New treatment of lumbar disc herniation involving 5-hydroxytryptamine\textsubscript{2A} receptor inhibitor: a randomized controlled trial

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Object. Serotonin or 5-hydroxytryptamine (5-HT) is a chemical mediator associated with nucleus pulposus–induced radiculopathy. Inhibition of 5-HT receptors may potentially alleviate symptoms in patients with lumbar disc herniation. This prospective randomized controlled study was performed to evaluate the efficacy of the 5-HT\textsubscript{2A} receptor inhibitor in the treatment of symptomatic lumbar disc herniation.

Methods. Forty patients with sciatica due to L4–5 or L5–S1 disc herniation were randomly allocated to treatment with the 5-HT\textsubscript{2A} inhibitor (sarpogrelate 300 mg/day) or nonsteroidal antiinflammatory drugs (NSAIDs; diclofenac 75 mg/day). Low-back pain, leg pain, and numbness were evaluated using a visual analog scale (VAS) before and after a 2-week course of treatment. The patients received only allocated medicine during the 2-week regimen and were thereafter allowed to choose any treatment options depending on their residual symptoms. One-year clinical outcomes were assessed based on the rates of additional medical interventions.

The mean VAS score improvements in the 5-HT\textsubscript{2A} and NSAID groups were 33 and 46\% for low-back pain, 32 and 32\% for leg pain, and 35 and 22\% for leg numbness, respectively. After the 2-week regimen, no additional medical interventions were required in 50\% of 5-HT\textsubscript{2A}–treated patients and 15\% of those receiving NSAIDs. Epidural or nerve root block procedures were performed in 35\% of the 5-HT\textsubscript{2A} group and 45\% of the NSAID group. Surgery was required in 20\% of the 5-HT\textsubscript{2A} group and 30\% of the NSAID group patients.

Conclusions. The current study provided evidence that the efficacy of the 5-HT\textsubscript{2A} inhibitor was comparable with that of NSAID therapy for lumbar disc herniation. The 5-HT\textsubscript{2A} inhibitor has the potential to alleviate symptoms in patients with lumbar disc herniation.

KEY WORDS • lumbar disc herniation • sciatica • 5-hydroxytryptamine receptor • sarpogrelate

SCIATIC pain is a common and disabling symptom that frequently occurs in patients with lumbar disc herniation. Mechanical compression of a nerve root is significantly linked to the symptoms of sciatica.\textsuperscript{1} Evidence based on recent research also indicates that not only mechanical compression of the spinal nerve root but also the biochemical influence secondary to an HNP contribute to nerve root inflammation and production of sciatic pain.\textsuperscript{1,3,15,18} Numerous cytokines and chemical mediators are involved in such nerve root inflammation.\textsuperscript{2,3,22} Currently, the role of TNF\textsubscript{\alpha} is being studied in the pathomechanism of HNP-induced nerve root damage.\textsuperscript{9,16} Immuno-histochemically TNF\textsubscript{\alpha} is expressed in the nucleus pulposus,\textsuperscript{16} and exogenous TNF\textsubscript{\alpha} produces neuropathological changes in the nerve root.\textsuperscript{3} Although clinical application of TNF\textsubscript{\alpha} antagonists is expected,\textsuperscript{11,17} their efficacy and safety have not been proven in the treatment of symptomatic lumbar disc herniation.

Serotonin (5-HT) is also a chemical mediator associated with nerve root inflammation.\textsuperscript{3,21,22} In previous studies involving a rat model, investigators have shown that 5-HT\textsubscript{3} receptors are identified at the dorsal root ganglia and are most likely related to 5-HT–induced hyperalgesia in acute inflammation.\textsuperscript{3,22} It has also been reported that a 5-HT\textsubscript{2A} receptor inhibitor can provoke an antinociceptive effect on 5-HT–induced inflammatory pain.\textsuperscript{14} Sarpogrelate is a selective 5-HT\textsubscript{2A} receptor inhibitor that has proven to be safe and effective for the management of ischemic vascular disorders.\textsuperscript{5,7,19} It may have the potential to block the cascade of acute inflammatory reaction in spinal nerve roots and to alleviate sciatic symptoms in patients with lumbar disc herniation.\textsuperscript{10} Therefore, we hypothesized that a selective 5-HT\textsubscript{2A} receptor inhibitor should alleviate HNP-induced low-back pain and sciatic symptoms effectively compared with NSAIDs.

The objective of this prospective randomized controlled...
study was to evaluate the efficacy of the 5-HT$_{2A}$ receptor inhibitor compared with an NSAID in the treatment of symptomatic lumbar disc herniation.

**Clinical Material and Methods**

All patients requesting treatment at the orthopedic department of our hospital with low-back pain and sciatic symptoms associated with an L4–5 or L5–S1 herniated disc were candidates for inclusion in the study. Excluded candidates were those referred to our hospital for surgical treatment in whom there were absolute surgical indications because of the presence of bladder/bowel dysfunction or drop foot. Additionally, all candidates were required to be ambulatory. The size of the herniated disc was not an exclusion criterion. A flow chart depicting inclusion, randomization, and intervention criteria is provided in Fig. 1. Herniated nucleus pulposus and associated symptoms were diagnosed by board-certified spine surgeons who performed preinterventional examinations and reviewed MR imaging studies. Patients were not included in the study if any of the following criteria were present: 1) degenerative spinal stenosis; 2) degenerative spondylolisthesis or scoliosis; 3) isthmic spondylolisthesis; 4) osteoporosis and associated vertebral fractures; 5) previous lumbar surgeries; 6) ischemic vascular disorders; 7) malignant tumors or metastasis; and 8) metabolic disease including diabetes mellitus. No medication was provided before enrollment in this study. The study protocol was fully approved by the institutional review board.

A total of 40 patients with sciatica due to an L4–5 or L5–S1 herniated disc were prospectively enrolled in the study between August 2001 and April 2003. There were 20 male and 20 female patients whose mean age was 32.7 years. The level of disc herniation was L4–5 in 16 patients and L5–S1 in 25 patients. One patient suffered from multilevel HNPs at L4–5 and L5–S1. Nine patients (22.5%) experienced muscle weakness, and 16 patients (40%) experienced sensory disturbance. The straight-leg raising test was positive in all patients. The duration of symptoms was less than 1 month in 14 patients, 1 to 3 months in 18, and more than 3 months in eight.

The patients were randomized to the following treatment groups of 20 patients each: 1) 5-HT$_{2A}$ receptor inhibitor (sarpogrelate hydroxychloride); or 2) NSAID (sodium diclofenac). Sarpogrelate hydroxychloride (Anplag; Mitsubishi Pharma Corp., Osaka, Japan) is a selective 5-HT$_{2A}$ receptor inhibitor that has been approved in Japan and South Korea for use in patients with ischemic vascular disorders. Potential side effects include GI events (0.81%), liver dysfunction (0.35%), bleeding or hemorrhage (0.25%), dizziness or headache (0.19%), skin eruption (0.19%), heart palpitation and tachycardia (0.15%), anemia (0.08%), and renal dysfunction (0.06%). The randomization procedure involved opening one of 40 envelopes for each of the 40 patients. The contents of the envelope allocated the patient to the 5-HT$_{2A}$ receptor inhibitor or NSAID group. Sarpogrelate hydroxychloride was administered orally (300 mg/day) for 2 weeks. In the NSAID treatment group, sodium diclofenac was administered orally (75 mg/day) for 2 weeks. The therapies were administered on an outpatient basis. Low-back pain, leg pain, and numbness were graded by the self-administered VAS before and immediately after the 2-week regimen. Improvement in VAS scores was calculated as a ratio of the difference between pre- and posttreatment values to the pretreatment value. Although the patients received only allocated medicine during the 2-week period, they were thereafter allowed to choose any treatment options depending on their residu-
Efficacy of the 5-HT\textsubscript{2A} receptor inhibitor for lumbar disc herniation

al symptoms. The treatment options included additional NSAID administration, epidural or nerve root block therapy, and surgery.

The primary end point with respect to efficacy in lumbar disc herniation was improvement in VAS scores for low-back pain and sciatic symptoms from baseline to immediate postintervention (after the 2-week regimen). Additional analyses were performed to determine the proportion of patients requiring other intervention (additional NSAID administration, epidural or nerve root block, and surgery) at any time point after the 2-week regimen. All the patients were followed for more than 1 year after the intervention.

**Statistical Analysis**

Pretreatment and posttreatment VAS data were statistically compared in each group by using a paired t-test. Improvement in scores for the 5-HT\textsubscript{2A} inhibitor–treated and NSAID-treated patients were also estimated using an unpaired t-test. Clinical outcomes were statistically analyzed using a chi-square test. Additionally, the statistical power analysis was conducted according to the following equations:\superscript{3,2}

\[ n = 2 \times \left( \frac{\alpha \delta}{\sigma} \right)^2 \times \left( \alpha, \nu + t(1 - P), \nu \right)^2 \quad (1) \]

\[ v = a (n - 1) \quad (2) \]

where \( n \) is the sample size (the number of independent observations per group); \( \sigma \) is the population SD; \( \delta \) is the detectable difference; \( \alpha \) is the significance level; \( \nu \) is the degree of freedom; \( \alpha, \nu \) is the t value corresponding to \( \alpha \) and \( \nu \); \( P \) is the statistical power; and \( a \) is the number of groups. When the significance level and statistical power are set to 0.05 and 0.9, respectively, the value of \( \sigma \delta / \sigma \) is calculated as 1.05. Thus, to have a 90% chance of detecting as significant (at the 5% level) 30% of the intergroup difference in the mean improvement rate of VAS scale scores, with an assumed SD of 30%, 20 patients (40 in total) in each group were required.

**Results**

Baseline demographic and clinical characteristics are presented in Table 1. Sex, age, and level of herniation were equivalently distributed in both groups. No patients were lost to follow up during the 2-week regimen; thus, VAS data were available for all cases. Visual analog scale scores (0–100) for low-back pain, leg pain, and numbness were significantly improved in both 5-HT\textsubscript{2A} inhibitor and NSAID treatment groups after the 2-week regimen (Table 2).

The improvement rate of VAS scores was calculated using the following formula:

Improvement rate (%) = (baseline VAS score – postintervention VAS score)/baseline VAS score × 100%

The mean VAS score improvement rates in the 5-HT\textsubscript{2A} inhibitor treatment and NSAID groups were 33 and 46% for low-back pain, 32 and 32% for leg pain, and 35 and 32% for leg numbness, respectively (Fig. 2). The improvement rates for low-back pain, leg pain, and numbness were comparable between the two groups, although not statistically significant (p > 0.05, unpaired t-test). No serious adverse effects related to 5-HT\textsubscript{2A} inhibitor medication were observed.

Although the patients received only allocated medicine for 2 weeks, they were thereafter allowed to choose any treatment options depending on their residual symptoms (Fig. 3). After the 2-week treatment period, epidural or nerve root block therapy was required in seven (35%) of the 5-HT\textsubscript{2A} inhibitor–treated patients and nine (45%) of the NSAID-treated patients for residual sciatic symptoms. The effect of the nerve root block treatment was long lasting in three of seven patients in the 5-HT\textsubscript{2A} inhibitor group and four of nine patients in the NSAID group. Four patients (20%) who had received 5-HT\textsubscript{2A} inhibitor treatment and six patients (30%) who had received NSAIDs eventually underwent surgery for unremitting sciatic symptoms or muscle weakness. Although 16 5-HT\textsubscript{2A} inhibitor–treated patients and 14 NSAID-treated patients did not undergo surgery after the 2-week regimen, 11 in the NSAID group (79%) and six in the 5-HT\textsubscript{2A} inhibitor group (38%) needed supplemental NSAIDs. Although three of 11 NSAID-treated patients continued to take NSAIDs at minimum 1-year follow up, none of the 5-HT\textsubscript{2A} inhibitor–treated patients received medication. The mean duration of supplemental NSAID treatment was 15 weeks in the NSAID group and that in the 5-HT\textsubscript{2A} inhibitor group was 8.8 weeks. Consequently, no additional medical interventions were required in 10 patients (50%) in the 5-HT\textsubscript{2A} group and three patients (15%) in the NSAID group.

**Table 1**

**Summary of mean VAS scores determined pre- and postintervention**

<table>
<thead>
<tr>
<th>Treatment Group &amp; Symptom</th>
<th>Baseline</th>
<th>Posttreatment</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-HT\textsubscript{2A} Inhibitor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>low-back pain</td>
<td>50 ± 23</td>
<td>38 ± 30</td>
<td>0.0222</td>
</tr>
<tr>
<td>leg pain</td>
<td>51 ± 22</td>
<td>36 ± 24</td>
<td>0.0078</td>
</tr>
<tr>
<td>leg numbness</td>
<td>44 ± 24</td>
<td>33 ± 28</td>
<td>0.0233</td>
</tr>
<tr>
<td>NSAID</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>low-back pain</td>
<td>66 ± 26</td>
<td>39 ± 34</td>
<td>0.0008</td>
</tr>
<tr>
<td>leg pain</td>
<td>68 ± 25</td>
<td>50 ± 32</td>
<td>0.0054</td>
</tr>
<tr>
<td>leg numbness</td>
<td>44 ± 34</td>
<td>31 ± 34</td>
<td>0.0098</td>
</tr>
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Discussion

Research into HNP-induced radiculopathy has revealed that numerous cytokines play significant roles in nerve root inflammation. Inhibition of such cytokines is a current topic in the treatment of HNP-induced radiculopathy. Recently, findings in basic science investigations have suggested that TNFα plays a significant role in the pathomechanism of HNP-induced sciatica. Additionally, TNFα inhibitors have been reported to prevent nucleus pulposus–induced functional and structural nerve root injury in a porcine model. Although there is enthusiasm for the use of anti-TNFα antagonists in the treatment of HNP-

Fig. 2. Graph demonstrating the improvement rate in VAS scores. Improvements in low-back pain, sciatic pain, and leg numbness scores in the 5-HT2A inhibitor group were comparable with those in the NSAID group. No statistical differences were observed.

Fig. 3. Flow diagram depicting the trial of 5-HT2A inhibitor for patients with symptomatic lumbar disc herniation, including data pertaining to those who required additional intervention after the 2-week therapy.
Efficacy of the 5-HT2A receptor inhibitor for lumbar disc herniation

TABLE 3

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Sarpogrelate (5-HT2A inhibitor)</th>
<th>Diclofenac (NSAID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>overall</td>
<td>107 (2.23%) of 4807 cases</td>
<td>2749 (7.21%) of 35,653 cases</td>
</tr>
<tr>
<td>GI events</td>
<td>39 (6.63%) of 4807 cases</td>
<td>2365 (0.81%) of 35,653 cases</td>
</tr>
</tbody>
</table>

Rates of side effects stratified by treatment*

* Derived from unpublished data reported by Mitsubishi Pharma Corp., Osaka, Japan, and Novartis Parma K.K., Tokyo, Japan.

induced sciatica, several issues should be addressed before extensive clinical application. Karppinen, et al., used a monoclonal antibody against TNFα, infliximab, in the treatment of HNP-induced sciatica. Although their short-term results were encouraging, some limitations might exist including the following: 1) the sample size was extremely small (only 10 patients); and 2) the study was neither prospective nor randomized. In addition, the following serious adverse effects of infliximab could not be ignored: it might 1) deteriorate undetected tuberculosis and other systemic infections; 2) place at risk patients with moderate or severe heart failure; and 3) cause serious allergic reactions including anaphylactic shock and delayed hypersensitivity reactions. Thus, the efficacy and safety of anti-TNFα therapy have not been clinically proven. To date, the only pharmaceutical options with proven efficacy remain NSAIDs.

Serotonin is one of the chemical mediators associated with HNP-induced sciatica, which has receptors classified into seven families based on cloning studies. Regarding the pathomechanism of pain production, it has long been thought that 5-HT3 receptors located on sensory nerve terminals are responsible for 5-HT–induced hyperalgesia. In several studies involving a rat model, however, investigators have shown that 5-HT2A receptors are identified at the DRGs and are most likely related to 5-HT–induced hyperalgesia in acute inflammation. Ebersberger, et al., reported that not only 5-HT3 receptors but also 5-HT2A receptors mediated the expression of c-fos-like protein by noxious stimulation. Tokunaga, et al., found in a rat model that injection of the 5-HT2A receptor agonist significantly reduced the paw-withdrawal latency, but the 5-HT2A receptor agonist did not produce hyperalgesia. Additionally, pretreatment with the 5-HT2A receptor inhibitor, but not with the 5-HT3 receptor inhibitor, attenuated the behavioral response after the injection of 5-HT. They also reported that inflammation of the spinal nerve root increased messenger RNA expression of 5-HT2A receptor in DRG. Therefore, a 5-HT2A receptor inhibitor may have the potential to block the cascade of acute inflammatory reaction in the spinal nerve root. Sarpogrelate is a selective 5-HT2A receptor inhibitor that has been proven safe and effective for the management of ischemic vascular disorders. Kanayama, et al., reported on the clinical application of sarpogrelate in patients with HNP-induced sciatica, suggesting the efficacy of a 5-HT2A receptor inhibitor in the treatment of symptomatic lumbar disc herniation. Because of the anticoagulant effects of 5-HT2A receptor inhibitor, however, caution should be exercised in patients in whom bleeding or hemorrhage is present; those undergoing anticoagulant therapy; women during menstruation; and those with severe renal failure. Carefully conducted clinical trials are required to prove the efficacy and safety of this new anti–5-HT2A 5-HT2A therapy.

The current prospective randomized controlled study demonstrated that the efficacy of 5-HT2A receptor inhibitor (sarpogrelate) was comparable with that of NSAIDs in the treatment of symptomatic lumbar disc herniation. Sarpogrelate was associated with a lower rate of side effects including GI events compared with NSAID therapy (Table 3). Thus, anti–5-HT2A treatment should be safe and have the potential to alleviate sciatic symptoms in the patients with lumbar disc herniation. We expect that it will be an alternative to NSAID treatment.

Conclusions

A prospective randomized controlled study was conducted to evaluate the efficacy of a 5-HT2A receptor inhibitor in the treatment of symptomatic lumbar disc herniation. Its efficacy was comparable with that of NSAIDs regarding improvement of low-back pain and sciatic symptoms. Thus, the 5-HT2A inhibitor has a potential to alleviate symptoms in lumbar disc herniation and to be an alternative to NSAIDs.

References

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Manuscript received August 13, 2004. Accepted in final form January 4, 2005.

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