ORIGINAL ARTICLE

COMPARATIVE STUDY OF ORAL NAPROXEN AND ASPIRIN FOR ACUTE RHEUMATIC FEVER TREATMENT: SAFETY AND EFFICACY ANALYSIS

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Objectives: This observational case-control study aimed to assess the safety and efficacy of oral Naproxen as an alternative to oral Aspirin/acetylsalicylic acid (ASA) for treating acute rheumatic fever (ARF).

Methodology: Patients meeting the revised Jones criteria 2015 for ARF were enrolled from November 2018 to May 2019 at a single tertiary care Children's Hospital. They were divided into two groups: Group-A receiving ASA (control) and Group-B receiving Naproxen (case). Primary outcome measures included the number of days until complete resolution of arthralgia or arthritis, while secondary outcome measures included resolution of fever and normalization of erythrocyte sedimentation rate (ESR).

Results: Sixty-four consecutive patients with ARF were enrolled, with 32 in each group, matched for age and gender. The majority (80%) had recurrent ARF. Median age at presentation was similar in both groups. ESR levels did not differ between the groups at admission or at the end of treatment. Median time for resolution of fever was 9(6-11) days in Group-A and 7.5(5-10) days in Group-B. Resolution time for arthritis was similar in both groups, with a median of 3(2-4) days. Gastric pain and vomiting were significantly lower in Group-B than in Group-A. Overall response rates were comparable between the groups.

Conclusion: Naproxen demonstrates equal effectiveness, safety, and better tolerance compared to Aspirin in treating ARF patients.

Keywords: Acute Rheumatic Fever, Rheumatic Heart Disease, Anti-inflammatory treatment, Naproxen

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INTRODUCTION

The cornerstone of treating acute rheumatic fever (ARF) symptoms has traditionally been aspirin (acetylsalicylic acid, ASA) for fever, arthralgia, arthritis, and mild to moderate carditis, while steroids are reserved for severe carditis and non-tolerance to non-steroidal anti-inflammatory drugs (NSAIDs).[1-3] However, naproxen sodium, another NSAID, is gaining attention for its superior safety profile and twice-daily dosing regimen, making it an attractive alternative for ARF treatment.[2-4] While a prospective, randomized trial comparing naproxen to aspirin demonstrated its efficacy and safety, studies supporting its use are limited.[5] Aspirin, on the other hand, is associated with adverse effects such as elevation of hepatic enzymes, dyspepsia, vomiting, and headaches, with rare but serious concerns about Reye's syndrome in children with certain viral infections.[6,7]

Although the prevalence of ARF has decreased globally, certain regions still face a significant burden.[8] In the absence of an effective vaccination, early recognition and optimal anti-inflammatory treatment are crucial for achieving desirable outcomes.[9-12] Naproxen sodium is now recommended as the first-line anti-inflammatory medication for ARF, but evidence supporting its use remains limited to case series and a small randomized controlled trial from 2000.

To address this gap, we conducted an observational case-control study to evaluate the safety and efficacy of naproxen sodium as an alternative to aspirin/ASA

in managing children with ARF presenting at a single tertiary care hospital. By elucidating the comparative effectiveness and safety of naproxen sodium in ARF treatment, our study aims to contribute to the evolving landscape of ARF management strategies and inform clinical practice guidelines.

METHODOLOGY

Study Design: This was an observational case-control study aimed at evaluating the efficacy of Aspirin and Naproxen in the treatment of arthritis or arthralgia with or without carditis, according to the modified Jones criteria 2015.

Setting: The study was conducted at the Children's Hospital, Lahore, from November 2018 to May 2019. The study protocol received approval from the institutional review board (CH/ICH 2018/24, dated 3rd November 2018).

Participants: Inclusion criteria encompassed all patients presenting with arthritis or arthralgia, with or without carditis, and meeting the modified Jones criteria 2015. Written informed consent was obtained from the parents or guardians of all participants. The exclusion criteria were:

1. Isolated chorea or carditis without arthralgia or arthritis;
2. Initial use of corticosteroids for severe carditis or pericardial effusion;
3. Prior use of Aspirin or any NSAIDs before hospital admission or study enrollment;
4. Known history of allergy or adverse reactions to NSAIDs.

Variables: The primary outcome variable was the number of days until complete resolution of arthralgia or arthritis. Arthralgia or arthritis was defined by joint pain or swelling, or by two of the following: joint tenderness (including pain on movement), limited movement, and local warmth. Secondary outcome variables included settlement of fever and normalization of ESR. Fever resolution was defined as a fever-free (<38°C) period of more than 24 hours after treatment initiation.

Data Sources / Measurement: Patients were retrospectively assigned to either Aspirin (80-100 mg/kg/day in four daily doses) or Naproxen sodium (15-20 mg/kg/day in two doses) groups based on their treatment received during the study period. Serum levels for aspirin were not monitored due to unavailability. Treatment was continued until all clinical signs and symptoms resolved and ESR returned to normal. Clinical data were collected on days 1, 7, 14, 28, and 42 of treatment, including age, sex, and other demographic variables. Adverse events were recorded for each group. Echocardiography was performed by a consultant pediatric cardiologist and confirmed by a colleague.

Bias: Efforts to minimize bias included careful selection of cases and controls, as well as detailed monitoring of confounding variables.

Study Size: The study included all eligible patients who presented during the specified study period from November 2018 to May 2019. The exact number of participants was not predetermined, as it was dependent on the number of patients meeting the inclusion criteria during the study period.

Quantitative Variables: Continuous variables were expressed as median and quartiles due to their non-normal distribution. Categorical variables were described using frequencies. Primary outcome measures were the duration until complete resolution of arthritis or arthralgia. Secondary outcome measures included the time to fever resolution.

Statistical Methods: Statistical methods involved in this observational case-control study included descriptive statistics to summarize demographic and clinical characteristics, with continuous variables expressed as median and quartiles due to non-normal distribution. Categorical variables were described as frequencies. Comparative analysis between treatment groups (Naproxen and Aspirin) was conducted using the Chi-square test for categorical variables, with a significance level set at $p < 0.05$. Outcome measures, including resolution of arthralgia/arthritis, fever, and normalization of ESR, were assessed based on predefined criteria. Bias mitigation strategies included blinded outcome assessments by experienced pediatric cardiologists and standardized data collection. Sample size calculation ensured adequate power to detect meaningful differences between groups, and ethical considerations were addressed with institutional review board approval and informed consent. Statistical analysis was performed using SPSS version 20.

RESULTS

Participants: A total of 64 patients with acute rheumatic fever (ARF), comprising both first episode and recurrent cases, were enrolled in the study and divided randomly into two groups, with 32 patients

each. Patients who refused participation, were non-compliant, or initially received other NSAIDs or steroids were excluded. Group-A served as the control group receiving Aspirin (ASA), while Group-B constituted the case group receiving Naproxen sodium.

Table 1: Demographic profile, clinical profile and laboratory parameters in both groups

	Control ASA	Case Naproxen	P-value
Total (N)	**32**	**32**	-
Age in years (Median with range)	10 (6-15)	11(6-14)	0.4
M: F ratio	1.3:1	1.3:1	>0.999
Acute Rheumatic Fever (first episode)	6 (18.8%)	7 (21.9%)	0.756
Rheumatic Recurrence	26 (81.2%)	25 (78.1%)	
Carditis	30 (93.8%)	30 (93.8%)	>0.999
Polyarthritis/Polyarthralgia	13 (40.6%)	12(37.5%)	0.79
Chorea	0 (0%)	0 (0%)	>0.999
Subcutaneous nodules	4 (12.5%)	5 (15.6%)	0.72
Erythema marginatum	2 (6.3%)	1 (3.1%)	>0.999
Fever	24(75%)	31(96.9%)	0.03
Prolong PR interval on ECG	11(34.4%)	15(46.9%)	0.45
Raised ESR	32(100%)	32(100%)	>0.999
Median ESR	60	68	
Raised CRP	31(96.9%)	31(96.9%)	>0.999
Median CRP level	32	31	
Leukocytosis	15(46.9%)	14(43.8%)	>0.999
Raised ASO titer	29(90.6%)	32(100%)	>0.999

Descriptive Data: The median age in Group-A was 10 years (range: 6-15) and in Group-B was 11 years (range: 6-14), with a male to female ratio of 1.3:1 in both groups. Most patients had a history of rheumatic heart disease, with recurrence being predominant (Group-A: 78%, Group-B: 81%). Carditis was the most common major manifestation, observed in 93.8% of patients in both groups. Mitral valve involvement was prevalent in all patients, with no significant difference between the groups. Fever was the most common minor criteria, presenting in 86% of the cases.

Outcome Data: Median time for resolution of fever was 9 days in Group-A and 7.5 days in Group-B, with no significant difference observed (p=0.15). Arthritis resolved in both groups at a median of 3 days. Gastric pain and vomiting were significantly lower in Group-B compared to Group-A (p=0.02 and p=0.03 respectively). Median ESR and CRP levels did not significantly differ between the groups at presentation, end of therapy, or at 6-week and 3-month follow-ups. Response rate to treatment was comparable between the groups, with resting tachycardia persisting in a small proportion of patients mainly due to valvular lesions and compensated heart failure.

Table 2: Cardiac involvement in both groups

	Control ASA	Case Naproxen	P-value
Total (N)	**32**	**32**	-
Mitral valve involvement	32 (100%)	32 (100%)	>0.999
Mitral regurgitation	30 (94%)	28 (87.5%)	0.85
Mitral stenosis	4 (12.5%)	2 (12.5%)	>0.999
Aortic and mitral involvement	17 (53.1%)	15 (46.9%)	0.8
Tricuspid valve involvement	4 (12.5%)	6 (18.8%)	0.5
Pulmonary hypertension	16 (50%)	15(46.9%)	>0.999
Pericardial effusion	14 (43.2%)	14 (43.2%)	>0.999
Median LVDd (mm)	48 (37-72)	49.5(38-75)	0.65
Median EF (%)	72 (64-84)	74 (64-85)	0.24
Median FS (%)	36	36	>0.999

Main Results: Both Aspirin and Naproxen sodium showed comparable efficacy in resolving arthritis or arthralgia in patients with acute rheumatic fever. However, Naproxen sodium demonstrated fewer gastric adverse effects compared to Aspirin. Carditis, the major manifestation of ARF, showed no significant difference in prevalence or severity between the two treatment groups. Overall, both drugs were well-tolerated, and none of the patients experienced adverse symptoms related to drug intake during the follow-up period.

Table 3: Response and side effects/complications

	Control ASA	Case Naproxen	P-value
Total (N)	**32**	**32**	-
Responsive after 6weeks	29 (90.6%)	29 (90.6%)	>0.999
Improvement in arthritis (median days)	3 (2-4)	3 (2-4)	>0.999
Resolution of fever (median days)	9 (6-11)	7.5 (5-10)	0.15
Final ESR at 6 weeks (median)	25 (78.1%)	27 (84.3%)	0.26
Final CRP at 6 weeks (median)	3 (9.4%)	3 (9.4%)	>0.999
Resting tachycardia after 6 weeks	2(6.25%)	3(9.4%)	>0.999
Complications			
Gastritis	12(37.5%)	3(9.4%)	0.02
Vomiting	11(34.4%)	3(9.4%)	0.03
Jaundice	2(6.3%)	1 (3.10%)	
Rash	5(15.6%)	5(15.6%)	>0.999
Headache	4(12.5%)	1(3.10%)	0.35
Reye's syndrome	0(0%)	0(0%)	-

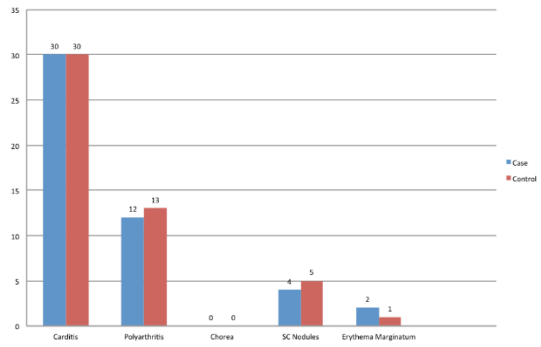

Figure 1: Comparison of frequency of major criteria in both groups

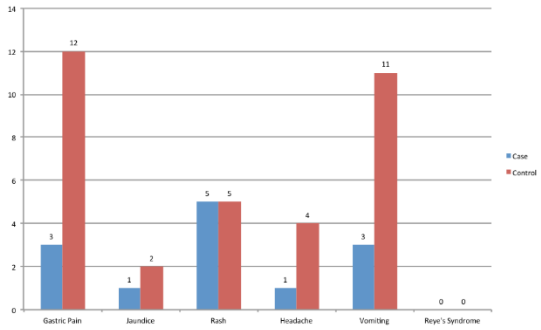

Figure 2: Adverse effects in both groups

DISCUSSION

Acute rheumatic fever (ARF) continues to be a significant health concern in developing countries, with varying incidence rates. The initial management typically involves restriction of physical activities, eradication of streptococcal organisms, and use of anti-inflammatory drugs.[9-12] Salicylates, particularly aspirin, have been a longstanding treatment option for arthritis and mild to moderate carditis associated with ARF. However, the use of high-dose aspirin in children with ARF is associated with various adverse effects, ranging from gastrointestinal discomfort to serious conditions such as Reye syndrome.[13]

Despite the availability of newer nonsteroidal anti-inflammatory drugs (NSAIDs) since the late 20th century, aspirin remains the drug of choice for ARF in many parts of the world due to its extensive experience and low cost.[14] However, there has been growing interest in exploring alternative treatments to minimize adverse effects. Naproxen, a NSAID commonly used for other inflammatory conditions, has shown promise in the treatment of ARF.[15-17]

Several studies have investigated the efficacy and safety of naproxen compared to aspirin in patients with ARF.[18-23] Uziel et al. reported favorable outcomes with naproxen treatment, particularly in patients without carditis.[7] Similarly, Hashkes et al. conducted a prospective study demonstrating the equivalence of naproxen and aspirin in resolving arthritis associated with ARF, with fewer liver enzyme elevations observed in the naproxen group.[5] Çetin et al. conducted a retrospective study comparing the clinical efficacy and safety of naproxen and aspirin in new-onset ARF, finding naproxen to be as effective as aspirin with a lower incidence of hepatic toxicity.[6]

Other NSAIDs such as indomethacin, tolmetin, and ibuprofen have also been investigated for ARF treatment, showing favorable responses and safety profiles in various studies.[20-23] Tolmetin was found to be effective and safe in patients with ARF without carditis, while ibuprofen demonstrated comparable outcomes to aspirin with fewer liver enzyme elevations.[24]

Among these NSAIDs, naproxen has emerged as a promising first-line therapy for ARF due to its favorable safety profile and convenient dosing regimen.[25] However, the available data on alternative treatments are primarily from case series and small randomized controlled trials.[26] Large-scale multicenter randomized controlled trials are challenging due to the declining prevalence and changing clinical profile of ARF.

Our study contributes to the understanding of naproxen's efficacy and safety in ARF treatment, particularly following the 2015 revision of diagnostic criteria. Echocardiography was incorporated as a major criterion in our study, reflecting updated diagnostic guidelines. The dramatic response to naproxen observed in our patients for fever and arthritis resolution underscores its potential as a viable treatment option for ARF.

LIMITATION

Despite the valuable insights garnered from our study, it is important to acknowledge several limitations that may impact the interpretation and generalizability of our findings. Firstly, the lack of serum level monitoring for aspirin represents a notable constraint, as it precludes a comprehensive evaluation of drug exposure and its potential correlation with clinical outcomes. Secondly, the absence of blinding in our study design introduces the possibility of bias in treatment administration and outcome assessment, despite the objective definition and assessment of primary outcome measures by experienced pediatric cardiologists. Moreover, the exclusion of patients with

moderate to severe carditis who received initial corticosteroid therapy limits the applicability of our conclusions to this specific subgroup, potentially overlooking important insights into the efficacy and safety of naproxen in more severe cases. Additionally, the single-center nature of our study and the relatively small sample size further restrict the generalizability of our findings, underscoring the need for larger, multicenter studies to validate our results across diverse populations and settings.

CONCLUSION

In conclusion, our study provides evidence supporting the efficacy and safety of naproxen as compared to aspirin in the treatment of acute rheumatic fever (ARF) and recurrent ARF. Naproxen emerges as a viable alternative treatment option, offering comparable effectiveness and improved compliance due to its twice-daily dosing regimen. However, the continued use of aspirin may still be warranted in resource-constrained settings where it remains more readily available and cost-effective. Close monitoring for potential side effects is essential regardless of the chosen treatment option. Despite the promising findings, further research, including larger multicenter studies, is needed to validate these results and refine treatment guidelines for ARF.

AUTHORS' CONTRIBUTION

MS, IA, TK, UK, and NH: Concept and design, data acquisition, interpretation, drafting, final approval, and agree to be accountable for all aspects of the work. MS, IA, TK, UK, and NH: Data acquisition, interpretation, drafting, final approval and agree to be accountable for all aspects of the work.

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