No benefit of additional tramadol or tizanidine to diclofenac for acute low back pain: abridged secondary publication

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KEY MESSAGES

1. There was no significant difference in improvement of functional recovery, pain intensity, and return to work among the three groups of diclofenac plus tramadol, diclofenac plus tizanidine, and diclofenac plus placebo.
2. Our findings do not support the use of tramadol or tizanidine in addition to diclofenac in patients with acute low back pain.

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Introduction

The prevalence of low back pain (LBP) in Hong Kong was estimated to be 21% to 44.1%,[1,2] which is higher than that reported by international studies. LBP can result from over 60 different medical conditions. Apart from malignancy, infection, and fracture, the common causes of mechanical LBP include lumbar strain, herniated disc with radiculopathy, facet osteoarthritis, and lumbar spinal stenosis. It is recommended that nonsurgical management is an effective initial management for these LBP, and there is no need for radiographic or laboratory evaluation.

Emergency departments (ED) play a vital role in the management of patients with acute LBP and severe symptoms. In the United States, among patients with acute LBP, 48% reported functional impairment 3 months after discharge from ED; 42% reported moderate or severe pain; and 46% continued to use analgesic drugs.[3] This shows the lack of optimal treatment for patients with acute LBP in the emergency setting.

For patients with recognised risk factors for chronic LBP, international guidelines from 13 countries recommend management with patient education, early and gradual activation and avoidance of bed rest, the use of analgesic medications and manipulation therapy, and early and aggressive multimodal treatments.[4] Most guidelines recommend non-steroidal anti-inflammatory drugs (NSAID) as the first-line medication. However, for patients with more severe symptoms and functional impairments, the recommendation for second-line analgesic as an add-on of NSAID is less clear. Tramadol and skeletal muscle relaxants have been recommended, but no evidence suggests that they are preferable.

Tramadol is a weak opioid with a dual-model action. It is a selective agonist of mu-opioid receptors; it inhibits neuronal norepinephrine and serotonin reuptake. Tramadol is largely metabolised by the CYP 2D6 enzyme, for which approximately 10% of the Caucasian population (but <1% in the Chinese population) have genetic polymorphism. This suggests a more consistent predictable response

to tramadol in our population. Its common adverse effects include constipation, nausea, dizziness, headache, and drowsiness. The abuse potential is low. Continuous use of tramadol for up to 3 months is safe and effective for patients with chronic pain.

Tizanidine is a commonly used muscle relaxant for acute and non-specific LBP. Tizanidine is an alpha2-adrenargic agonist and an antispasticity and antispasmodic drug. Its onset is 1 to 2 hours, and the action duration is 3 to 6 hours. Its adverse effects are mild and include xerostomia (39%), somnolence (38%), asthenia (25%), and dizziness (12%). Tizanidine decreases the gastrointestinal adverse effects of NSAID (diclofenac); this suggests combined use of diclofenac and tizanidine for patients with more severe symptoms.

Methods

We conducted a multicentre, double-blind, randomised controlled trial.[5] Adult patients with acute non-specific LBP who attended the ED of the Prince of Wales Hospital, Pamela Youde Nethersole Eastern Hospital, and United Christian Hospital were randomly assigned to receive diclofenac plus tramadol, diclofenac plus tizanidine, or diclofenac plus placebo in a 1:1:1 ratio. Patients with a direct injury or fall or with signs of major pathologies were excluded. Patients were followed up for 4 weeks. Outcome measures include the Roland-Morris Disability Questionnaire (RMDQ), numeric rating scale (NRS), adverse effect profile, drug compliance, sick leave period, and return to work capacity (including light duty).

Results

A total of 291 patients were randomly assigned to receive diclofenac plus tramadol (n=93), diclofenac plus tizanidine (n=99), or diclofenac plus placebo (n=99). Of the patients, 90.4% had lower back pain and 9.6% had sciatica. All patients had severe pain and disability, with RMDQ scores ranging from 15.3 to 16.3, NRS (rest) ranging from 4.1 to 4.6, and NRS (activity) ranging from 7.3 to 7.9. However, only 23.7% of patients fully complied with the regimen of at least three of four recommended doses; 53.6% of participants were non-compliant with intake of less than one of the four recommended doses.

Using the intention-to-treat analysis, there were no significant differences between groups in terms of changes in RMDQ score, NRS (at rest), and NRS (activity) on day 7.

Significantly more patients in the tizanidine group and tramadol group than the placebo group reported adverse events including sleepiness and dizziness. There were also more nausea and vomiting in the tramadol group than the placebo group.

Discussion

Adding tramadol or tizanidine to diclofenac did not improve functional recovery of patients with acute LBP. Therefore, the use of additional tramadol or tizanidine in the ED setting is not supported. However, the low compliance drove the effect estimate towards the null hypothesis (ie, no difference). Further studies should take into account of the low compliance.

In a systematic review of muscle relaxants for non-specific LBP, non-benzodiazepine antispasmodics are suggested to increase the risk of an adverse event. Furthermore, in patients taking tramadol, adverse events of dizziness, sleepiness, nausea, and vomiting are reported as causes for discontinuation of treatment. The high incidence of adverse events may have resulted in the low compliance in our study. Thus, physicians should be cautious when prescribing tramadol or tizanidine to patients with acute LBP.

Despite the poor compliance, patients in all three groups had improvements in functional outcomes (RMDQ score) and pain relief (NRS) at days 7 and 28. This is consistent with the results from the United States population that functional impairment improved in most patients from 1 week to 3 months. However, 31% to 45% of our patients could not return to their work capacity at day 28.

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Disclosure

The results of this research have been previously published in:

1. Hung KKC, Lam RPK, Lee HKH, et al. Comparison of diclofenac with tramadol, tizanidine or placebo in the treatment of acute low back pain and sciatica: multi-center randomized controlled trial. Postgrad Med J 2024:qgae052.

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