Nonsteroid anti-inflammatory drug choices in patients with juvenile idiopathic arthritis: A systematic review

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ABSTRACT

Background: Disease-modifying anti-rheumatic drugs (DMARDs) are still a priority in treating juvenile idiopathic arthritis (JIA). The choice of drug therapy for the NSAIDs as an alternative to the therapy used in managing JIA cases due to the side effects of DMARDs. However, the former discussion of the choices therapy of NSAID therapy in JIA patients is still limited. This systematic review was conducted to present any choices of NSAIDs used for the treatment JIA and presented their effectiveness and adverse reaction compared with other NSAIDs used for treating JIA.

Methods: Comprehensive electronic searches were performed in PubMed/MDline, EMBASE, and Cochrane Library, choosing Randomized Controlled Trials of NSAIDs for treating children with JIA up to January 2009. The risk of bias was assessed using the Cochrane Risk of Bias Tools for randomized controlled trials.

Results: Eight eligible randomized controlled trials (RCT) out of 1309 studies were included, with a total of 1112 participants with JIA identified, addressing 19 kinds of interventions with nine types of medications. First RCT concluded that Celecoxib 3 mg/kg and Celecoxib 6 mg/kg were at least as effective as naproxen 7.5 mg/kg in terms of reducing clinical symptoms of arthritis and joint swelling. Second RCT concluded that Low Dose (0.3 mg/kg) and High Dose (0.6mg/kg) Celecoxib showed a greater improvement than the Naproxen group to relieve the pain. The third RCT stated that good efficacy or satisfaction is most frequent in the patient diagnosed with JIA which has each adverse reaction. The fourth RCT informed that Acetylsalicylic acid 75 mg/kg/day has better efficacy than Naproxen 10 mg/kg/day. Sixth RCT concluded that Celecoxib 3 mg/kg and Tolmetin Sodium 7.5 mg/kg/day decreased the duration of morning stiffness and reduced joint pain. Also, aspirin 50mg/kg/day resulted in ROM improvement in JIA patients.

Conclusions: We present Celecoxib, Rofecoxib, Meloxicam, Ibuprofen, Piroxicam, Acetylsalicylic Acid (ASA), Diclofenac Sodium, Tolmetin Sodium, and Naproxen as the NSAIDs choice drugs on pediatric patient diagnosed with JIA. which has each adverse event on each therapy.

Keywords: Juvenile Idiopathic Arthritis (JIA), Drugs, Non-Steroidal Anti-Inflammatory Drugs (NSAID), Disease-Modifying Anti-Rheumatic Drugs (DMARDs), Clinical Effectivity, Adverse event.


INTRODUCTION

Juvenile Idiopathic Arthritis (JIA) is a rheumatic disease that most often affects children and is one of the causes of childhood disability.1-3 This disease is characterized by a collection of symptoms of chronic arthritis.2 Until now, the etiology is unknown (idiopathic), with the onset of symptoms lasting for six weeks or more with the characteristics of patients under sixteen years. The International League of Association for Rheumatology (ILAR) classifies JIA into seven subtypes: oligoarticular JIA, seropositive polyarticular JIA, seronegative polyarticular JIA, systemic JIA (sJIA), Enthesitis-related arthritis (ERA), Juvenile Psoriatic Arthritis (JPsA), and JIA which undifferentiated category.4,5 Juvenile idiopathic arthritis (JIA) diagnosis was based on the criteria for the onset of arthritis symptoms more than six weeks before age sixteen and excluding other possible causes of arthritis.4 The initial classification was made according to the clinical features of the first six months of the disease course.1,6 The emergence of new clinical features during the disease determines the final disease subtype. The main purpose of classifying this disease is...
to unify the disease group, determine the choice of therapy, choose the follow-up strategy and determine the prognosis of the disease.2,3

Until now, Disease-Modifying Anti-Rheumatic Drugs (DMARDs) are still the main treatment of choice for diagnosing JIA.5,6 However, nonsteroid anti-inflammatory drugs (NSAIDs) are also recommended as options for managing JIA cases, especially in the initial phase to the escalation phase of treatment with DMARDs.1 NSAIDs produce analgesic and anti-inflammatory effects by inhibiting the formation of prostaglandins through the inhibition of cyclooxygenase (COX) isoenzymes, which are inhibitory enzymes in prostaglandin biosynthesis, either nonselective (COX-1 and COX-2) or selective (COX-2 only).1,5

A recent systematic review and meta-analysis presented data that DMARDs are still considered a priority in the treatment of JIA. The side effects of elevated liver enzymes (AST/ALT) and gastrointestinal disturbances are still common in many cases of treatment in JIA pediatric patients. The choice of drug therapy for the NSAIDs was chosen in JIA cases. However, former discussion of NSAID therapy classification in JIA patients is still limited.5,7 This systematic review was conducted to present any NSAIDs used for the treatment of JIA and find their effectiveness and adverse reaction compared with other NSAIDs used for treating JIA.8,9

METHODS

This study was designed with a systematic review. The review has conducted the choices therapy of Nonsteroid Anti-inflammatory Drugs (NSAIDs) in children with Juvenile Idiopathic Arthritis (JIA). We evaluated and interpreted the qualified studies using the PRISMA method (Figure 1).10-13 We determined a research topic and objectives and developed research questions before conducting search activities; next, we determined the keywords for the journal review. The author uses a logic grid method with the PICO approach to search for suitable keywords. The criteria for this review are full-text English journals and observational studies from 1st January 1965 to 1st January 2019.

After collecting the appropriate journals, we screened them based on the inclusion criteria. Finally, we report the outcome of the studies for analysis.

RESULT

Literature search

We conducted a systematic review of the open-access literature on the choices and effectiveness of nonsteroid anti-inflammatory drugs (NSAIDs) in pediatric patients (under 16 years) with a diagnosis of idiopathic juvenile arthritis (JIA). We identified literature from open-access databases, including MEDLINE (via PUBMED), EMBASE, and the Cochrane Library, published from 1st January, 1965 to 1st January, 2009 devoted to the category of Randomized Controlled Trial (RCT) studies comparing various NSAIDs to other NSAIDs or placebo in the management of JIA. The search keywords were developed based on the Population, Intervention, Comparison and Outcome (PICO).

The final keywords used are as follows:

- “Juvenile Idiopathic Arthritis” OR “Arthritis” OR “Still Disease” OR “Rheumatoid”
- “NSAIDs” OR “Agents” OR “Non-Steroidal Anti-Inflammatory Drugs” OR “Analgesics” OR “Indomethacin” OR “Naproxen” OR “Naprosyn” OR “Aspirin” OR “Acetylsalicylic Acid” OR “Celecoxib” OR “Celebrex” OR “Rofecoxib” OR “Piroxicam” OR

Figure 1. The diagram flow of PRISMA
REVIEW

“Ibuprofen” OR “Meloxicam” OR “Tolmetin” OR “Diclofenac” OR “Voltaren” OR “Voltarol” AND
• “Randomized Controlled Trial” OR “Control Clinical Trial” OR “Placebo” OR “Drug therapy” OR “groups”

From the title, we screened the literature that was likely to report relevant results based on these criteria. The study group that passed the title screening was then assessed for abstracts based on inclusion and exclusion criteria. We downloaded full articles that met the criteria, which were then evaluated for quality assessment and underwent data extraction.

Quality of Studies
The risk of bias was assessed using the Cochrane Risk of Bias Tool with seven components: i) random sequencing, ii) allocation concealment, iii) blinding of participants and personnel, iv) blinding of outcome assessment, v) incomplete outcome data, vi) selective reporting, and vii) other biases. Then, from these components, we label them into three groups: low risk, moderate, and high risk of bias. A total of 8 studies are known to have low-quality risk of bias.

Data Characteristics
Data characteristics of all studies that meet the inclusion criteria are compiled in table 1. All of the reviewed studies are randomized controlled trial written in English. The study designs include 8 randomized controlled trial finding the efficacy of each NSAIDs compare to another NSAIDs or same NSAIDs with different dosage or placebo. The follow up periods duration is from 2 until 24 weeks, the total number of interventions is 19 with 9 kind of medications, whereas Celecoxib 3 mg/kg, Celecoxib 6 mg/kg, Naproxen 7,5 mg/kg, Rofecoxib 0,3 mg/kg/d, Rofecoxib 0,6 mg/kg/d, Naproxen 7,5 mg/kg, Meloxicam 0,125 mg/kg, Meloxicam 0,25 mg/kg, Naproxen 7,5 mg/kg, Ibuprofen 30-40 mg/kg/d, Aspirin 60-80 mg/kg/d, Diclofenac 2-3 mg/kg/d, Aspirin 50-100

Table 1. Randomized Controlled trials Included in the systematic review Nonsteroid Anti-inflammatory Drug Choices In Patients With Juvenile Idiopathic Arthritis.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Follow Up (wk)</th>
<th>Study Design</th>
<th>Country</th>
<th>Type of JIA</th>
<th>Mean Duration</th>
<th>Treatment NSAIDs</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foeldvari, et al (2009)</td>
<td>12</td>
<td>RCT</td>
<td>Germany</td>
<td>pJIA, oJIA</td>
<td>2.71 (2.8)/ 3.77 (3.4)/ 3.41 (3.2)</td>
<td>Celecoxib 3mg/kg bid</td>
<td>2-16 yo</td>
</tr>
<tr>
<td>Reiff, et al (2006)</td>
<td>12</td>
<td>RCT</td>
<td>Brazil</td>
<td>pJIA, oJIA</td>
<td>4.0 (3.6)/ 3.4</td>
<td>Rofecoxib 0.3 mg/kg qd</td>
<td>2-16 yo</td>
</tr>
<tr>
<td>Rupert, et al (2005)</td>
<td>12</td>
<td>RCT</td>
<td>Russia</td>
<td>pJIA, oJIA</td>
<td>3.47 (3.4)/ 2.5 (2.8)/ 2.31 (2.1)</td>
<td>Meloxicam 0.125 qd</td>
<td>2-16 yo</td>
</tr>
<tr>
<td>Edward, et al (1990)</td>
<td>12</td>
<td>RCT</td>
<td>USA</td>
<td>pJIA, oJIA, sJIA</td>
<td>NA</td>
<td>Ibuprofen 30-40 mg/kg/d</td>
<td>-</td>
</tr>
<tr>
<td>Morteo, et al (1987)</td>
<td>12</td>
<td>RCT</td>
<td>Argentina</td>
<td>pJIA, oJIA, sJIA</td>
<td>2.7/1.6</td>
<td>Piroxicam*</td>
<td>2-15 yo</td>
</tr>
<tr>
<td>Kvien, et al (1984)</td>
<td>24</td>
<td>RCT</td>
<td>Norway</td>
<td>pJIA, oJIA, sJIA</td>
<td>1.0/1.3</td>
<td>Naproxen 10 mg/kg/d</td>
<td>3-16 yo</td>
</tr>
<tr>
<td>Haapassari, et al (1983)</td>
<td>2</td>
<td>RCT</td>
<td>Finland</td>
<td>pJIA, oJIA, sJIA</td>
<td>NA</td>
<td>Diclofenac 2-3 mg/kg/d</td>
<td>3-15 yo</td>
</tr>
<tr>
<td>Levinson, et al (1977)</td>
<td>12</td>
<td>RCT</td>
<td>Philippines</td>
<td>pJIA, oJIA, sJIA</td>
<td>3.7/3.4</td>
<td>Tolmetin 15 mg/kg/d</td>
<td>2-16 yo</td>
</tr>
</tbody>
</table>

pJIA: polyarticular juvenile idiopathic arthritis; oJIA: oligoarticular juvenile idiopathic arthritis; sJIA: systemic juvenile idiopathic arthritis.
mg/kg/d, Piroxicam, Naproxen 12.5 mg/kg/d, Naproxen 10 mg/kg/d, Aspirin 75 mg/kg/d, Tolmetin 15 mg/kg/d, and Aspirin 50 mg/kg/d. The age range of every participant was 2 – 16 years old.

Outcomes of Studies
The outcome of all studies included in this systematic review is summarized in Table 2. The results are categorized into Clinical Effectivity (CE) and Adverse Event (AE). First RCT study proves that Celecoxib (3 mg/kg) and Celecoxib (6 mg/kg) show a greater CE in reducing symptoms of arthritis and joint swelling. The AE of cytomegalovirus hepatitis and other viral infection more frequently occurred in celecoxib (3 mg/kg). Also, the exacerbations of JIA and asthma are found in celecoxib (6 mg/kg). Second RCT study proves that CE shows in the treatment of Low Dose (0.3 mg/kg) and HD (0.6 mg/kg) Rofecoxib compared with Naproxen (7.5 mg/kg) in terms of improving pain; however, AE of allergic-type of hypersensitivity and increasing rate of AST/ALT are common showed in those

### Table 2. The outcome of Clinical Effectivity and Adverse Event of each NSAIDs treated JIA.

<table>
<thead>
<tr>
<th>Author (Year)</th>
<th>Outcome Clinical Effectivity</th>
<th>Adverse Event</th>
<th>Quality of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Foeldvari, et al (2009)</td>
<td>Celecoxib 3 mg/kg and Celecoxib 6 mg/kg were both at least as effective as naproxen 7.5 mg/kg in terms of reducing clinical symptoms of arthritis and joint swelling.</td>
<td>GI disorder were observed more frequently in participant treated with Naproxen than celecoxib group. Other serious AE included acute cytomegalovirus hepatitis and viral infection in the celecoxib 3 mg/kg group. Exacerbations of JRA and asthma in the celecoxib 6 mg/kg group.</td>
<td>Low Risk</td>
</tr>
<tr>
<td>Reiff, et al (2006)</td>
<td>LD and HD Rofecoxib showed a greater improvement compared to the Naproxen group to relieve the pain</td>
<td>The most common AE are abdominal pain, upper abdominal pain and headache. GI disorder was most frequently in the participant of naproxen group. Mild to moderate allergic type skin and hypersensitivity most occurred in the participants with HD Rofecoxib and increase of ALT and/or AST are most common in the LD Rofecoxib group.</td>
<td>Low Risk</td>
</tr>
<tr>
<td>Ruperto, et al (2005)</td>
<td>The good efficacy or satisfactory is most frequently in the participant with Meloxicam 0.125 mg/kg rather than Meloxicam 0.25 mg/kg or Naproxen 10 mg/kg</td>
<td>Both Meloxicam 0.125 mg/kg, Meloxicam 0.25 mg/kg or Naproxen 10 mg/kg showing significant result of adverse event such as musculoskeletal and connective tissues disorder, skin disorders, eczema, erythema, pruritus, and rashes. Bleeding associated disorder and skin disorder are more often in the Naproxen group.</td>
<td>Low Risk</td>
</tr>
<tr>
<td>Edward, et al (1990)</td>
<td>Ibuprofen 30-40 mg/kg/d is an effective agent for symptomatic treatment of JIA and well tolerated in large proportion of children.</td>
<td>Adverse event that frequently occurred was gastrointestinal bleeding and vomiting in this study.</td>
<td>Moderate Risk</td>
</tr>
<tr>
<td>Morteo, et al (1987)</td>
<td>Piroxicam show more effective to control the symptoms and improving function than Naproxen 10 mg/kg/d</td>
<td>Piroxicam show an adverse event such as abdominal pain, diarrhea, mild elevation of transaminase levels. Abdominal pain, vomiting and hematuria that occurred in the adverse event with naproxen group.</td>
<td>Moderate Risk</td>
</tr>
<tr>
<td>Kvien, et al (1984)</td>
<td>Acetylsalicylic acid 75 mg/kg/d has better efficacy than Naproxen 10 mg/kg/d to relieve the symptoms.</td>
<td>N/A</td>
<td>Moderate Risk</td>
</tr>
<tr>
<td>Haapassari, et al (1983)</td>
<td>Both of diclofenac sodium 2-3 mg/kg/d and acetylsalicylic acid 50-100 mg/kg/d at least as good than placebo.</td>
<td>N/A</td>
<td>Moderate Risk</td>
</tr>
<tr>
<td>Levinson, et al (1977)</td>
<td>Tolmetin sodium 15 mg/kg/d group decrease the duration of morning stiffness and reduce joint pain. The significant result of ROM improvement is seen at aspirin 50 mg/kg/d group. Both of tolmetin sodium and aspirin show the elevated of serum transaminase value. Mild abnormalities of SGOT and SGPT may occur in the patient with aspirin group.</td>
<td>Low Risk</td>
<td></td>
</tr>
</tbody>
</table>
group of Rofecoxib. The third RCT study shows that Meloxicam (0.125 mg/kg) has a good CE compared with Naproxen group. At the same time, AE occurred in Meloxicam, showing significant result of adverse event such as musculoskeletal and connective tissues disorder, skin disorders, eczema, erythema, pruritus, and rashes. Fourth RCT study concludes that Ibuprofen (30 – 40 mg/kg) is an effective agent for symptomatic treatment of JIA and well-tolerated in large proportion of children, giving AE of Gastrointestinal (GI) bleeding and vomiting. Sixth and Eighth RCT studies of Piroxicam and Tolmetin give better CE than Acetylsalicylic Acid, but giving AE of elevated serum transaminase value and mild abnormalities of SGOT and SGPT may occur in the patient with aspirin group. Fifth and seventh studies are proved that acetylsalicylic acid and diclofenac sodium has better CE than Naproxen in treating the clinical symptoms but has no information of AE in those studies.

**DISCUSSION**

Juvenile Idiopathic Arthritis, also called an autoimmune disorder, is the most common chronic rheumatic disease characterized by persistent joint inflammation in childhood that causes by unknown etiology. JIA usually occurs in children before 16 years old, which has similar frequency effect in boys and girl. Globally, the prevalence of JIA has been estimated to range from 3.8 to 400/100.000 with an incidence of 1.6 to 23/100.000. Clinical features of JIA include fever, rash, joint pain, morning stiffness, swelling, and usually palpable warm, reduced joint motion with the specific sign and symptom on each subtype. Laboratory investigation show elevated White Blood Cells (WBC), Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), Rheumatoid Factor, and HLA B27 should be tested in JIA. X-ray showed the erosions and ultrasonic to confirm the joint effusion. Whole Body Bone Scan and Magnetic Resonance Imaging (MRI) are usually tested by pediatric rheumatologists. NSAID has now been chosen as one of the drug choices for treating the pediatric patient with JIA. NSAID is an analgesic and anti-inflammatory mechanism by inhibiting prostaglandins’ formation through the inhibition of cyclooxygenase (COX) isoenzymes, inhibitory enzymes in prostaglandin biosynthesis, either nonselective COX-1 and COX-2 or selectively COX-2 only.

In this study, NSAIDs such as Celecoxib, Rofecoxib, Ibuprofen, Piroxicam, Meloxicam, ASA, Tolmetin sodium are as effective and safe therapy JIA in pediatric patient but Naproxen has less efficacy compared with the other NSAIDs. American College of Rheumatology treatment recommended initiation of NSAID monotherapy for 1–2 months in most cases of oligoarticular and polyarticular JIA per 2011. Adverse events of each NSAID treatment for JIA patients are different. An adverse event that can be occurred such as gastrointestinal disorder, abdominal pain, vomiting, headache, skin hypersensitivity, hematuria, and bleeding associated disorder. This study shows gastrointestinal disorders more frequently occur in the Naproxen group than in celecoxib.

**CONCLUSION**

This systematic review discusses the NSAIDs choices as the alternative therapy for JIA. We present Celecoxib, Rofecoxib, Meloxicam, Ibuprofen, Piroxicam, ASA, Diclofenac sodium, Tolmetin Sodium and Naproxen, which has an adverse event on each therapy. Further studies that discussed the drug choices of JIA and its efficacies were required to increase the knowledge and guide the physician in selecting effective NSAIDs of JIA patients with least adverse event.

**CONFLICT OF INTEREST**

All authors declared that there is no conflict of interest related to the publication of this article.

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Each author has an equal contribution to the process of article writing.

**REFERENCES**


