Prospective, Real-World, Open-Label, Longitudinal Study on the Effectiveness of Fixed-Dose Combination of Naproxen and Paracetamol 275/325 mg/tablet among Filipino Patients with Osteoarthritis, A Phase IV Study

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ABSTRACT

Introduction

Osteoarthritis (OA) is a prevalent degenerative joint condition that significantly impacts mobility and quality of life. This study investigates the effectiveness and safety of a fixed-dose combination of naproxen and paracetamol in reducing pain scores among Filipino patients with OA.

Methodology

This observational, open-label, non-blinded phase 4 clinical trial included adult patients over 18 years old with mild to moderate OA-related pain. Participants were prescribed a fixed-dose combination of naproxen (275 mg) and paracetamol (325 mg) taken twice daily for five days. Pain scores were assessed at baseline and follow-up using a visual analog scale. Secondary endpoints included medication adherence and the incidence of adverse events. Wilcoxon matched-pairs signed-rank test was used for statistical analysis.

Results

A total of 67 patients participated, with a mean age of 58 years. There was a statistically significant reduction in pain scores at rest (52.9%) and during movement (45.85%) after five days ($p < 0.001$). Complete pain resolution was achieved in 31.34% of patients at rest and 10.45% during movement. The combination therapy was well-tolerated, with three mild adverse events (skin rash, abdominal pain, and palpitations), all resolving without further treatment.

Conclusion

The fixed-dose combination of naproxen and paracetamol was effective in reducing pain associated with osteoarthritis, showing early onset of pain relief and a favorable safety profile. This combination offers a promising option for managing osteoarthritis pain, providing significant analgesic benefits while minimizing the risks associated with higher doses of NSAIDs, making it particularly suitable for elderly patients.

Keywords: Naproxen, Paracetamol, fixed-dose combination, pain relief, osteoarthritis, safety

INTRODUCTION

Osteoarthritis (OA) is a degenerative joint condition characterized by pain, swelling, and stiffness, significantly affecting an individual's ability to move freely. This condition impacts the entire joint, including surrounding tissues, and is most prevalent in the knees, hips, spine, and hands.[1] In 2019, approximately 528 million people worldwide were living with osteoarthritis, with about 73% of these individuals being older than 55 years and 60% being female. The pooled prevalence of OA was reported as 16.4% (CI 11.60–21.78%) in South Asia, 15.7% (CI 5.31–30.25%) in East Asia and the Pacific, and 14.2% (CI 7.95–21.89%) in Sub-Saharan Africa.[2]

Analgesic therapy that combines individual agents with different mechanisms of action has potential advantages for managing mild-to-moderate pain in outpatient settings. Although the precise mechanism of action for the analgesic effect of acetaminophen remains uncertain, evidence suggests that its activity primarily resides in the central nervous system. In contrast, nonsteroidal anti-inflammatory drugs (NSAIDs) exert their analgesic effects predominantly in peripheral tissues that are injured or inflamed. Several controlled clinical studies involving patients with musculoskeletal conditions, dental pain, or postoperative pain have demonstrated that combinations of acetaminophen and NSAIDs provide additive pain-relieving activity, leading to dose-sparing effects and improved safety.[3] However, there are very few studies on fixed-dose combinations of paracetamol and NSAIDs, with almost no published research conducted in the Philippine setting.

This study aims to evaluate the effectiveness and safety of a fixed-dose combination of naproxen and paracetamol in decreasing pain scores among Filipino patients with osteoarthritis in a real-world setting.

METHODOLOGY

This study is an observational, real-world, open-label, non-blinded, phase 4 clinical trial. Ethics approval was granted by the Research Institute for Health Science Ethics Review Committee, which is accredited by the Philippine Health Research Ethics Board (PHREB) and recognized by the Forum for Ethical Review Committees in the Asian and Western Pacific Region (FERCAP) and the Strategic Initiative for Developing Capacity in Ethical Review (SIDCER).

Participants were adult patients (>18 years old) experiencing mild-to-moderate pain and inflammation due to osteoarthritis, seen at the outpatient clinic of the Philippine Orthopedic Center. These patients were prescribed a fixed-dose combination of naproxen and paracetamol following local prescribing information and routine clinical practice. Patients with hypersensitivity to NSAIDs or paracetamol, pregnancy, concurrent NSAID use, and certain medical conditions (e.g., uncontrolled hypertension, diabetes, chronic kidney disease) were excluded from the study.

Using data from a previous study on the additive effect of naproxen and paracetamol in rheumatoid arthritis, which showed a reduction in pain score from 75.0 ± 16.0 to 45.7 ± 14.6

after two weeks, the required sample size was calculated using the OpenEpi sample size calculator, yielding a minimum of 10.4 participants at 95% confidence and 80% power.[4]

Patients were enrolled consecutively during their regular visits to minimize selection bias. Eligible patients were given the fixed-dose combination of naproxen (275 mg) and paracetamol (325 mg), administered as one tablet twice daily for five days. Patients recorded their daily pain scores in a diary, and follow-up assessments occurred within 5–7 days. Pain at rest and during movement was recorded at baseline and follow-up using the Visual Analog Scale (VAS). The primary endpoint was the change in pain score from baseline to follow-up. Secondary endpoints included medication compliance, as measured by the number of tablets left during follow-up, and treatment safety, assessed by the occurrence of adverse events up to one month post-treatment.

Statistical analysis was performed using GraphPad Version 5. Summary statistics were calculated for continuous variables (e.g., age), and absolute and relative frequencies were provided for discrete variables (e.g., gender). The Wilcoxon matched-pairs signed-rank test was used to assess the significance of changes in pain scores, and incidence rates of safety outcomes were reported with 95% confidence intervals (CI).

RESULTS

The mean age of the 67 participants was 58 years, with 75.76% female and 43.94% classified as having a normal BMI. Bilateral knee osteoarthritis was the most common site of pain, affecting 48.15% of participants, with nearly all patients exhibiting radiographic findings consistent with degenerative osteoarthritis accompanied by tenderness on physical examination. (See Table 1.)

Table 1. Clinico-demographic profile of osteoarthritic patients (n=67)

Characteristics	Mean (SD); frequency (%)
Age (years) (n=66)	58.30 (11.37)
Sex (n=66)	
Male	16 (24.24)
Female	50 (75.76)
BMI status (n=66)	
Underweight (below 18.5)	1 (1.52)

Normal (18.5-24.9)	29 (43.94)
Overweight (25.0-29.9)	22 (33.33)
Obese (30.0 and above)	14 (21.21)
Location of osteoarthritis (n=54)	
Bilateral knees	26 (48.15)
Left knee	5 (9.26)
Right knee	3 (5.56)
Left hip	3 (5.56)
Right hip	2 (3.70)
Right hip / right knee	1 (1.85)
Bilateral knees / bilateral shoulders	1 (1.85)
Left shoulder	5 (9.26)
Right shoulder	3 (5.56)
Bilateral hand	2 (3.70)
Right metacarpal joint	1 (1.85)
Bilateral fingers	1 (1.85)
Left foot	1 (1.85))

A significant reduction in pain scores was observed after treatment, with a 52.9% reduction in pain at rest and a 45.85% reduction during movement ($p < 0.001$). The median pain score at rest decreased from 4 (IQR = 3) at baseline to 2 (IQR = 3) at follow-up. For pain during movement, the score decreased from 6 (IQR = 2) to 3 (IQR = 3). (See Table 2)

Table 2. Comparison between median (IQR) pain score at baseline and at follow-up (n=53)
[a] *p-value from the Wilcoxon matched-pairs signed-rank test. Sig. at p<0.05.*

Pain score	Median (IQR)		P-value
	At baseline	At follow-up	
At rest	4 (3)	2 (3)	<0.001
During movement	6 (2)	3 (3)	<0.001

A total of 31.34% of patients experienced complete resolution of pain at rest, and 10.45% reported no pain during movement after five days. The fastest pain resolution occurred 30 minutes after medication intake in two patients. (See Table 3.)

Table 3. Degree of pain during screening and follow-up

	Screening at rest	Follow up at rest	Screening with movement	Follow up with movement
No pain (0)	0	21	0	7
Mild (1 -3)	24	36	5	34
Moderate (4 – 6)	32	6	36	22
Severe (7 - 9)	9	4	23	4
Worst (10)	0	0	1	0

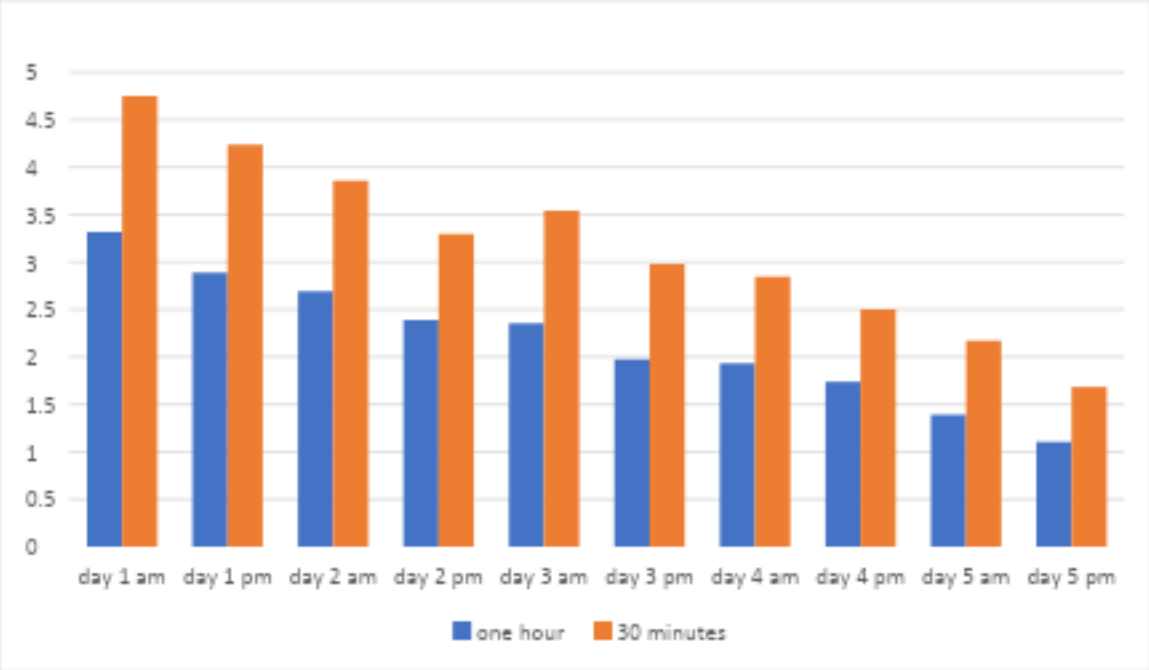
There was no statistically significant difference in blood pressure between baseline and follow-up visits. (see Table 4)

Table 4. Comparison of the BP during baseline and at follow up

	Baseline	*Follow up*	*P value*
Systolic BP	*127.3*	*127.4*	*0.9521*
Diagnostic BP	*86.09*	*86.76*	*0.4606*

Repeated-measures ANOVA indicated a statistically significant decrease in pain scores from baseline to day 5 for both measurements taken at 30 minutes and 1-hour post-medication ($p < 0.0001$). (See Figure 1)

Figure 1. Daily pain score



No serious adverse events were noted during this study; however, three patients reported mild adverse events—one experienced skin rashes, another had abdominal pain, and one reported palpitations—all resolving without additional medication. (See Table 5)

Table 5: Safety profile: Incidence of Adverse Events (n 67)

Adverse events	Frequency	Proportion
Palpitation	1	1.49%
Abdominal pain	1	1.49%
Skin rashes	1	1.49%

DISCUSSION

Pain is a fundamentally subjective experience, reflecting an individual's response to physical or emotional stimuli, and it can profoundly affect quality of life—particularly among older adults, who often present with pain-related complaints in clinical settings. The World Health Organization projects that the global population aged over sixty will double from one billion in 2020 to two billion by 2050, a demographic shift likely to increase the prevalence of chronic conditions such as osteoarthritis (OA).[1,5] Osteoarthritis, in particular, is a leading cause of disability worldwide, with a high burden observed in low- and middle-income countries.[2]

The present study demonstrates that a fixed-dose combination (FDC) of naproxen and paracetamol is effective in reducing osteoarthritis-related pain. Notably, significant pain reduction was observed after five days of treatment, and some patients experienced rapid onset

of analgesia, with complete pain relief as early as 30 minutes post-administration. These findings are consistent with previous studies, which have shown that the combination of paracetamol and naproxen produces more pronounced effects across multiple domains—including global effect assessments, joint pain indices, and morning stiffness—compared to monotherapy or placebo.[3.4.6.7.]

The enhanced analgesic efficacy of this combination can be attributed to the complementary mechanisms of action of the two agents. Non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen primarily exert their effects peripherally by inhibiting cyclooxygenase (COX) enzymes and reducing prostaglandin synthesis, whereas paracetamol acts centrally, possibly via inhibition of a COX-3 variant and modulation of serotonergic pathways.[8-12.] The synergy achieved by targeting both peripheral and central pain pathways allows for greater analgesic activity and may enable a reduction in the required NSAID dose, thereby mitigating the risk of dose-dependent adverse effects.[13-15.]

The combination therapy observed here not only provides effective analgesia but also minimizes potential risks associated with higher doses typically required when using NSAIDs alone. This is particularly advantageous in the elderly population, who are more susceptible to NSAID-induced gastrointestinal, renal, and cardiovascular complications. [3,15-17.]

The rapid onset of analgesia observed in this study aligns with the proposed synergistic mechanisms and is clinically relevant for patients seeking prompt relief from OA-related pain, which can significantly impair functional capacity and quality of life.[4,18.] This finding is particularly relevant for patients seeking quick relief from osteoarthritis-related pain, which can dramatically impair daily activities.

Importantly, moreover, the safety profile observed was favorable, with only three mild adverse events reported, all of which resolved without intervention. This is consistent with existing literature suggesting that the fixed-dose combination of naproxen and paracetamol does not confer significant additional safety risks compared to monotherapy, and that lower doses of naproxen in combination therapy are associated with fewer gastrointestinal complaints.[17-19.]

Nevertheless, the study's open-label design imposes limitations, including potential bias and the inability to directly compare outcomes with those of a placebo or single-agent regimen. Additionally, the relatively short duration of follow-up precludes assessment of long-term safety and efficacy. Larger, randomized controlled trials with extended observation periods are warranted to confirm these findings and to further elucidate the risk-benefit profile of this combination therapy in diverse patient populations.

Conclusion

In summary, this real-world study suggests that a fixed-dose combination of naproxen and paracetamol is an effective and well-tolerated option for managing osteoarthritis-related pain among Filipino patients. The combination allows for lower NSAID dosing without compromising analgesic efficacy, potentially reducing the risk of adverse effects in older adults.

These findings support the use of combination analgesic therapy as a rational approach to pain management in osteoarthritis.

Recommendations

Clinical Practice: Clinicians should consider the use of fixed-dose naproxen-paracetamol combinations for patients with osteoarthritis, particularly those at increased risk for NSAID-related adverse events. Dose minimization strategies should be employed to enhance safety.

Policy: Healthcare systems should facilitate access to combination analgesic therapies and support educational initiatives aimed at optimizing pain management in the aging population.

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