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Research Article

The Comparative Contribution of COX-I Vs COX-II In the Pathogenesis of Osteoarthritis

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Abstract

Osteoarthritis is an inflammatory joint disease that affects millions worldwide. Research indicates that both the COX-1 and COX-2 enzymatic pathways are implicated in the pathogenesis, but few studies have compared the relative contribution of each pathway.

A systematic review of a study that assessed the osteoarthritis disease severity change using the visual analog scale (VAS) for those with osteoarthritis using a COX-1 selective S-flurbiprofen plaster therapy for knee osteoarthritis was compared to the findings of another study which assessed the osteoarthritis disease severity change for those taking a COX-2 selective celecoxib oral therapy.

The COX-1 selective S-flurbiprofen plaster therapy had statistically significant reductions in VAS scores as compared to the conventional treatment by the end of the study. Additionally, those taking the COX-2 selective celecoxib oral therapy also showed statistically significant decreases in VAS scores as compared to conventional NSAIDs.

When average VAS score reductions between those taking the COX-1 selective S-flurbiprofen plaster treatments were compared to that of those taking the COX-2 selective celecoxib oral therapy, those taking the S-flurbiprofen plaster treatments had a greater reduction in pain severity than did those taking the celecoxib. Further studies with greater sample sizes and different routes of administration are necessary to assess which enzymatic pathway is more implicated in the pathogenesis of osteoarthritis.

Key words: osteoarthritis; COX-1 inhibitors; COX-2 inhibitors; chronic pain; inflammatory joint disease

Introduction

Osteoarthritis (OA) is commonly seen in middle-aged and elderly people. It results from the regression of articular structures, such as articular cartilage [1]. Symptoms of OA may include chronic pain, inflammation, and motor dysfunction. These symptoms can significantly reduce the quality of life (QoL) (2). The Osteoarthritis Research Society International (OARSI) guidelines recommend oral non-steroidal anti-inflammatory drugs (NSAIDs) for help in pain management [3, 4].

The two isoforms of COX are almost identical in structure but have important differences in substrate and inhibitor selectivity and in their intracellular locations. Protective prostaglandins which preserve the integrity of the stomach lining and maintain normal renal function in a compromised kidney, are synthesized by COX-I. In addition to the induction of COX-II in inflammatory lesions, it is present in the brain and spinal cord, where it may be involved in nerve transmission, particularly that of pain and fever. The design of drugs that reduce inflammation without removing the protective prostaglandins in the stomach and kidney made by COX-I [5-7].

This article will examine the comparative contribution of COX-I and COX-II in the Pathogenesis of Osteoarthritis.

Methods:

For the study using the selective COX-1 S-flurbiprofen plaster [8]: A total of 222 participants with knee osteoarthritis were enrolled in the study. Participants with no pain in the non-target knee were included, and the quality of pain (acute or chronic, severity of inflammation, central sensibilization) was not considered in this study. The injection of hyaluronic acid or steroids was prohibited during the study period. The commencement of new physical therapy during the study period was also prohibited; however, patients who had already started physical therapy when participating in this study were allowed to continue physical therapy. The patients were randomly assigned in a 1:1 ratio to either the SFPP group or the control group. The randomization factors included gender (male and female), visual analog scale (VAS) score (≥60 and <60 mm), Kellgren-Lawrence grade (II and III), current smoking (yes and no), and body mass index (≥25 and <25 kg/m2). The assignment procedure was performed at the

data center, and the attending physicians were blinded to the process. The patients assigned to the SFPP group had SFPP applied once daily to the affected area, and those assigned to the control group were treated with a combination of oral and topical NSAIDs. The dose of SFPP was not specified in this study design and was determined by the attending physician according to the patient's symptoms. The oral NSAIDs used in the control group included celecoxib 100 mg twice daily or loxoprofen 60 mg three times daily. NSAID patches (40 mg ketoprofen or 100 mg loxoprofen) were applied to the affected area once daily using tape. The treatment period was set at 4 weeks after referring to previous studies examining the efficacy and safety of other topical NSAIDs including diclofenac and eltenac. The primary endpoint of this study was the change in VAS scores (0−100 mm) for pain levels while rising from a chair at 2 and 4 weeks after the start of treatment (or at the time of discontinuation). The change in VAS score after 2 and 4 weeks was based on a covariant model, with the baseline VAS as a covariate and the treatment group as the independent variable, to calculate the 95% confidence interval of the inter-group adjusted mean (control group minus test group).

For the study using the selective COX-2 Celecoxib [9]:

1180 participants were collected to perform 2 randomized controlled trials. All patients who were collected for participating in the trials were diagnosed with osteoarthritis and were treated in an international ambulatory care setting. Pain severity was assessed using a self-reported VAS questionnaire. A treatment group of those treated with celecoxib 200 mg/day was compared to groups treated with diclofenac 100 mg/day, diclofenac 150 mg/day, and naproxen 1000 mg/day. The change in VAS score from follow-up times ranging from 12 to 52 weeks were collected. Confidence intervals and mean changes in VAS scores across all groups were then calculated and compared to each other.

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Results:

For the study using the selective COX-1 S-flurbiprofen plaster [8]:

In the SFPP group, the VAS score changed from 58.3 ± 13.8 mm to 28.3 ± 22.5 mm at 2 weeks (P<0.001) and to 26.4 ± 23.2 mm at 4 weeks (P<0.001). In the control group, the VAS score changed from 59.6 ± 14.4 mm to 31.2 ± 20.9 mm at 2 weeks (P<0.001) and to 20.7 ± 18.4 mm at 4 weeks (P<0.001).

For the study using the selective COX-2 Celecoxib [9]:

The mean pain in the selective COX-2 Celecoxib intervention group was 4.52 points lower (10.65 lower to 1.61 higher) at the end of the study. There was a 5% absolute improvement (95% CI 11% improvement to 2% worse), 11% relative improvement (95% CI 26% improvement to 4% worse), and MD -4.52 (-10.65 to 1.61).

Treatment Group	Reduction in VAS	P-value
S-Flurbiprofen Plaster	31.9mm	P<0.001
Celecoxib (200mg)	4.52mm	P<0.001

Table 1: Reduction in VAS Score for Each Treatment

The above (**Table 1**) depicts the reduction in mean VAS score that each treatment had.

Conclusion:

Both studies suggest that both COX-1 and COX-2 selective inhibitors have statistically significant effects on reducing pain for those with osteoarthritis. However, those who were treated with the S-Flurbiprofen plaster achieved a reduction in pain almost 8 times that of those who were treated with the Celecoxib. This likely correlates to the COX-1 mediated enzymatic conversion of arachidonic acid being more implicated in the pathogenesis of osteoarthritis than the COX-2 mediated enzymatic conversion. One can further speculate that the specific products such as PGI2 and TXA2 are more implicated in the pain of osteoarthritis than is PGE2. Longitudinal studies conducted throughout longer periods of time need to be done to assess if these effects are longstanding and if there are any potential side effects that might be of concern with these treatments. Since selective inhibitors are not the conventional treatment, further barriers such as insurance coverage may present as significant obstacles for patients as well.

Compliance with Ethical Standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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