

Treatment Efficacy of Celecoxib and Diclofenac Sodium in Rheumatoid Arthritis: A Review



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Submission: October 10, 2018; Published: December 14, 2018

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Abstract

Administrations of drugs that reduce pain and inflammation in Rheumatoid Arthritis (RA) have resulted in the experience of adverse effects. It is important to identify most suitable drug with increased treatment efficacy and reduced adverse effects for improved quality of life. RA is an inflammatory condition that affects joints resulting in chronic pain. Due to pain and stiffness of joints, the affected have a reduced quality of life. NSAIDs are commonly administered to reduce the pain and stiffness of joints. The most commonly prescribed drugs are Celecoxib and Diclofenac Sodium which are considered in this study. This study aims to determine the suitability and effectiveness of the drugs Celecoxib and Diclofenac Na in patients having rheumatoid arthritis in terms of efficacy and tolerance. This is a systematic review for which, using Cochrane review, Google Scholar and PubMed, 5 randomized control trials were chosen. According to this study, the treatment efficacy of both the drugs was similar in reducing pain and inflammation. But it is revealed that Celecoxib had lower probability of developing GI ulcers when compared to Diclofenac Na.

In order to provide improved healthcare service to rheumatoid arthritis patients, it is essential to identify treatment efficacy of drugs. There were reduced GI ulcers when using Celecoxib compared to Diclofenac Na. But it is essential that a stable conclusion is determined for both short-term and long-term administration. According to this study, the treatment efficacy of both the drugs was similar in reducing pain and inflammation. Most commonly observed adverse effect is the endoscopical GI ulcers which were observed among patients administered with both the drugs. It is important that the treatment efficacy in terms of reduced pain and inflammation, increased tolerance and reduced adverse effects be identified in order to ensure that patients are provided with appropriate healthcare.

Keywords: Adverse effects; Celecoxib; Diclofenac Na; Gastrointestinal Ulcers; Non-Steroidal Anti-Inflammatory Drug; Rheumatoid Arthritis; Treatment Efficacy

Introduction

Rheumatoid arthritis is a chronic inflammatory condition caused by degeneration of joints and swelling or hyperplasia that results in disability. It is one of the foremost causes of prolonged pain among the elderly population reducing the quality of lives Sangha O [1], Scott DL [2], Bijlsma JW [3]. Commonly, rheumatoid arthritis is first seen when the age is over 20 to 45 years where about 75% of the affected patients are female Simon LS [4]. It is observed among more than 0.5 to 1% of the total world population. According to the recent statistics, an annual incidence of 0.5 is noted per every 1000 and there is a gradual increment of statistic over time. Due to chronic pain, the affected elderly is unable to work, are depressed, have deranged social relationships and are having suicidal tendency as well Firestein GS [5], Goldberg [6].

Mostly rheumatoid patients are prescribed with Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) to reduce the inflammation and pain and improve the patient's mobility. NSAIDs have both anti-inflammatory and analgesic effects. The most prominent drugs administered are Celecoxib and Diclofenac Na. One of the adverse effects observed among the patients is gastrointestinal

damages such as ulcers, bleeding and perforation. The resulted peptic ulceration can range from superficial ulcer to the perforation where bleeding is experienced in both the stages Seminerio J [7]. This has led to the prevalence of injuries in the gastrointestinal tract following the administration of NSAIDs resulting in ulcers Masferrer [8]. In the USA, this has resulted in about 10,000 cases of hospitalization and around 16,500 deaths annually Singh [9].

According to statistics, about 1.5 percent of the patients suffering with rheumatoid arthritis are hospitalized every year presenting with gastrointestinal problems Singh G [10]. It is found that the factors such as age, usage of corticosteroids and previous history of peptic ulcers are found to elevate the condition. Due to the administration of NSAIDs, endoscopic ulcers were presented in 10-30% of the participants while serious complications from ulcer were observed among the 1-2% of the study population Conaghan PG [11]. Different studies have been conducted to relate the treatment efficacy and analgesic properties of the drugs. They can be administered in both oral and topical ways and therefore are used widely Kidd et al. [12]. This research is aimed at determining the suitability of administrations of Celecoxib and Diclofenac Sodium on patients diagnosed with rheumatoid

arthritis with respect to adverse effects on gastrointestinal tract. This study is conducted to perform a meta-analysis on randomly chosen clinical trials to determine the difference between the two different drugs.

Celecoxib as a Prescription for Rheumatoid Arthritis

Celecoxib is a selective cyclooxygenase-2 (COX-2) inhibitor, administered in place of non-selective NSAIDs. It is prescribed for patients having arthritis, disseminated pain, menstruation cramps and colonic polyps. They are administered in place of other NSAIDs due to comparatively lower levels of inflammation in the gastrointestinal tract. When compared with the classical NSAIDs, Celecoxib shows an equivalent anti-inflammatory effect with reduced endoscopic ulcers. Yet, several side effects were resulted from the admission of Celecoxib.

The efficacy of Celecoxib with the resulting side effects was carried out on a placebo-controlled trial using SC-58635. According to this study conducted by Simon et al. [13], the dosage of 100 to 400 mg was found to be effective when compared to the placebo in providing relief from inflammatory pain. In this study, the safety of administration of Celecoxib in the given dosages was found to be similar to placebo with no effect on GI tract (Simon et al., 1998). A systemic review was conducted by Deeks et al. [14]. It evaluates the effect of Celecoxib on the GI tract revealed that the efficacy was like that of NSAIDs, but the rate of withdrawal from the drug by the patients administered with the Celecoxib was lesser than that of NSAIDs. Also, the presence of endoscopic ulcers was 71% lower in patients administered with Celecoxib when compared to NSAIDs and there was a 39% reduction in the presence of ulcers, GI bleeding and GI obstructions in the former group when compared to the latter Deeks et al. [14].

Another study included five different randomized controlled trials and the efficacy of Celecoxib was compared with other drugs. In this, it was concluded that the efficacy of Celecoxib functioned in similar manner to naproxen (a non-selective COX inhibitor), diclofenac and ibuprofen (a NSAID). Also, the dosage regime was compared with treatment improvement. Accordingly, at a dose of 200mg twice per day, there was a 51% improvement while there was a 52% improvement when this dosage was 400mg. This study confirmed the absence of GI complications on short-term administration of Celecoxib while it was unable to determine the effect in long-term administration Garner S [15]. Therefore, it is essential to identify the usefulness of administering Celecoxib in terms of both pain relief and reduced adverse effects to prevent treatment withdrawal.

Diclofenac sodium for Rheumatoid Arthritis

Diclofenac is a phenyl acetic acid derivative Emery P [16]. It is commonly administered against pain, inflammation, swelling, joint pain and stiffness. As with other NSAIDs, gastrointestinal side effects are a common but when compared to other drugs, it is well tolerated by the human body. There are rarely observed GI ulcers due to administration of Diclofenac sodium. In a study

by Todd and Sorkin (1988) with 85,361 patients, only 8 patients reported GI ulcers Todd [17].

Several studies support this evidence. A double-blind parallel controlled was carried out by Caldwell in 1986 with 468 patients. It revealed that effectiveness of a daily dosage of 150 mg when compared to a placebo comparable to ibuprofen or aspirin. Also, the drug retrieval rate was less when compared to aspirin confirming that the administration of Diclofenac is healthier and safer Caldwell [18]. In contrast, another study conducted with patients having cardiovascular risk showed increased adverse effect on GI tract with Diclofenac with a hazard ratio of 69% Cannon CP, et al. [19].

Effectiveness of the administration of Celecoxib against rheumatoid arthritis when compared to Diclofenac Na

Many supportive studies compare the difference in the effectiveness of the two drugs. A study was conducted by Emery et al. [16] to determine the difference in the efficacy, administration safety and tolerance of the long-term administration of Celecoxib and Diclofenac with 55 patients having adult-onset rheumatoid arthritis. Among the participants, gastric ulcers were seen in 15% of the patients administered with Diclofenac and 4% in Celecoxib. This study concluded that the activity is similar for both drugs while Celecoxib was more effective in reduced GI ulcers and increased tolerability.

Another study was conducted by Walsem et al. [20] as a network meta-analysis to determine the benefit to risk ratio, efficacy, tolerability and safety of the administration of Diclofenac Na and Celecoxib using studies that considered 146,524 patients. According to this study, it was concluded that the treatment efficacy was high when administered with Diclofenac Na but the lack of information on the dosage regimen and the type of patient condition was a drawback in determining whether the most suitable drug is Diclofenac Na or Celecoxib against rheumatoid arthritis in long term administration.

Another study conducted using 326 patients revealed a higher pain score for Diclofenac with longer stiffness of joints. This was conducted by Walling [21] using 655 patients who enrolled in the international, multicenter study. The inflammation of rheumatoid arthritis was improved similar to both the drugs. This study revealed a percentage of 48 in GI ulcers for Diclofenac when compared to a 36% in Celecoxib resulting in increased withdrawal from the former Walling [21]. A similar study was conducted by Moore et al in 2005, 39,605 patients were randomly selected from thirty different trials in order to compare the effectiveness of Celecoxib with various types of drugs. One such group of drugs included naproxen, diclofenac, ibuprofen, and loxoprofen and the effectiveness of administration of the drugs were inspected. According to this study, there were reduced incidences of adverse effects due to administration of the drug Celecoxib when compared to other NSAIDs including Diclofenac Na Moore et al. [22].

Methods

Search strategy

This study is a systematic analysis on the randomly selected clinical trials where a conclusion can be derived on the efficacy of the two drugs, Celecoxib and Diclofenac NA and their efficacy with relation to minimal side effects in order to determine the most suitable drug for administration for patients with rheumatoid arthritis.

Inclusion Criteria

This includes studies conducted on patients having rheumatoid arthritis, prescribed with Celecoxib and/or Diclofenac So-

dium. The studies are those conducted using at least 50 affected individuals diagnosed with adult-onset rheumatoid arthritis and which are focused on the adverse effects to the GI tract. The patients chosen for the studies must be in a condition which requires the administration of the chosen drug over the period of the trial.

Exclusion Criteria

Studies which were conducted as trials on patients administered with Celecoxib and Diclofenac Sodium in combination with antiulcerative drugs and the studies which are not random clinical trials are excluded from the study. The study population which already was diagnosed with gastrointestinal ulcers was also excluded (Figure 1).

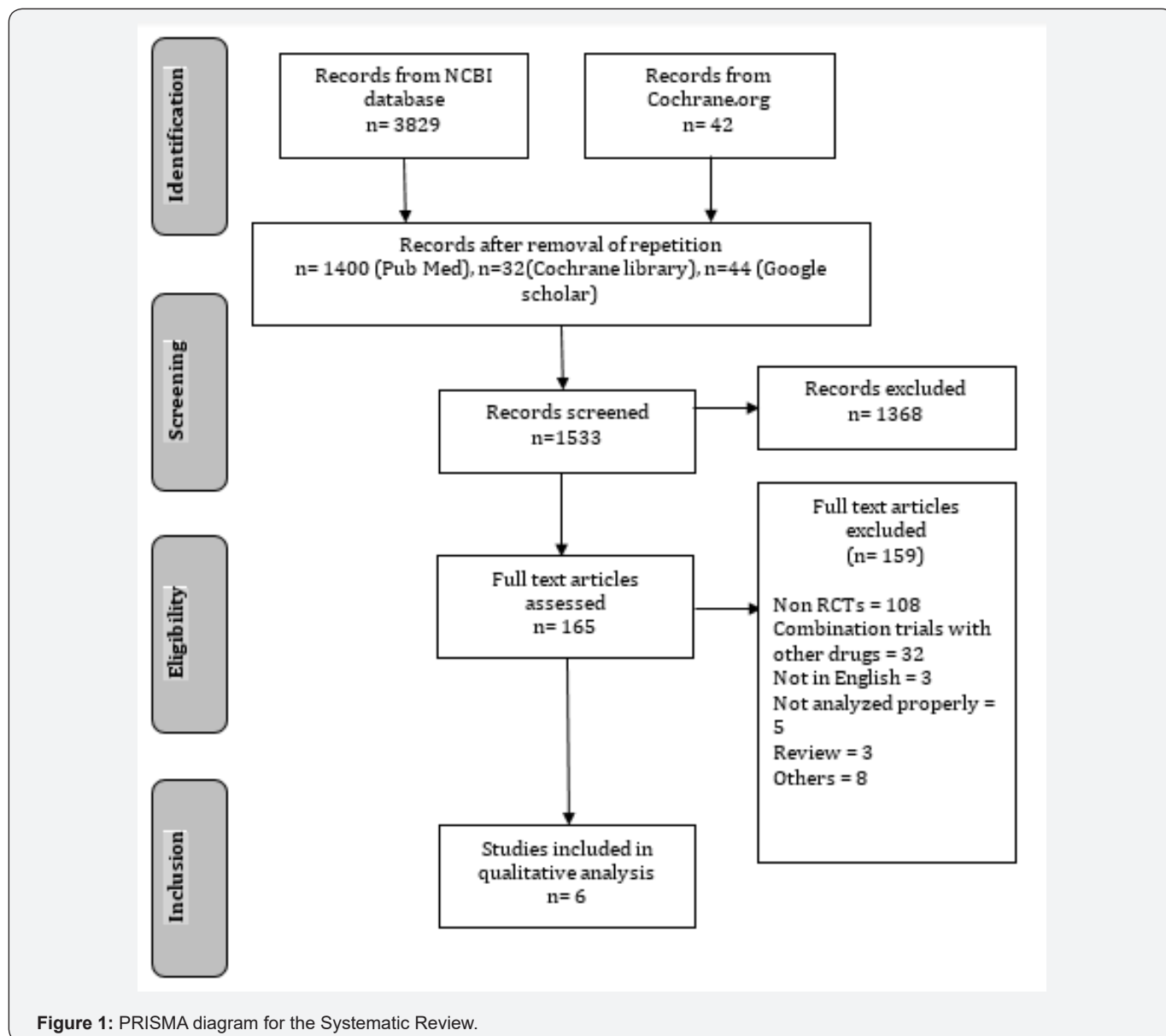


Figure 1: PRISMA diagram for the Systematic Review.

Results

A study was conducted to determine the efficacy of both the drugs. This was a double-blind parallel study conducted by Emery et al. [16] who randomly chose 655 male and female patients

who were diagnosed with the adult-onset rheumatoid arthritis for a month of 6 or more. They were administered with two daily doses of 200 mg of oral Celecoxib or two daily doses of 75 mg of Diclofenac SR for a timeline of 24 weeks. The anti-inflammatory property and tolerability of each patient were assigned at three

different levels; right before the initiation of the trial, per every 4 weeks and at the end of the timeline. Patients were requested to refrain from the use of anticoagulants, NSAIDs and any other types of drugs including any analgesics and antiulcer drugs. The overall safety of the drug administration was assessed by the examination of upper-gastrointestinal endoscopy within a week after the last dosage of the drugs. The efficacy of the treatment was based on the assessment of both the physician and the patient which was determined based on the pain and stiffness of joints, swelling, functional disability, C-reactive protein levels and withdrawal from treatment due to intolerance.

The sample size considered for withdrawal rate is 250 patients while that of the development of ulcer was 144. Both statistical analyses were conducted as a two-sided analysis with α value of 0.05 and β of 0.10. The assessment on primary arthritis was carried out using analysis of covariance with a related baseline score as a covariate factor. Using Cochran-Mantel-Haenszel method, the variations observed from the baseline was compared. The assessment of secondary arthritis was conducted using ANCOVA. Withdrawals in case of undiagnosed patients without the condition of arthritis was analysed using the Fisher's exact test. The statistical analysis on the upper gastrointestinal endoscopy was performed as a between-group comparison using the Cochran-Mantel-Haenszel method. The difference between the ulcers from *H pylori* was differentiated from arthritic gastric ulcers. From these statistical analyses, it was evident that the two drugs functioned in similar fashion in combating inflammation and pain. In both groups, the pain reduced with time, confirming the similarity in their efficacy.

According to the research it was revealed that there was a respectively 25% and 22% of treatment efficacy for Celecoxib and Diclofenac Sodium by week 24. There was a higher rate of gastric ulcers in patients administered with Diclofenac Sodium than Celecoxib. The mild to moderate adverse effects from Diclofenac Sodium was higher (48%) than from Celecoxib (36%) Emery P, et al. [16].

Silverstein et al. [23] conducted a double-blinded, randomized control trial at 386 clinical settings using a total of 8059 patients who are above the age of 18, diagnosed with osteoarthritis or rheumatoid arthritis. It was performed to determine the difference between the gastrointestinal adverse effects that result due to Celecoxib and other conventional NSAIDs. Patients were randomly administered with Celecoxib, Ibuprofen or Diclofenac and could continue the drug therapy of Aspirin in the case of cardiovascular disease conditions. Celecoxib was assigned at a dose of 400 mg two time a day; Ibuprofen at three times interval at a dosage of 800 mg; Diclofenac at a dose of 75 mg twice a day. All patients completed a 6-month period of the complete dosage regime of the assigned drug.

The clinicians and involved inspectors were advised to note any adverse effects related to GI tract. Using a two-sided statistical analysis with α value of 0.05 and β of 0.10, the event of gastrointestinal outcomes was analysed. According to the study,

the rates of having gastrointestinal ulcers in the use of Celecoxib and NSAIDs respectively were 1.45% and 3.54%. A difference was observed between patients who continued their therapy for Aspirin from those who did not. Patients who are taking Aspirin had a lesser probability in developing upper GI ulcers than who take Aspirin concomitantly in combination with Celecoxib or NSAIDs. Also, this study revealed that at dosages higher than that of which is clinically indicated, the resulting GI ulcers from Celecoxib was less than when considered otherwise. This probability was higher when compared with the incidence of GI ulcers from other NSAIDs at their clinically preferred doses Silverstein FE et al. [23].

Final study was conducted by Al et al. [24] on the cost versus the treatment effect and side effects of different analgesics such as Celecoxib, with and without misoprostol or histamine-2 receptor antagonist (H2RA) or proton pump inhibitor or Arthrotec. This study was based in Netherlands. This study used six treatment strategies against rheumatoid arthritis and evaluated the cost effectiveness of each strategy in terms of the treatment and the side effects Feinberg J, Japour AJ, et al. [25]. This was conducted for a time period of 6 months and the study used a social perspective for analysis. The results were evaluated based on two different outcomes. One is the intermediate outcome in the form of gastrointestinal effects which are symptomatic ulcer, anaemia and other effects that require hospitalization. The outcome is considered as the number of lives saved during the 6-month time period. According to this study, it was concluded that for patients with medium-risk of life-threatening consequences, Arthrotec was the treatment of choice while it was economical to use Celecoxib in patients with high risk Al et al. [24].

Sakamoto & Soen [26] conducted a study in Japan using patients diagnosed with rheumatoid arthritis and osteoarthritis. This study compared the efficacy of Celecoxib against Loxoprofen, a drug which was used before the introduction of Celecoxib in 2007. This study analysed previously conducted studies based on patients from Japan, and the information gathered was compared to that of studies conducted in the West. For this, 12 different clinical trials conducted using Celecoxib were considered. 2,410 patients had received Celecoxib, 1,190 had received Loxoprofen and 414 had received the placebo. Out of this, 771 patients from four trials were used to determine the clinical efficacy of Celecoxib at a dose of 200mg and Loxoprofen at a dose of 60mg. The efficacy of Loxoprofen was comparable to that of Celecoxib according to American College of Rheumatology (ACR) Improvement Criteria. Patient satisfaction was determined using visual analog scale (VAS) where it was stated that at the week number 2 and 4, the treatment improvement felt by the patients was higher when compared to patients administered with Loxoprofen in the same weeks since start of the treatment.

Kellner et al. [27] conducted a study to compare the effect of Celecoxib and Diclofenac with Omaprazole in patients diagnosed with rheumatoid arthritis. The patients chosen for this study had a higher risk of developing gastrointestinal adverse effects and those who were enrolled in the CONDOR trial. It was conducted

for a span of 6 months as a double-blind triple-dummy, parallel-group trial where patients were randomly assigned with a daily dose of 200 mg Celecoxib, twice a day and 75 mg of twice daily dose of diclofenac (SR) with Omeprazole at a daily twice dose of 20 mg. The two groups of participants were above the age of 60 with osteoarthritis or rheumatoid arthritis without a previous history of gastric ulcers and patients above the age of 18 with previous history of gastric ulcerations. Least squares mean (LSM) (standard error [SE]) was used to determine treatment efficacy. The study used 2238 patients for Celecoxib and 2246 for Diclofenac SR. Improvement was observed at 2nd, 4th and 6th months in both groups and the LSM difference in patients administered with Diclofenac SR was 0.77 (SE=0.02) and of those treated with Celecoxib was 0.75 (SE=0.02). It concluded that the treatment efficacy for both the conditions to be similar and that there was no difference in their risk towards developing gastrointestinal ulcers.

Discussion

Numerous studies have been conducted in combination with other drugs or alone to determine the effect of the administration of the drugs in patients diagnosed with rheumatoid arthritis. This study selected 5 different studies based on the inclusion-exclusion criteria using PRISMA mode. They all were randomized controlled trials and the participants were independently requested to be a part of the study. The studies were conducted on patients having rheumatoid arthritis or osteoarthritis and the patients could take Aspirin in some of the studies. This study is intended to summarize the existing strong body of evidence that support the effects of different drugs on patients.

Treatment Efficacy of Celecoxib and Diclofenac Na

According to this study, the treatment effectiveness of both the drugs was equal in terms of pain and inflammation. The tolerance levels of the two drugs were also observed to be similar. This evidence is supported by the study conducted based on Diclofenac Sodium alone by Garcia Rodriguez and Gonzalez-Perez in 2005 which confirmed the effectiveness of administration Diclofenac Sodium in reducing the adverse effects from other NSAIDs Garcia Rodriguez, et al. [28].

This was confirmed by several studies conducted on Celecoxib as well. One such study was conducted by Garner et al., in 2002 using five different randomized controlled trials and the efficacy of Celecoxib was compared with other drugs while it was revealed that with the increase in dosage, the efficacy also was high. This is further confirmed by the study conducted by Deeks et al. [14] which compared the effect of Celecoxib with other NSAIDs. One such study carried out by Simon et al. [29] using a randomized, multicentre, placebo-controlled, double-blind trial conducted from September 1996 to February 1998, using 1149 subjects in United States and Canada. According to this study, it was determined that Celecoxib was a more efficient drug than placebo in treating rheumatoid arthritis. The conclusions derived by Al et al. [24] regarding the different treatment regimes also suggested that the use of Celecoxib in high-risk patients was more effective in terms of cost and adverse gastrointestinal outcomes.

The study conducted by Sakamoto & Soen et al. [26] was used to compare the effectiveness of the drugs Celecoxib with the conventional drug which is commonly prescribed in Japan. According to this study, the effect of Celecoxib on the gastrointestinal tract was less and there was an improvement in the patients administered with Celecoxib from pain and inflammation than conventional drug. The study conducted by Silverstein et al. [23] compared the effect of Diclofenac Sodium from Celecoxib in patients with rheumatoid arthritis. This study revealed the treatment effectiveness in using Celecoxib to be higher when compared to Diclofenac Sodium. But this contrasted with another study conducted by Emery et al., in 1999; it was evident that the anti-inflammatory and analgesic activities of the two drugs Celecoxib and Diclofenac Sodium are similar Emery et al. [16].

Also, a network meta-analysis by Walsem et al. [20] to determine the benefit to risk ratio, efficacy, tolerability and safety of the administration of Diclofenac Na and Celecoxib considered 146,524 patients using Medline and EMBASE. According to this study, it was concluded that the treatment efficacy was high with Diclofenac Na but the dosage regimen and the type of patient condition was required to determine whether the most suitable drug is Diclofenac Na or Celecoxib. As such, it can be revealed that to be more effective, Diclofenac Na must be administered according to patient conditions. This was confirmed by Deeks et al. [14] in their study as well. This is also confirmed by Caldwell, in 1986 in the United States using 681 patients diagnosed with rheumatoid arthritis Caldwell [18].

Adverse effects from Celecoxib and Diclofenac Na in patients with Rheumatoid Arthritis

The gastrointestinal adverse effects resulting from the two drugs were studied. The participants were examined using endoscopy and it was found that the frequency of ulcers due to Celecoxib to be lesser when compared to other drugs. This conclusion is supported by previous literature. The study conducted by Garner et al. [15] using five different randomized controlled trials confirmed the absence of GI complications on short-term administration of Celecoxib while it was unable to determine the effect in long-term administration. The study conducted by Walling in 2000 using 625 patients revealed 48% in GI ulcers for Diclofenac when compared to a 36% in Celecoxib Walling [21]. Also use of the stated drugs shows reduced adverse effects when compared to other NSAIDs from the study conducted by Garcia Rodriguez and Garcia Rodriguez et al. [28] using 4,975 cases. Also, according to the study conducted by Al et al. [24] regarding different regimes for patients with rheumatoid arthritis, it was evident that, in terms of adverse effects for high-risk patients, Celecoxib was more effective.

Treatment withdrawal due to Adverse Effects

According to this study, it was evident that the rate of withdrawal from the treatment was higher in patients administered with Diclofenac Sodium than Celecoxib Emery et al. [16]. This was supported by other study evidences. Accordingly, the rate of en-

oscopic ulcers observed in patients administered with Celecoxib was less while there was a reduced incidence of other side effects related to the gastrointestinal tract as well Deeks et al. [14].

According to the research conducted by Silverstein et al. [23] it was suggested that a reduced rate of withdrawal was observed from Celecoxib due to higher effectiveness. This evidence is supported more by a study conducted using 625 patients by Walling [21]. It revealed a higher pain score for Diclofenac with longer stiffness of joints, with an increased withdrawal rate among patients administered with Diclofenac due to adverse effects on GI tract when compared to Celecoxib [30].

Implications for Nursing & Health Policy

During the treatment of patients with rheumatoid arthritis, it is important to identify the most suitable NSAID to be administered. There is an increased requirement to provide relief from pain and inflammation to improve the quality of lives of the patients. In nursing and healthcare setting, patients being administered with Celecoxib and Diclofenac Na require prominent attention since the adverse effects resulting must be recognized. According to the above studies, it is evident that adverse effects may result to the GI tract from the administration of the drugs. Since the actual context of using these drugs is to improve the quality of life, it is essential to make sure that the patients do not suffer from any other adverse effects that may in turn reduce their quality of life. Therefore, during healthcare service provision, such adverse effects can be identified and be addressed appropriately.

Conclusion

All the studies considered in this systematic review targets both the effectiveness of the drugs in rheumatoid arthritis treatment and its ability to reduce adverse side effects. From all the given studies, it is evident that the complete cure of rheumatoid arthritis cannot be achieved from both drugs. Different studies suggest different prevalence rates of adverse effects while no study confirms the complete absence of gastrointestinal ulcers and bleeding. The overall body of evidence that support the research question is limited to certain ethnicities and geographical areas, but each study can be considered to provide a strong body of evidence. This is due to the presence of many participants which increase the sensitivity of the study, predefined inclusion and exclusion criteria and the time duration through which the study was conducted.

The number of patients having rheumatoid arthritis is high and the adverse effects resulted from these drugs are very important in determining treatment regime. In any patient administered with the drugs, the responsibility falls on the physician and the nursing staff to identify the potential adverse effects and to decide the most suitable drug to be administered to reduce the pain and inflammation. This can help to determine the cause behind the most commonly observed side effects. It will be a useful strategy to identify the most common adverse effects with relation to the patient conditions and determine the most suitable drug for the particular patient rather than considering an overall population.

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DOI: [10.19080/OROAJ.2018.13.555861](https://doi.org/10.19080/OROAJ.2018.13.555861)

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