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Original Article

Randomized open-label non-inferiority trial of acetaminophen or loxoprofen for patients with acute low back pain

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ABSTRACT

Background: Current worldwide clinical practice guidelines recommend acetaminophen as the first option for the treatment of acute low back pain. However, there is no concrete evidence regarding whether acetaminophen or nonsteroidal anti-inflammatory drugs (NSAIDs) is more effective for treating acute low back pain (LBP) in Japan. The present study aimed to investigate whether acetaminophen treatment for acute musculoskeletal pain was comparable with loxoprofen (a traditional NSAID in Japan) treatment.

Methods: Of the 140 patients with acute LBP who visited out-patient hospitals, 127 were considered eligible and were randomly allocated to a group taking acetaminophen or one taking loxoprofen. As primary outcome measure, pain intensity was measured using a 0–10-numeric rating scale (NRS). Moreover, pain disability, pain catastrophizing, anxiety, depression, and quality of life, as well as adverse events, were assessed as secondary outcomes. The primary outcome was tested with a noninferiority margin (0.84 on changes in pain-NRS), and the secondary outcomes were compared using conventional statistical methods at week 2 and week 4.

Results: Seventy patients completed the study (acetaminophen: 35, loxoprofen: 35). The dropout rates showed no significant difference between the two medication-groups. We found that the mean differences of changes in pain-NRS from baseline to week 2 or 4 between the two medication groups were not statistically beyond the noninferiority margin (mean [95% confidence interval]: –0.51 [–1.70, 0.67], at week 2 and –0.80 [–2.08, 0.48] at week 4). There were no consistent differences between the two medication groups in terms of secondary outcomes.

Conclusions: The results suggest that acetaminophen has comparable analgesic effects on acute LBP, based on at least a noninferiority margin, compared with loxoprofen at 4 weeks. Acetaminophen seems to be a reasonable first-line option for patients with acute LBP in Japan.

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1. Introduction

Low back pain (LBP) is one of the most prevalent health problems not only in Japan [1,2] but also globally [3]. Over 80% of people experience LBP at least once in their lifetime [2,4]. Acute LBP is

often defined as pain that persists for <12 weeks; it is regarded as nonspecific and therefore, cannot be attributed to a definite cause [5]. Although 95% of patients with acute LBP seem to recover within a few months after onset [6], it is essential for medical practitioners to prevent the development of chronic LBP.

Current evidence indicates that two traditional medications, nonsteroidal anti-inflammatory drugs (NSAIDs) or acetaminophen, are often used as a pharmacological intervention for acute LBP [7]. NSAIDs, a first-line analgesic agent, activates an analgesic pathway via inhibition of cyclooxygenase, and their efficacy for treating

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acute pain has been well-documented. Another first-line agent, acetaminophen is also a popular analgesic drug worldwide, despite an incompletely elucidated mechanism [8]. In general, it is often believed that the analgesic effects of NSAIDs are superior to acetaminophen for acute pain, because acetaminophen has a poor anti-inflammatory effect [9]. However, a previous systematic review showed that NSAIDs were not more effective than acetaminophen for acute LBP [10]. Furthermore, acetaminophen is a reasonable first-line option for acute pain conditions because of a low incidence of gastrointestinal adverse effects and its low cost [7]. An increased dosage of acetaminophen (up to 4000 mg/day) has been an approved indication for acute musculoskeletal pain in Japan since 2011. However, superior efficacy for nonspecific acute LBP between NSAIDs and acetaminophen has not been evident among medical practitioners in Japan.

Loxoprofen sodium, diclofenac sodium, and etodolac have been frequently used as representative NSAIDs in Japan [11]. Among them, loxoprofen sodium seems to be the most frequently prescribed drug by Japanese orthopedists [11,12]. Therefore, in this study, we investigated the efficacy of two traditional medications, acetaminophen or loxoprofen, in patients with acute LBP.

To date, most clinicians have become familiar with interpreting the results of randomized controlled trials (RCTs) designed to assess whether an experimental therapy is superior to another therapy such as placebo, known as “superiority trials.” Current evidence shows that the efficacies of NSAIDs and acetaminophen for pain relief were comparable for LBP in superiority trials [12]. Thus, determination of which medication is superior for acute LBP is difficult. Therefore, in this study, we performed a noninferiority trial [13,14] to compare the analgesic effects of loxoprofen and acetaminophen. This noninferiority trial tested the hypothesis that acetaminophen is as effective as loxoprofen for acute LBP within a prespecified noninferiority margin.

Treatments for acute pain are commonly assessed by the degree of pain relief using self-rating scales [15], which are often adopted as a primary outcome. Additionally, there is a growing consensus that psychological aspects, as well as functional disabilities with low back pain are also important to determine whether the pain develops into a chronic condition [16]. Hence, in addition to a subjective pain rating, it was reasonable to assess several secondary outcomes associated with risk factors for the development of chronic pain: The Pain Disability Assessment Scale (PDAS) [17], the Pain Catastrophizing Scale (PCS) [18], the Hospital Anxiety and Depression Scale (HADS) [19,20], and the EuroQol-5 Dimensions (EQ-5D) [21].

2. Methods

2.1. Subjects

Participants were recruited consecutively from a single outpatient hospital located in Wakayama prefecture in Japan, between July 2014 and September 2017. The inclusion criteria were age more than 20 years old and initiation of LBP in the 4 weeks prior to study entry. Exclusion criteria were: seeking a second opinion for a prior consultation, cancer-related pain, presence of neurological symptoms (e.g., pain radiating down the leg), traumatic cases such as falls, evidence of bone fractures, surgery within the prior 6 months, current use of full, regularly recommended doses of an analgesic, a positive pregnancy test, autoimmune diseases, inflammatory rheumatic disorders, cardiopulmonary restrictions, severe kidney or liver function disorders, acute duodenal or ventricular ulcer, psychiatric disorders, and the presence of laboratory data outside of normal limits. Limits of laboratory data were defined as 35 U/L for both aspartate transaminase (AST) and alanine aminotransferase

(ALT) for liver function, and 30 mL/min/1.73 m² for estimated glomerular filtration rate (eGFR) for kidney function. Laboratory samples were only taken when the patient took two or more medications, excluding the medication used in this study.

The Research Ethics Committee of Osaka University School of Medicine approved this study, and all study participants provided written informed consent.

2.2. Randomization and treatment

Patients were allocated to one of two groups using computer-generated random numbers: the acetaminophen group received 600 mg acetaminophen 4 times daily for 4 weeks, which was a dosage similar to that reported by Onda et al. [22]; the loxoprofen group received 60 mg loxoprofen 3 times daily for 4 weeks, which is the traditional dosage in Japan. Treatment was performed by a single orthopedist (K.M) throughout this study, and a person (Y.A) who was not involved in treating the patients performed the randomization procedure. External medication for pain was not allowed, with the exception of topical anesthetics. No other supplementary analgesic medication was given during the treatment period. Any prior medications used for the treatment of comorbidities, such as hypertension and diabetes, were unchanged. The physician instructed the patients that they can stop the medication if their symptoms improved or any adverse events occurred during the 4 weeks. Patients were advised to stay active as possible regardless of whether lumbar corset was used.

2.3. Outcomes

2.3.1. Primary outcome

Outcome measures were assessed at baseline, and at week 2 and week 4 after starting the study medication. As a primary outcome measure, a Numeric Rating Scale (NRS) was used to measure pain severity at each assessment, where 0 = no pain and 10 = worst pain imaginable.

2.3.2. Secondary outcome

Secondary outcomes were measured by using the following questionnaires: PDAS, PCS, HADS, and EQ-5D simultaneously. All of these questionnaires included translated versions in Japanese.

(i) PDAS [17]

The PDAS score assesses the degree to which chronic pain interferes with various daily activities during the past week. PDAS includes 20 items reflecting pain interference in a broad range of daily activities, and respondents indicated the extent to which pain interferes. Scores for the total PDAS range from 0 to 60, with higher scores indicating higher levels of pain interference.

(ii) PCS [18]

The PCS score consists of 13 items, and subjects rate how frequently they have experienced such cognition/emotions. The total PCS score can range from 0 to 52, with higher scores indicating higher levels of catastrophizing.

(iii) HADS [19,20]

The HADS scores were designed to assess two separate dimensions of anxiety and depression. The HADS score consists of 14 items; the anxiety (HADS-A) and depression (HADS-D) subscales each include 7 items. A four-point response scale (from 0 representing absence of symptoms, to 3 representing maximum

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