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SHORT-TERM EFFICACY AND SAFETY OF SUBLINGUAL KETOROLAC–TRAMADOL (KETOTRAM) COMBINATION IN ACUTE EXACERBATIONS OF KNEE OSTEOARTHRITIS: A PROSPECTIVE CASE SERIES.

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ABSTRACT

Osteoarthritis of the knee is commonly associated with pain, stiffness, and functional limitation, with acute exacerbations requiring effective short-term analgesia. This prospective case series evaluated the short-term clinical response and tolerability of a sublingual ketorolac–tramadol combination in patients with acute exacerbations of symptomatic unilateral knee osteoarthritis. Fifteen patients with moderate symptomatic knee osteoarthritis received sublingual ketorolac 10 mg plus tramadol 25 mg twice daily for 5 consecutive days. Paracetamol 650 mg was used as rescue medication. Pain intensity and osteoarthritis-related functional status were assessed using the Numerical Rating Scale (NRS) and Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at baseline and Day 5. Patient-reported treatment response, rescue analgesic requirement, and adverse events were also recorded. The mean NRS score decreased from 6.67 ± 0.82 at baseline to 3.60 ± 1.40 on Day 5, representing a mean reduction of 3.07 points (paired t-test, $t = 10.21$, $p < 0.001$). Mean WOMAC score decreased from 59.80 ± 1.57 to 35.27 ± 3.81, with a mean reduction of 24.53 points ($t = 22.87$, $p < 0.001$). The mean Likert score for overall treatment response was 3.73 ± 0.59. Fourteen patients (93.3%) required no rescue analgesia, while one (6.7%) required paracetamol 650 mg. No adverse events were reported during the 5-day observation period. These preliminary findings suggest favourable short-term clinical response and tolerability; however, the small sample size, absence of a comparator, concomitant paracetamol use, and short follow-up limit causal interpretation. Larger controlled studies are warranted

INTRODUCTION

Osteoarthritis (OA) is one of the most common musculoskeletal disorders and a major cause of pain, stiffness, functional limitation, and reduced quality of life in older adults. Although OA is a chronic joint disorder, patients may experience periods of increased pain and functional limitation that require short-term symptomatic treatment. During these episodes, effective analgesia is important to facilitate mobility and daily activities. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used for symptomatic management of knee OA because of their analgesic and anti-inflammatory effects; however, treatment should be individualized, taking into account patient-specific gastrointestinal, renal, hepatic, and cardiovascular risks, and used at the lowest effective dose for the shortest appropriate duration [1,2]. Ketorolac is a potent NSAID with established analgesic efficacy for the short-term treatment of acute pain. Tramadol is a centrally acting analgesic with opioid and monoaminergic mechanisms and has been evaluated in patients with symptomatic knee and hip OA. Clinical trials have demonstrated improvements in pain and functional outcomes with some tramadol regimens, although its use may be limited by gastrointestinal and central nervous system adverse effects [3, 4]. Combining an NSAID with a centrally acting analgesic may provide complementary analgesic effects. Clinical evidence from acute postoperative pain has demonstrated that ketorolac-containing combinations with tramadol-containing regimens can influence pain intensity and rescue analgesic requirements, although the magnitude of benefit varies according to the clinical setting and combination used [5].

Despite clinical experience with ketorolac and tramadol, evidence specifically evaluating a fixed-dose ketorolac–

tramadol combination during acute painful exacerbations of knee OA remains limited. Patient-reported functional improvement, treatment response, rescue analgesic requirements, and short-term tolerability are clinically relevant outcomes that may complement conventional pain scores. The present case series was therefore undertaken to describe the short-term effectiveness and tolerability of a sublingual ketorolac–tramadol combination (Ketotram) administered for 5 consecutive days in patients experiencing an acute exacerbation of symptomatic knee OA. Changes in pain intensity and WOMAC scores, patient-perceived treatment response, requirement for rescue paracetamol, and treatment-related adverse effects were evaluated.

METHODOLOGY

This was an observational case series involving patients with clinically diagnosed unilateral knee osteoarthritis of moderate severity who were treated with a sublingual twice daily ketorolac–tramadol combination (Ketotram) for 5 consecutive days. Patients were evaluated clinically at baseline and followed throughout the treatment period, with particular emphasis on pain intensity, functional limitation, night-time symptoms, requirement for additional analgesia, patient-reported response, and treatment-related adverse effects.

Patient selection

Patients aged 18 years or older with symptomatic unilateral knee osteoarthritis of moderate severity with sudden exacerbation were considered for inclusion. The study was done in a pain clinic outside Puducherry. The diagnosis was based on the patient's clinical history and examination, including characteristic knee pain associated with activity or weight bearing, stiffness, and functional limitation. The severity of symptoms was assessed clinically using the WOMAC score and Numerical Rating Scale (NRS). Patients were required to have clinically significant knee pain at baseline and to be suitable for oral analgesic treatment.

Patients were excluded if they had bilateral symptomatic knee osteoarthritis, severe or end-stage osteoarthritis requiring surgical intervention, acute knee trauma, acute infection of the knee, or another significant musculoskeletal condition likely to influence pain or functional assessment. Patients with a known history of renal disease, hepatic disease, active peptic ulcer disease or gastrointestinal bleeding, significant bleeding or coagulation disorders, or known hypersensitivity/intolerance to ketorolac, tramadol, paracetamol, or other non-steroidal anti-inflammatory drugswere excluded. Patients receiving chronic opioid therapy or other analgesic treatment that could substantially interfere with assessment were also excluded. Patients with conditions in which tramadol or ketorolac was considered clinically inappropriate were not included.

Treatment protocol

All included patients received sublingual Ketotram (ketorolac and tramadol)(MedleyPharmaceuticals) atafternoon and night for 5 consecutive days. Patients were instructed to allow the sublingual formulation to dissolve as directed and were observed for any immediate intolerance or adverse effects.

Additional paracetamol 650 mg was permitted as rescue analgesia for breakthrough pain during the 5-day treatment period. Patients were instructed to record each occasion on which rescue medication was required. The total number of additional paracetamol doses used by each patient during the 5-day period was documented.

Clinical assessment and outcome measures

Assessment was primarily based on clinical symptoms and patient-reported outcomes and no routine laboratory investigations were performed solely for outcome assessment. At baseline, demographic characteristics, duration and severity of knee symptoms, baseline pain intensity, functional limitation, and relevant medical history were documented.

Pain intensity was assessed using the 11-point Numerical Rating Scale (NRS), ranging from 0 to 10, where 0 represented no pain and 10 represented the worst pain imaginable. Patients were asked to report their knee pain at baseline and again on Day 5.

Osteoarthritis-related pain, stiffness, and physical functional limitation were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)at baseline and on Day 5. Changes in the WOMAC score were used to assess the overall clinical response in terms of pain and functional status.

During the 5-day observation period, patients were specifically asked about changes in knee pain during walking and routine activities, stiffness, difficulty in movement, difficulty in climbing stairs or performing other daily activities, night-time pain, sleep disturbance related to knee pain, and overall improvement in comfort and mobility. These symptoms were documented based on patient reports during follow-up. On Day 5, the patient's overall perception of treatment response was assessed using a 5-point Likert scale, with higher scores indicating greater satisfaction or perceived benefit. Patients were also asked whether they felt that the treatment had provided meaningful improvement in their knee symptoms and whether they would consider the treatment beneficial for similar episodes of pain.

The requirement for rescue analgesia was recorded throughout the treatment period. Both the number of patients requiring rescue paracetamol and the total number of additional paracetamol doses used during the 5 days were documented.

Safety assessment

Safety assessment was based on clinical observation and spontaneous reporting of symptoms throughout the treatment period. Patients were specifically questioned regarding nausea, vomiting, dizziness, drowsiness, headache, constipation, abdominal discomfort, dyspepsia, gastrointestinal symptoms, allergic symptoms, excessive sedation, and any other new symptom occurring after treatment. Any adverse effect, its approximate timing, severity, and relationship to treatment were documented. Serious or clinically significant adverse events, if encountered, were recorded separately.

At the end of the 5-day observation period, all clinical and patient-reported outcomes were reviewed to assess the overall effectiveness, tolerability, rescue analgesic

requirement, and patient-perceived benefit of the sublingual ketorolac–tramadol regimen.

RESULTS

A total of 15 patients with complete data were included in the case series. The mean age of the patients was 68.4 ± 5.5 years, with an age range of 56–75 years. The mean body weight was 70.8 ± 7.4 kg (range, 59–82 kg). There were 7 male and 8 female patients. All patients received the sublingual ketorolac–tramadol combination at afternoon and night as part of the analgesic regimen. Paracetamol was administered in the morning in all patients.

Pain intensity was assessed using the Numerical Rating Scale (NRS). The mean pre-treatment NRS score was 6.67 ± 0.82, with individual scores ranging from 6 to 8. Following administration of sublingual ketorolac–tramadol, the mean NRS score decreased to 3.60 ± 1.40, with scores ranging from 2 to 6. The mean reduction in NRS score was 3.07 points. On paired analysis, the reduction in pain score was statistically significant (paired t-test, $t = 10.21$, $p < 0.001$).

Functional status was assessed using the WOMAC score. The mean pre-treatment WOMAC score was 59.80 ± 1.57 (range, 57–63), which decreased to 35.27 ± 3.81 (range, 29–40) following treatment. The mean reduction in WOMAC score was 24.53 points. This reduction was statistically significant on paired analysis (paired t-test, $t = 22.87$, $p < 0.001$).

Patient satisfaction with the overnight analgesic regimen was assessed using a 5-point Likert scale. The mean post-treatment Likert score was 3.73 ± 0.59. Seven patients (46.7%) reported a score of 4, five patients (33.3%) reported a score of 3, and three patients (20.0%) reported a score of 5. No patient reported a Likert score below 3, indicating an overall favourable patient-reported response to the treatment.

The requirement for rescue analgesia was low. Fourteen patients (93.3%) did not require any rescue analgesic during the observation period. One patient (6.7%) required paracetamol 650 mg as rescue analgesia. No other rescue analgesic was required. No adverse effects were reported in any of the 15 patients during the observation period.

Overall, the case series demonstrated a reduction in both pain intensity and WOMAC scores following administration of sublingual ketorolac–tramadol, with favourable patient satisfaction and minimal requirement for rescue analgesia. The treatment was well tolerated, with no adverse effects reported in this series. These findings are descriptive and should be interpreted cautiously because of the small sample size, absence of a comparator group, and observational nature of the case series.

DISCUSSION

The present case series evaluated the short-term use of a sublingual ketorolac–tramadol combination in patients experiencing symptomatic exacerbations of unilateral knee osteoarthritis. Over 5 days of treatment, clinically meaningful reductions in pain intensity and WOMAC scores were observed, accompanied by favourable patient-reported treatment response and minimal requirement for rescue paracetamol. Although these findings are encouraging, they should be interpreted as descriptive observations rather than evidence of comparative efficacy because of the small sample size and absence of a control group.

The rationale for combining an NSAID with a centrally acting analgesic is supported by previous clinical evidence. Tramadol has been investigated in osteoarthritis, including as adjunctive treatment during painful exacerbations. In a randomized, placebo-controlled study of patients with OA flare pain inadequately controlled with NSAIDs or COX-2 inhibitors, tramadol/acetaminophen added to existing therapy significantly improved pain intensity, pain relief, and several WOMAC domains over 5–10 days. 6 Similarly, a 5-day study involving patients with acute musculoskeletal pain, acute OA flares, acute rheumatoid arthritis flares, and postoperative pain found greater reductions in pain with tramadol–diclofenac than with tramadol–paracetamol.7These findings support the potential role of combining a centrally acting analgesic with an NSAID-containing regimen for short-term management of acute pain, although the specific formulations and clinical settings differ from those of the present study.

Evidence specifically examining ketorolac combined with tramadol is also available, although predominantly in postoperative settings. A randomized, triple-blind clinical trial after third molar surgery compared ketorolac 10 mg alone with ketorolac 10 mg combined with tramadol/acetaminophen and found lower pain at one assessment point and reduced rescue analgesic requirements with the combination, although the authors considered the magnitude of the pain difference clinically small. 8 In another study involving patients undergoing major abdominal surgery, intravenous tramadol and ketorolac were administered as a combined postoperative analgesic regimen, with assessment of pain, additional analgesic requirements, sedation, and adverse effects.9 These studies provide supportive evidence for the pharmacological rationale of multimodal analgesia but cannot be directly extrapolated to patients with knee osteoarthritis or to the sublingual formulation evaluated in the present study.

Importantly, in our literature search, we did not identify a clinical study specifically evaluating a sublingual ketorolac 10 mg–tramadol 25 mg fixed-dose combination for acute exacerbations of knee osteoarthritis. Thus, the present case series provides preliminary clinical experience with this formulation and route of administration. Nevertheless, the absence of reported adverse events in this small series should not be interpreted as evidence of established safety. Larger controlled studies with longer follow-up, standardized functional outcomes, and systematic adverse-event monitoring are required to determine the efficacy and safety of this combination in acute exacerbations of knee osteoarthritis.

LIMITATIONS

The present study has several limitations. First, the sample size was small, with only 15 patients, which limits the statistical power and the generalizability of the findings. Second, the study was an observational case series without a control or comparator group; therefore, the observed improvements in NRS and WOMAC scores cannot be

attributed definitively to the ketorolac–tramadol combination, and placebo effects, natural fluctuation of osteoarthritis symptoms, and other components of the analgesic regimen may have contributed. Third, , safety assessment was based primarily on clinical observation and patient reporting, and no routine laboratory investigations were performed specifically for outcome assessment. Consequently, asymptomatic or laboratory-detectable adverse effects, particularly renal or hematological abnormalities potentially associated with NSAID therapy, may not have been identified. Fourth, the follow-up period was limited to 5 days, precluding assessment of longer-term efficacy, recurrence of symptoms, or delayed adverse effects. Finally, the study was conducted at a single pain clinic and included patients with unilateral symptomatic knee OA, which may limit the applicability of the findings to broader OA populations.

In summary, these findings should be considered preliminary and hypothesis-generating. Controlled studies with larger samples, appropriate comparators, standardized background analgesia, serial outcome assessment, and systematic laboratory and adverse-event monitoring are warranted.

CONCLUSION

In this prospective case series, 5-day treatment with sublingual ketorolac–tramadol was associated with substantial reductions in pain intensity and WOMAC scores in patients experiencing acute exacerbations of symptomatic knee osteoarthritis. Most patients reported favourable treatment response, and the requirement for additional rescue analgesia was minimal. No adverse events were reported during the short observation period. However, these findings are preliminary and descriptive because of the small sample size, absence of a comparator group, concomitant paracetamol use, and short follow-up. Larger controlled studies with standardized background analgesia and systematic safety monitoring are warranted to confirm these observations.

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AUTHOR CONTRIBUTION

Both the authors were involved in the study.

PATIENT CONSENT

YES

ETHICAL ISSUES

Addressed – a case series only

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