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Research Article

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Real World Effectiveness of Orphenadrine Citrate 35 mg + Paracetamol 450 mg (Norgesic®) on Low Back Pain of Filipino Patients

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Abstract

Introduction: *Low back pain (LBP) is a prevalent musculoskeletal condition, believed to impact as many as 84% of adults during their lifetime. It ranks among the primary reasons for limitations in activity, absenteeism from work, and reduced productivity, resulting in significant costs to health, social, and economic systems. Furthermore, the Philippines has been identified as one of the countries where 56% of its population suffers from weekly body aches. Thus, the study determined the effectiveness of orphenadrine citrate 35 mg + paracetamol 450 mg (Norgesic®) in relieving acute, non-specific moderate to severe musculoskeletal LBP among adult Filipino patients in a real-world setting.*

Methods: *A prospective, multi-center, uncontrolled, open label, longitudinal study was done. Study participants were recruited via purposive sampling by their attending physicians, and they were given Norgesic® according to local prescribing guidelines and standard clinical practices. Pain levels were measured using the visual analogue scale (VAS), while self-reported physical disability was assessed using the Roland-Morris Disability Questionnaire (RMDQ). Patients were monitored until their low back pain completely resolved or for a maximum of ten (10) days. This real-world evidence study also documented any adverse effects occurring during this ten-day period.*

Results: *The median onset of pain relief in the 255 study participants occurred an hour after the first dose of Norgesic® tablet, the fastest by 30 minutes and the slowest by the 8th hour, and it lasted for six (6) hours. At baseline, the median VAS score was seven (7) which subsequently decreased to 0 by day 7 up to day 10 and differed significantly from baseline ($p<0.0001$). The median number of Norgesic® tablets consumed for pain relief likewise decreased from three tablets on day 1 to one tablet on day 7 to none on the succeeding days until the end of study period. The mean duration of LBP before total resolution, was 5.1 SD ± 2.2 days. The incremental increase in the proportion of those with complete resolution (VAS score=0) was highest by day 7. The median physical disability score significantly decreased to zero (0) on day 11 from nine (9) at baseline. Adverse events reported in 22 participants were generally mild dizziness and somnolence, which lasted for 1-6 days and resolved with rest.*

Conclusion: *In this study, orphenadrine 35 mg + paracetamol 450 mg (Norgesic®) was noted to be effective in alleviating acute nonspecific moderate to severe musculoskeletal LBP of Filipino patients. In addition, Norgesic® aided study subjects in regaining functional capacity for them to continue with their impaired activities of daily living. Only few non-severe, self-limiting adverse reactions were noted during the treatment period.*

Keywords: Orphenadrine citrate + paracetamol, Low back pain, Physical disability

1. Introduction

Low back pain (LBP) is a prevalent musculoskeletal condition, believed to impact as many as 84% of adults during their lifetime [1-3]. It ranks among the primary reasons for limitations in activity, absenteeism from work, and reduced productivity, resulting in significant costs to health, social, and economic systems [1,4-6].

Worldwide, back pain contributes more to disability than any other condition. As reported in the 2019 Global Burden of Disease Study, LBP rose to ninth place among the top ten conditions with increasing burden from 1990 to 2019 across all age groups. It had one of the largest absolute increases in disability-adjusted life years [7] According to the Global Pain Index 2017 report, the Philippines was identified as one of the countries where 56% of its population suffered from weekly body pain. Of those experiencing weekly pain, 28% specifically reported LBP [8].

LBP is characterized as pain, muscle tightness, or stiffness that occurs between the rib cage and the lower buttocks, with or without leg pain. It can be categorized as acute (lasting less than 4 weeks), sub-acute (lasting between 4 to 12 weeks), or chronic, depending on how long symptoms persist [9]. LBP can arise from various causes such as spine diseases, infections, tumors, autoimmune inflammatory arthritis, and minor injuries. Among these, over 85% of patients seen in primary care present with non-specific back pain, primarily related to musculoskeletal issues [10].

The standard approach to treatment involves both non-pharmacologic and pharmacologic therapies. Non-pharmacologic options encompass heat, massage, acupuncture, spinal manipulation, and exercise and physical therapy. However, there are currently no available data indicating one method's superiority over another [11]. Instead, the choice is influenced by the patient's preferences, cost considerations, and accessibility. If the patient opts for pharmacological treatment, initial prescription typically includes a non-steroidal anti-inflammatory drug (NSAID) like ibuprofen or naproxen, with non-benzodiazepines potentially added if pain persists despite initial therapy. In this study, the combination of orphenadrine 35 mg and paracetamol 450mg (Norgesic®) in acute non-specific LBP was explored.

2. Methods

A prospective, multi-center, uncontrolled, open label, longitudinal study on the effectiveness of orphenadrine citrate 35 mg + paracetamol 450 mg (Norgesic®) in alleviating discomfort of Filipino patients who presented with acute non-specific musculoskeletal LBP was conducted. This study was approved by the University of the East Ramon Magsaysay Memorial Medical Center, Inc. Research Institute for Health Sciences–Ethics Research Committee (1650/P/2024/017).

The study participants were prescribed with orphenadrine citrate 35 mg + paracetamol 450 mg (Norgesic®) by their attending physicians. Patients included in the study were aged 18-59 years old, who presented with acute (less than 4 weeks) of non-specific LBP that was musculoskeletal in nature. Patients were excluded from the study if (1) they were hypersensitive to either orphenadrine citrate or paracetamol; (2) they used any other used any other oral preparations like NSAIDs, cyclobenzaprine, methocarbamol, or opioids for the past 48 hours prior to initiation of treatment; (3) they were undergoing any other non-pharmacologic therapies for the LBP, including complementary and alternative medicine modalities (e.g., acupuncture, acupressure, therapeutic massage, etc.); (4) they were pregnant; or (5) they had glaucoma, prostatic hypertrophy, bladder neck obstruction, or myasthenia gravis.

Study participants were prescribed with orphenadrine citrate 35 mg + paracetamol 450 mg (Norgesic®) one to two tablets three times a day for a maximum of ten (10) days. They were followed-up until the resolution of their LBP or until a maximum of ten (10) days were reached. Sixty (60) tablets were given for free to study participants upon consultation. Participating physicians included primary care physicians, general medical practitioners, family physicians, community medicine and public health practitioners, general internists, rehabilitation medicine specialists/physiatrists, and orthopedic surgeons in the Philippines.

Patient demographic and baseline characteristic data were collected on all patients that included age, sex, and nature of work or profession. Pain intensity was measured by the visual analog scale (VAS), wherein, a 20-mm reduction in pain intensity was considered statistically significant [12-13] The Roland-Morris Disability Questionnaire was used to evaluate the self-rated physical disability resulting from LBP of the patients [14]. Assessments were conducted both at the beginning (baseline) and upon completion of the study (day 11).

The primary endpoints of interest of the study were: (1) the decrease in VAS scores for pain from the baseline until the total resolution of LBP, possibly with no recurrence for a maximum of ten (10) days; (2) the decrease in physical disability scores from baseline until completion of study; and (3) the time to total resolution of LBP after use of orphenadrine citrate 35 mg + paracetamol 450 mg, again with non-recurrence of back discomfort.

The secondary endpoints of the study were: (1) the time to total resolution of LBP after use of orphenadrine citrate 35 mg + paracetamol 450 mg, again with non-recurrence of pain; (2) the decrease in VAS score of two (2) from baseline; (3) time to onset of pain relief after first dose, 4) duration of pain free period after first dose; (5) the decrease in physical disability scores from baseline until completion of study; and (6) occurrence of adverse effects, including but not limited to, hypersensitivity reaction.

Daily dose of orphenadrine citrate 35 mg + paracetamol 450 mg was described and the number of drugs per day was tabulated. Study participants who discontinued usage of orphenadrine citrate 35 mg + paracetamol 450 were reported and reasons for stopping was noted and collated.

No special protocol-mandated visits or procedures were associated with the study since this was an observational, and uncontrolled study. Study participants were allowed to switch their treatment during the study, but were encouraged to continue the given medication. Attending physicians were advised to encourage patients to follow-up at least once (i.e. on day 11 as end of the treatment). Follow-up was done as either via face-to-face or tele-consult. The VAS and physical disability scores were gathered after initiation of treatment.

Incidence rates with respective 95% confidence intervals (CI) were calculated, when applicable, for selected safety outcomes. Continuous variables were expressed as mean ± SD or median (min and max) for non- normally distributed data. Categorical variables were expressed as percentages. Significant differences in VAS scores and number of tablets consumed between baseline and each succeeding day up to ten (10) days was determined using Wilcoxon signed rank test. Likewise, differences in physical disability scores between baseline and end of study period were

determined using Wilcoxon signed rank test. A p-value <0.05 was accepted to be statistically significant. Data were analyzed using Stata version 13 software.

3. Results

There were 255 study participants, 54.9% of whom were females and 43.1% of whom were males with a mean age of 38.3 SD ± 10.5 years. Forty two (42) % were white-collar workers, 40% were blue-collar workers, and 15% were unemployed (Table 1).

Gender (n, %)	
Male	110 (43.1)
Female	140 (54.9)
No answer	5 (2.0)
Age in Years (mean, SD)	38.3, 10.5
Work/Profession	
White-Collar (administration officer, accountant, BPO agent, businessman,	
clerk/secretary, educator, engineer, encoder/IT, lawyer, medical staff)	108 (42.4)
Blue-Collar (construction worker, cook, driver, factory worker, farmer, gardener, housekeeper, vendor, janitor, warehouse personnel)	101 (39.6)
Unemployed	38 (14.9)
No response	8 (3.1)

Table 1: Demographic profile of respondents

The median onset of LBP relief occurred an hour after the first dose of Norgesic® tablet, the fastest by 30 minutes and the slowest by the eight (8th) hour. The median length of time after the first dose and before the next episode of pain was six (6) hours, with one hour as the shortest and 24 hours as the longest period of relief from pain. Ninety (93)% were compliant to the medications. Non-compliance was attributed to immediate pain relief and pain perceived as tolerable (Table 2).

Onset of pain relief in hours after the first dose (median, minimum/ maximum)	1 (30 minutes, 8 hours)
Duration of pain-free period before the next dose in hours after the first dose (median, minimum/ maximum)	6 (1 hour, 24 hours)
Compliance to medications (n, %)	
Yes No No response	236 (92.5) 3 (1.2) 16 (6.3)

Table 2: Clinical outcomes of respondents

At baseline, the median VAS score was seven (7), with two (2) as the lowest and ten (10) as the highest. Except for a unit increase in median VAS score, from four (4) at bedtime of day 1 to five (5) on the morning of day 2, there was a decreasing trend observed on subsequent time points which differed significantly from baseline ($p<0.0001$). It was only on day 7 when VAS scores dropped to zero (0) until day 10. The median number of Norgesic® tablets consumed for pain relief likewise decreased from three (3) tablets on day 1 to one (1) tablet on day 7 to none (0) on the succeeding days till end of study period. The number of tablets consumed obviously coincided with the decrease in VAS scores to zero (0) by day 7. The number of tablets consumed on day 2 and day 3 did not differ significantly from baseline ($p=0.1121$ and $p=0.2547$, respectively) but reached statistical significance by day 4 until day 10 ($p<0.0001$) (Table 3).

Time	VAS scores	p-value*	p-value*	Number of tablets consumed		p-value*
	Median	Min. Max		Median	Min. Max	
Day 1				3	1, 9	
Baseline	7	2, 10				
After 60 minutes	6	0, 10	<0.0001			
At bedtime	4	0, 10	<0.0001			
Day 2				3	0, 9	0.1121
After 60 minutes	5	0, 10	<0.0001			
At bedtime	4	0, 10	<0.0001			
Day 3				3	0, 9	0.2547
After 60 minutes	4	0, 9	<0.0001			
At bedtime	3	0, 9	<0.0001			
Day 4	2	0, 8	<0.0001	3	0, 9	<0.0001
Day 5	1	0, 8	<0.0001	3	0, 6	<0.0001
Day 6	1	0, 8	<0.0001	3	0, 6	<0.0001
Day 7	0	0, 6	<0.0001	1	0, 6	<0.0001
Day 8	0	0, 6	<0.0001	0	0, 6	<0.0001
Day 9	0	0, 6	<0.0001	0	0, 6	<0.0001
Day 10	0	0, 6	<0.0001	0	0, 6	<0.0001

*Wilcoxon signed-rank test

Table 3: VAS scores and number of tablets consumed from Day 1 to Day 10

The mean duration of LBP before total resolution, which meant having a VAS score equal to zero (0) with no recurrence of symptoms, was 5.1 SD ± 2.2 days. As many as 71.8% of the study participants had a decrease of at least two (2) points from baseline in their VAS scores on day 1. This increased to 86.7% by day 3, 97.3% by day 5, and 98% by day 6. From day 7 onwards, 99.6% of the participants exhibited a decrease of more than two (2) points from baseline in their VAS scores (Table 4). The VAS score of the lone participant with less than two (2) points decrease from baseline was six (6) with a baseline value of seven (7). In most of the study participants, it was a 6-point decline each day from day 5 to day 10.

The incremental increase in the proportion of those with complete resolution (VAS score=0) was highest by day 7 with 14.9 percentage points difference from day 6 versus a 10.5 percentage points difference from day 8, suggesting that most cases were completely resolved by day 7 (Table 4).

Duration of low back pain before complete resolution (VAS=0) with no recurrence in days (mean, SD)		5.1, 2.2
Time in days	Proportion of those whose VAS scores decreased by at least two (2) points from baseline, n (%)	Proportion of those with complete resolution (VAS=0), n (%)
Day 1	183 (71.8)	15 (5.9)
Day 2	209 (82.0)	19 (7.4)
Day 3	221 (86.7)	45 (17.7)
Day 4	243 (95.3)	58 (22.7)
Day 5	248 (97.3)	91 (35.7)
Day 6	250 (98.0)	121 (47.5)
Day 7	254 (99.6)	159 (62.4)
Day 8	254 (99.6)	186 (72.9)
Day 9	254 (99.6)	197 (77.3)
Day 10	254 (99.6)	213 (83.5)

Table 4: Duration of symptoms before complete resolution and proportion of resolved cases

The median physical disability score on day 1 was nine (9), with a minimum value at zero (0) and a maximum value at 25. On day 11, this decreased significantly to zero (0), with values ranging from zero (0) to 16 ($p<0.0001$) (Table 5).

Physical Disability Scores	Median	Minimum, Maximum	p-value*
Day 1	11	0, 25	<0.0001
Day 11	0	0, 16	

*Wilcoxon signed-rank test

Table 5: Physical disability scores

Adverse events were reported in 22 study participants which consisted of the following: nausea and vomiting (1), dry mouth (2), dizziness (6), somnolence (12), and blurring of vision (1). They were generally mild, lasting for a minimum of one day to a maximum of six (6) days and resolved spontaneously with rest (Table 6).

Adverse Event	Total	Severity	Duration in days	Action	Outcome
Nausea and vomiting	1	Mild	3	no response	no response
Dry mouth	2	Mild	2 3	water (2)	resolved (2)
Dizziness	6	Mild (5) Moderate (1)	2 (1), 6 (4) 3 (1)	sleep (1) no response (5)	improved (2) no response (4)
Somnolence	12	Mild	1 (1) 3 (3) 4 (2) 6 (5) unspecified (1)	none (2) rest/sleep (5) no response (5)	improved (6) no response (6)
Blurring of vision	1	Mild	2	none	Resolved

Table 6: Adverse events

Discussion

Global data have shown that LBP is one of the most common conditions that have increasing burden for years, yielding one of the largest increases in terms of disability-adjusted life years (DALY) [7]. Furthermore, epidemiologic data also document the Philippines as one of the countries that have the highest incidence of LBP [8].

In the ambulatory primary care clinical setting, musculoskeletal LBP is often managed medically with analgesic preparations, using NSAIDs, cyclooxygenase (COX-2) inhibitors, weak opioids, muscle relaxants, on top of lifestyle modification (i.e., weight reduction, proper posturing, good ergonomics in the workplace, etc.) and other treatment interventions (i.e., physical therapy and rehabilitation, heat therapy, ultrasound, complementary and alternative modalities, etc.), especially of pain is refractory to initial oral medical treatment [12].

Paracetamol is one of the most common oral medications given for LBP and is usually preferred over NSAIDs due to its better safety profile, but some studies have shown that it did not any significant difference in shortening to total number of days to recovery [15,16]. On the other hand, orphenadrine, a muscle relaxant, is also used to treat LBP because of its non-specific analgesic properties [13]. Moreover, the combination of both orphenadrine and paracetamol was shown to be effective in treating pain with better safety profile [17-18].

Two instruments were involved in the current study to determine the effectiveness of the Norgesic®. First, the visual analog scale (VAS) was used to measure pain before, during, and after the treatment [12-13]. Second, the previously validated Roland-Morris Disability Questionnaire was used to assess the physical disability caused by LBP as rated by the patients, as it was considered a reliable test to determine affectation of pain to the patients [14,19-20].

Onset of pain relief was noted with a median of one hour after taking Norgesic®, fastest within 30 minutes and with a median pain-free interval of six (6) hours. This was comparable to the known pharmacokinetics of the said drug, which were 40 minutes for paracetamol and one (1) hour for orphenadrine [21-22]. A 93% compliance was also commendable, and only 2% of patients were non-compliant mostly due to patient factors such as immediate pain-relief or the amount of pain perceived, stating the combination of orphenadrine and paracetamol was clinically effective [12,18].

Baseline median VAS score was seven (7). This was comparatively higher in comparison to other VAS noted in other studies [23-25]. Apart from a one-unit rise in the median VAS score, increase from four (4) at bedtime on day 1 to day 5 the following morning on day 2, there was a notable decreasing trend observed at subsequent time points that significantly differed from the baseline. A median VAS score of zero (0) was documented on day 7, which continued until day 10. This decreased trend was significant as other studies stated higher VAS scores on subsequent days of treatment, further reiterating the real-world effectiveness of the combination of muscle relaxants and NSAIDs [26-27]. This was comparable to studies involving muscle relaxants and NSAIDs, which also reported significant clinical LBP alleviation on day 7 [28]. Another preparation, Orphenadrine Citrate 50 mg + Paracetamol 650 mg (Norgesic® Forte), as previously shown in a study, was shown to have median VAS of zero (0) noted on day 5 [29]. This may be attributed to the increased dosage of paracetamol in Norgesic® Forte, which was 650 mg, as increased dosage would entail significantly superior effect, faster onset, and longer duration of pain relief (i.e., dose- response relationship) [30]. Tablet intake was also noted to significantly decrease from the start of the treatment until the end, which agreed with the Norgesic® Forte study previously [29]. further reiterating the synergistic action of orphenadrine and paracetamol.

Study participants alleged total resolution of their symptoms with VAS score of zero (0) in about five (5) days. Furthermore, majority already experienced a significant decrease in VAS score on day 1, with increasing number of study participants recovering each day until day 7. This number of improvements from patients would imply the effectiveness of not only muscle relaxants, but also of paracetamol as a combination therapy, since paracetamol, when given alone in some evidence, appeared to be ineffective in addressing LBP [31-33] However, only one study participant reported to have minimal LBP relief, from a baseline VAS of seven (7) to six (6). Such an observation could be explained by the fact that the LBP might not be purely musculoskeletal in origin, but further diagnostic work-up could be warranted to rule out other etiologies of LBP, which might have a neuropathic component (e.g., herniated nucleus pulposus, lumbar radiculopathy, etc.) [34].

Paracetamol is generally known for its anti-pyretic and analgesic properties; however, its exact mechanism of action for pain relief is not fully elucidated [16,22,30]. Paracetamol is believed to inhibit cyclooxygenase (COX), which has a pivotal role in prostaglandin synthesis. In particular, paracetamol's COX inhibition is more pronounced in the central nervous system (i.e., brain). Likewise, paracetamol may enhance the effects of serotonin in the brain, which consequently modulates pain perception. Lastly, others theorize that paracetamol metabolites have significant interaction with cannabinoid receptors, thereby further modulating pain perception [16-18,22,24,30,32,33-35].

Orphenadrine is a popular muscle relaxant and an anti-cholinergic agent, indicated for acute muscle strain [21,31]. This agent works on the central nervous system to reduce transmission of nerve impulses, thereby lessening the perception of pain and the reflexive muscle spasm. By blocking acetylcholine, it consequently reduces muscle stiffness and spasm. Orphenadrine is also believed to enhance blood perfusion to the muscles, further contributing to its analgesic property and muscle relaxant capability [17-18,21,23,31,32-35].

Physical disability scores were also noted to significantly improve from a median of 11 on day 1 to zero (0) on day 11. This indicated that after treatment, patients' daily activities were no longer hindered by acute pain, suggesting that Norgesic® conferred not only LBP relief, but also alleviated acute muscle spasm, thereby addressing impaired activity versus paracetamol therapy alone [35].

Though self-limiting adverse effects were also reported by the study subjects, the safety profile of Norgesic® was favorable and often did not cause serious, life-threatening complications/ sequelae. The most common side effect noted with Norgesic® use was somnolence. Majority of the adverse events resolved after a few days and were all anticipated. These were all documented on the medication's safety information sheet [36].

Results from this real-world study affirmed that Norgesic® provided pain relief as compared to the baseline data. Not only that it was noted to alleviate pain and spasm, but it also supported that it would be beneficial in patients with impaired physical activity/ mobility secondary to pain [35]. Furthermore, studies have shown that the combination of orphenadrine and paracetamol also aided in improvement of quality-of-life [37]. This could be adopted for future studies that would encompass in a more holistic approach in determining effectiveness of Norgesic®.

Limitations, like all studies, were also present. Metabolism of the medications might differ from each patient. Pharmacokinetic properties might be affected by certain factors, as demonstrated by certain animal studies, in which could be considered in succeeding studies. Co-morbidities affecting metabolism could be looked into [38]. Usage of non-pharmacologic treatment for pain was not monitored that might have affected the study. Time of onset of adverse effects could have been monitored for patients' anticipation. And due to the nature of the study, biases might not determine true causality. Mode of follow-up consults might provide inaccurate information, such that tele-consultations hindered attending physicians from performing proper physical examination, that would be pertinent in determining pain scoring. do proper physical examination, that is pertinent in determining pain scoring.

Conclusion

Acute musculoskeletal LBP is a common medical condition that afflicts millions of people worldwide. It is not only considered a physical burden amongst patients, but it also impacts on the social, economic, and psychological aspects of patients. Holistic management of acute musculoskeletal LBP entails both non-pharmacologic interventions and medical therapy. The single

pill combination of orphenadrine 35 mg and paracetamol 450 mg (Norgesic®) is effective in alleviating LBP, with complete resolution of pain being noted after seven days of treatment, as well as in improving perceived disability scores. Self-limiting adverse events were reported with Norgesic® use, but over-all safety of and tolerance to the combination pill were also documented.

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