If remission was not achieved at 8 months, participants were randomly assigned to either arm 1, consisting of a combination of MTX (25 mg/week), hydroxychloroquine (400 mg/day), sulfasalazine (2000 mg/day), and prednisone (7.5 mg/day), or arm 2, consisting of adalimumab (ADA) at

40 mg every 2 weeks along with MTX at 25 mg/week. The findings demonstrated that for those not achieving early remission, treatment with ADA leads to higher remission rate compared to a combination of DMARDs with a low dose of prednisone (19). Considering the diverse findings from various studies, further research is warranted for the treatment of patients with UA.

5.1. Conclusions

While pain decreased significantly after intervention in both groups, the alleviation was more pronounced in the sulfasalazine group than in the hydroxychloroquine group. In addition, the frequency of patients with a complete clinical response was higher in the sulfasalazine group. Therefore, it appears that sulfasalazine played a more prominent role in treatment of UA patients in the short term.

5.2. Limitations

Although sulfasalazine generally has a faster onset of action compared to hydroxychloroquine — which may require 24 - 48 weeks to achieve maximal effect — our 12-week evaluation primarily reflects short-term clinical response and may not fully capture hydroxychloroquine's potential efficacy. Furthermore, important patient information, such as medical history (e.g., hypothyroidism, diabetes), concurrent medication use, and disease complications, was not consistently recorded in the medical files.

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Footnotes

Authors' Contribution: Gh. D. contributed to the study concept and designed the study. M. B. O. contributed to the statistical analysis and interpretation of data. H. S. designed the study and collected data, and wrote the paper.

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