The radiographic effects of ketorolac on patients with spondylolisthesis

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Research article

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Abstract

**Background:** Low back pain may inhibit patients’ spinal range of motion during radiography. Little is known about the dynamic changes of measurement variables and diagnosis of unstable segments in flexion/extension radiographs before and after analgesic injections. We hypothesise that pain control with intramuscular (IM) ketorolac could reveal more radiographic instability segments currently masked by low back pain.

**Methods:** One hundred patients with symptomatic spondylolisthesis from outpatient clinics were recruited. Standing flexion-extension radiographs before and after analgesic injections (IM ketorolac 30 mg) were examined. The visual analog scale (VAS) score and the parameters of segmental instability, including dynamic lumbar lordosis (º; DL), dynamic segmental angulation (º; DA), dynamic segmental translation (mm; DT), and slip percentage (dynamic translation divided with vertebral body width; SP) (%), before and after ketorolac injection were measured. In addition, newly diagnosed unstable segments by different instability criteria were recorded. Pre-post changes between the two groups were analysed using paired t-tests.

**Results:** The VAS score decreased significantly after analgesic injections (66.9 ± 0.97 vs. 32.2 ± 13.1 mm, \( P < 0.001 \)). DL, DA, DT, and SP were significantly increased \( (P < 0.001) \) after providing analgesia compared to pre-analgesia. More unstable segments were found from radiography after ketorolac injection.

**Conclusion:** Kortolac 30 mg injections provided effective analgesia. The radiographic change and diagnosis of instability segments, which might be masked by back pain, significantly changed after IM Kortolac in patients with symptomatic spondylolisthesis.

**Background**

Low back pain (LBP) is a serious and complex medical condition with high compensation costs [1]. It is believed that approximately ten percent of people develop some form of low back pain (LBP) in their lifetime [2,3]. Spondylolisthesis in combination with unstable spinal motion segments can lead to disabling chronic LBP symptoms and neurologic deficits [4,5]. A spinal motion segment is often considered mechanically unstable when it exhibits increased or abnormal motion [6,7]. Management tends to involve spinal fusion surgery when conservative treatment fails [8,9]. This surgery stabilises the instability segments that cause the LBP and neurogenic symptoms. The decision to perform spinal fusion requires evidence of segmental instability as incorrect determination of the fusion level leads to persistent pain, progressive weakness, and the possibility of reoperation [10,11]. Therefore, locating the correct spinal instability level is key to achieving successful spinal surgery.

Currently, there is no consensus concerning the definition of segmental instability. Several methods have been proposed to measure segmental instability, including “facet opening” on T2-weighted magnetic resonance imaging (MRI) (axial views), three-dimensional (3D) reconstruction computed tomography
(CT), and intra-operative measurements (IOM) [8,12,13]. Nevertheless, flexion-extension functional radiographs are considered the gold standard for diagnosing degenerative spondylolisthesis and quantifying segmental instability [4,14]. This method is often combined with clinical findings to determine the spinal fusion level [15,16].

However, the spinal curve and instability segments may be masked due to LBP [17,18]. Previous studies demonstrated that lumbar range of motion (ROM) or curvature might change with LBP relief in patients with spondylolisthesis [19]. Conversely, some authors showed that simple targeted pain relief had little to no effect on spinal ROM or curve [20,21]. Unfortunately, few studies report on actual flexion/extension radiographs, and neither focused on motion segment movements with changes in the level of low back pain.

We hypothesized that reduced pain could alter the flexion/extension radiograph, thus affecting the diagnostic rate of segmental instability. Ketorolac, a nonsteroidal anti-inflammatory drug (NSAID), is commonly used to relieve pain with clinical safety. The purposes of this study were to investigate: 1) the effects of fast-acting Ketorolac in patients with chronic symptomatic spondylolisthesis, and 2) the changes on flexion-extension radiographs of the lumbar spine, including lumbar range of motion, segmental instability, and newly diagnosed unstable segments before and after pain relief.

**Methods**

**Patient Recruitment**

This before-after cohort study was approved by our institutional review board (KMUH-IRB-F(I)-20170129). Informed consent was obtained from each patient before examinations were performed. From February 2018 through May 2019, outpatients visiting the first author’s clinic for LBP with or without leg pain were recruited. The inclusion criteria were as follows: patients with LBP lasting more than six months and diagnosed with low grades (grade I and grade II, based on Meyerding classification [16]) of lumbar spondylolisthesis by standard lumbar anteroposterior and lateral radiographs. The exclusion criteria were as follows: age <20 years or >70 years; history of spine surgery or congenital deformity; current neurological disorder; allergy to non-steroidal anti-inflammatory drugs (NSAIDs); pregnancy; or moderate-to-severe kidney failure (³stage 3) [22]. Demographic data were recorded, including sex, age, height, and body weight (Table 1). The presenting chief complaint for all patients was mechanical LBP, defined as worsening symptoms with standing and sitting for prolonged periods of time, or upon standing from seated position and bending forward, with/without radicular symptoms.

**Analgesia drug injection**

Intramuscular (IM) (deltoid muscle) injection with ketorolac 30 mg (30 mg/1 Amp) was adopted for the treatment of back pain. Vital signs, including blood pressure, heart rate, temperature, and respiration rate,
were recorded within 30 minutes after the injections. Patients with abnormal vital signs were excluded from the study. Injection side effects were recorded, such as nausea/vomiting, headache, or dizziness.

**Flexion extension radiography**

Standing flexion-extension radiographs before and after ketorolac injections were obtained. Images were acquired on 10/17 inch digital X-ray cassettes with a film focus distance of 100 cm and at 90 KV. During the radiographic procedure, patients were asked to flex and extend their backs as much as possible with knee extension.

**Clinical evaluation**

To evaluate the effect of IM ketorolac to relieve low back pain in studied patients, the visual analog scale (VAS) scoring system was recorded before and after analgesia.

**Radiographic evaluation**

The digital images were evaluated on the Picture Archiving and Communication System (PACS) system. We recorded and analysed the target motion segments (TS), forward or backward displacement of one vertebra over a lower vertebra, which were detected by prior standard lumbar X-rays. The radiographic measurement parameters (Fig. 1) were evaluated as follows: (1) vertebral body width (mm; "W" in Fig. 1), (2) lumbar lordosis angle (LA) (°), (3) segmental angulation (SA) (°), and (4) sagittal translation (ST) (mm). The dynamic radiographic changes before and after IM ketorolac injection included (5) dynamic lumbar lordosis (DL) (°), (6) dynamic segmental angulation (DA) (°), (7) dynamic segmental translation (DT) (mm), and (8) slip percentage (DT divided with vertebral body width; SP) (%). Except for the previously identified TS, newly recognized motion segments with listhesis after analgesia were diagnosed using different segment instability criteria as below. Segmental instability was defined as DT >4.5 mm or SP >15% in all lumbar motion segments or DA > 15° at L1/L2, L2/L3, L3/L4, or DA >20° at L4/L5, or DA >25° at L5/S1 [6]. Radiographic parameters from the flexion-extension radiographs were measured by two observers and the mean measurement values between the two observers were adopted for analysis. The two observers were completely blinded to all information, including age, name of patients, and time of image (before or after injection).

**Statistical analysis**
All analyses were performed with SPSS version 19.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation. A paired-t test was used to assess the difference between pre- and post-injection. $P < 0.05$ was considered significant. To validate the assessed data, interobserver reliability was assessed by intraclass correlation coefficient (ICC) analysis.

Results

A Ketorolac injection effectively improved low back pain in patients with spondylolisthesis

A total of 100 patients with symptomatic spondylolisthesis were enrolled in the study. The aetiology of spondylolisthesis in this study included all degenerative types; there were no isthmic, congenital, or traumatic types.

After the injection, the VAS score significantly decreased (pre-analgesia vs. post-analgesia, 66.9 ± 0.97 mm vs. 32.2 ± 13.1 mm; $P < 0.001$). Generally, ketorolac IM injections provided significant analgesia for LBP. None of the patients felt uncomfortable or experienced any side effects after the injection.

Increased radiographic dynamic lumbar lordosis, segmental angulation, segmental translation, and slip percentage after the Ketorolac injection

The radiographic changes between pre-analgesia and post-analgesia in this study are shown in Table 2. Extension and dynamic lumbar lordosis significantly increased in the post-analgesia radiographs. The mean post-analgesia dynamic lumbar lordosis (DL) was 109.17% (post-analgesia/pre-analgesia; 42.61/39.03 = 109.17) of the respective in pre-analgesia; therefore, the mean DL increased by 9.17% after analgesia. This result indicated that the spinal range of motion was restored in the radiograph obtained after the ketorolac injection. Regarding the segmental angulation angles, higher flexion, extension, and dynamic segmental angulations were present in the post-analgesia radiography compared to pre-analgesia. The radiographic segmental translation increased significantly in flexion, extension, and dynamic segmental translation in the post-analgesia compared to pre-analgesia. The SP was significantly increased after injection, demonstrating a 6.23% difference ($P < 0.001$) compared to that of pre-analgesia.

Measurements of LA, SA, ST demonstrated good interrater reliability (ICC = 0.89, 0.91 and 0.93, respectively).

Increased unstable segments were observed after the Ketorolac injection

A total of 150 TSs (target motion segments) were observed before the Ketorolac injection; one level was observed in 56 patients, two levels in 38 patients, and three levels in six patients. Of the 150 TSs, 7 TSs
were located at L2/L3, 48 at L3/L4, 88 at L4/L5, and 7 at L5/S1.

Using the segmental angulation criteria to determine instability [6], there were 48 (48/150 = 32%) unstable segments in the post-analgesia images compared with 6 (4%) in the pre-analgesia images. When dynamic segmental translation (DT) >4.5 mm was considered as instability [6], 63 of 150 (42%) total target motion segments showed instability in post-analgesia radiography compared with 6 (4%) in pre-analgesia ($P < 0.001$). However, considering SP instability criteria [6], the patients after analgesia showed significantly more instability segments (25/150; 16.67%) compared with those before analgesia (1/150; 0.67%; $P < 0.001$) The results of diagnosed unstable segments before and after the Ketorolac injection according to different instability criteria are shown in Fig 2. The number of patients diagnosed with unstable spondylolisthesis (motion segment reached the anyone of above instability criteria) increased from 6 (pre-analgesia) to 38 (post-analgesia).

**Discussion**

The present study investigated the effect of alleviating LBP on the variables measured from flexion-extension radiographs of the lumbar spine in patients with symptomatic spondylolisthesis. We found that 30 mg of IM ketorolac was rapidly effective for alleviating LBP in an outpatient clinic setting. After the ketorolac injection, the dynamic lumbar lordosis angle, dynamic segmental angulation, dynamic segmental translation, and slip percentage significantly increased compared to the pre-analgesia radiograph. The dynamic lumbar lordosis and slip percentage of spondylolisthesis motion segments increased by 9.17% and 6.23%, respectively. In addition, we found an increased number of unstable motion segments after LBP relief on the flexion/extension radiographs. The study results indicated that administering a ketorolac injection to patients with low back pain could help to obtain accurate lumbar flexion/extension radiographs and detect masked instability segments.

In this study, we assumed that the degree and number of instability segments might be underestimated in patients who are suffering from LBP. It has been reported that spinal ROMs decrease during periods of back pain [17]. Hu’s study demonstrated that muscle coordination was impaired during episodes of low back pain [23]. Mellin et al. [24] also reported that extension strength was weaker than flexion strength, with further reduction of extension moments, in patients with severe back pain. Conversely, normal spinal range of motion was regained after pain reduction in patients with chronic LBP [18]. Previous studies discussed the relationship of spinal motion with pain level, utilising the spine curvature measurement or gravity goniometer [19-21]. In this study, we analysed the spinal range of motion by direct measurement with radiographic lumbar lordosis in flexion/extension position. We found the lordosis angle increased after Ketorolac injection, which would help present the normal spine motion during the radiography examination and unveil masked instability segments.

In the literature review, a high reoperation rate (7.4%-14%) was reported after spine surgery [11,25,26]. The most common pathology is instability occurrence on adjacent segments after lumbar fusion or dynamic stabilization surgery [11,25]. To decrease the reoperation rate, the determination of potential unstable
segments is particularly vital at the time of the primary decompression or fusion surgery. Patients who sustained low back pain could not fully flex or extend their backs during examination. This may mask lumbar segmental instability, leading to a false negative diagnosis [27]. To the best of our knowledge, the present study was the first to demonstrate segmental instability parameters after analgesia, and the results show that translation and angulation values increased after analgesia. Also, some newly diagnosed hidden unstable motion segments were detected after pain reduction in our study (Fig. 3). These newly diagnosed instability segments, which were masked by back pain, could help determine the index level of spinal surgery.

This study was the first to investigate the effect of fast-acting pain relief on the measurements of flexion/extension radiographs at outpatient clinics. Analgesic methods and outcomes of spinal mobility examinations were variable from previous studies (Table 3) [19-21]. Regarding the analgesia method, an intramuscular injection is less invasive than facet joint injection or transcutaneous electrical nerve stimulation [19,20]. Compared to intramuscular injection, oral analgesia methods may achieve slow-acting or insufficient pain relief [21]. According to our results, ketorolac 30 mg intramuscular injections were safe and efficient in terms of the early-onset of action (30 minutes), and alleviation of pain which could be achieved in the clinic prior to the radiography examination.

We acknowledge limitations to this study. First, we did not investigate whether pain reduction could decrease back muscle splinting. Further studies are necessary to elucidate spinal muscle tone measurements via the electromyography method. Second, the clinical study of novel unstable segments detection and their relationship with fusion level requires clarification. Finally, there is a substantial risk that a participant injection placebo effect may have influenced the results. Future studies should incorporate an additional injection comparison group to clarify the possible placebo effect.

**Conclusions**

The study results indicate that Ketorolac 30 mg injections can provide effective analgesia in patients with LBP. Further, the lumbar lordosis, segmental angulation, sagittal translation, slip percentage, and instability diagnosis rate increased after analgesia. This short-term pain relief facilitates reliable mechanical functional imaging of the spine and is feasible for administration in outpatient clinics.

**Abbreviations**

LBP: Low back pain; ROM: Range of motion; IM: Intramuscular; VAS: Visual analog scale; TS: Target motion segments; LA: Lumbar lordosis angle; SA: Segmental angulation; ST: Sagittal translation; DL: Dynamic lumbar lordosis; DA: Dynamic segmental angulation; DT: Dynamic segmental translation; SP: Slip percentage. ICC: intraclass correlation coefficient.

**Declarations**
Ethics approval: This before-after cohort study was approved by Institutional Review Board of Kaohsiung Medical University Chung-Ho Memorial Hospital. (Reference number: KMUH-IRB-F(I)-20170129). Each author certifies that all investigations were conducted in conformity with ethical principles.

Consent to participate: All participants provided informed consent before their participation in the study and written were obtained from all participants.

Consent for publication: Patients signed informed consent regarding publishing their data and photographs.

Availability of data and material: The Manuscript has associated data in a data repository.

Competing interests: The authors declare that they have no financial or non-financial competing interests.

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Authors’ contributions

Conceptualization: SHC, PCS, YCT; Methodology: SHC; Formal analysis and investigation: CCL, KLL; Writing - original draft preparation: SHC, PCS; Writing - review and editing: CCL, SYL, HPT, CLS; Supervision: PJH, YCT, YHH, PCS.

All authors have read and approved the manuscript.

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Tables

Table 1 Patient Demographics

|         | Mean (median) | SD  | Range    |
|---------|---------------|-----|----------|
| Age (years) | 53.3 (median: 57) | 13.1 | 20-75    |
| Sex (F/M)      | 77/23         |      |          |
| Height (cm)    | 162.8         | 8.4  | 155-181  |
| Body weight (kg)| 67.6          | 7.9  | 52-87    |
| BMI (kg/m²)    | 27.5          | 5.2  | 18.7-33.6|
F = female; M = man; BMI = body mass index; SD = standard deviation; TSs = target motion segments.

Table 2 Parameters measured from flexion-extension radiographs before and after analgesic injections

| Measured parameters       | Pre-analgesia | Post-analgesia | Difference | p-value |
|---------------------------|---------------|----------------|------------|---------|
| **Lumbar lordosis angle (°)** |               |                |            |         |
| Flexion                   | 9.06 ± 14.21  | 7.57 ± 12.55   | -1.49 ± 8.07 | 0.007   |
| Extension                 | 47.70 ± 11.81 | 50.18 ± 11.23  | 2.48 ± 0.55 | <0.001  |
| DL                        | 39.03 ± 13.61 | 42.61 ± 12.94  | 3.57 ± 8.07 | <0.001  |
| **Segmental angulation (°)** |               |                |            |         |
| Flexion                   | -1.36 ± 4.86  | -3.64 ± 5.08   | -2.27 ± 3.7 | <0.001  |
| Extension                 | 9.52 ± 4.12   | 12.10 ± 4.46   | 2.57 ± 2.89 | <0.001  |
| DA                        | 10.89 ± 4.30  | 15.74 ± 4.72   | 4.85 ± 4.59 | <0.001  |
| **Segmental translation (mm)** |             |                |            |         |
| Flexion                   | -2.73 ± 3.49  | -4.24 ± 3.94   | -1.51 ± 1.34 | <0.001  |
| Extension                 | -0.79 ± 3.75  | 0.10 ± 4.06    | 0.89 ± 1.33 | <0.001  |
| DT                        | 1.94 ± 1.34   | 4.36 ± 1.56    | 2.4 ± 1.36  | <0.001  |
| **Slip percentage (%)**   | 4.95 ± 3.41   | 11.11 ± 4.00   | 6.23 ± 3.46 | <0.001  |

\[ \text{\textsuperscript{\#}} = \text{difference of measure parameters between post-analgesia and pre-analgesia status. DL: Dynamic lumbar lordosis, DA: Dynamic segmental angulation, DT: Dynamic segmental translation.} \]

Table 3 Investigation of segmental instability by study
|                                | This study | Jarzem et al.[19] | Lilius et al.[20] | Williams et al.[21] |
|--------------------------------|------------|-------------------|-------------------|--------------------|
| Number of patients             | 100        | 50                | 67 (109)\(\ddagger\) | 40\(\psi\)       |
| Age (range)                    | 53 (20-75) | U (18-70)         | 44 (19-64)        | 40 (18-55)         |
| **Treatment**                  |            |                   |                   |                    |
| Methods                        | IM analgesia (ketolorac 30mg) | Transcutaneous electrical nerve stimulation | Facet joint injection | Self-administer oral analgesia |
| Duration demand                | 30 minutes | Within one hour   | Within one hour   | 45-60 minutes      |
| **Assessment**                 |            |                   |                   |                    |
| Pain score reduction           | Average 34.7 mm reduction | U                   | Average 18.3 mm reduction | Around 23-30 mm reduction |
| Spinal motion                  | Radiographic Flexion/extensio n | Gravity goniometer | Spine curvature measurement\(\ddagger\) | Spine curvature measurement\(\Phi\) |
| The treatment effect on flexion-extension radiographs | Increased dynamic lumbar lordosis by 9.17% and slip percentage in motion segments by 6.65%. | Increase in ROM during flexion and extension as measured by an inclinometer. | Pain relief did not change flexion extension ROM | Pain reduction did not attenuate the lumbar curvatures except for flexion and lifting in the acute low back pain group. |

IM = intramuscular injection; U = un-mentioned; \(\ddagger\) = 42 patients received placebo injection (normal saline); \(\psi\) = including 20 acute and 20 chronic low back pain participants; \(\ddagger\) = skin marker method; \(\Phi\) = Fiber-optic base reference.

**Figures**
Figure 1

The measurement diagram for detecting motion segments of lumbar spine in flexion (A) and extension (B) views. Lumbar lordosis angle (LA) was defined as the angle between the tangential lines of the superior endplates of L1 and S1. To measure the segmental angulation (SA), tangent lines were drawn along the lower endplate of superior vertebra (such as L4) and upper endplate of inferior vertebra (such as L5); those two lines form SA. To measure segmental translation (ST), a perpendicular line from posterior margin of lower endplate of superior vertebra of L4 to the line of upper endplate of inferior vertebra of L5 was added, and the length between A and B was defined as ST. The distance between the anterior and posterior walls of the L5 vertebra was defined as the vertebral body width (w). Dynamic lumbar lordosis (DL) was defined as the difference in lumbar lordosis angle between flexion and extension; Dynamic segmental angulation (DA) was defined as the sagittal angulation change between flexion and extension; Dynamic segmental translation (DT) was the difference in segmental translation between flexion and extension. The slip percentage (SP) (%) was equivalent to DT divided by vertebral body width (w).
Figure 2

Graphs showing the numbers of unstable motion segments diagnosed using different instability criteria before and after ketorolac injection
Figure 3

Example of an additional motion segment which was diagnosed after analgesic treatment (A-B) X-ray images of lumbar spine flexion and extension before analgesic treatment. L34 was identified as stable listhesis with posterior displacement (L34, DA: 6.4°, DT: 2.5mm, SP: 7.3%). (C-D) X-ray images of lumbar spine flexion and extension after analgesic treatment. Both anterior displacement L45 and posterior displacement of L34 were increased. (L34, DA: 16.6°, DT: 3.5mm, SP: 10.2%; L45, DA: 15.4°, DT: 4.7 mm, SP: 12%). Additional unstable spondylolisthesis at L45 was identified and L34 was diagnosed as unstable retrolithesis after analgesic treatment.