Effectiveness of various non-steroidal anti-inflammatory drugs in pain management of patients with vertebral fracture: A comparative clinical study

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Abstract

Purpose: To study the effectiveness of various nonsteroidal anti-inflammatory drugs (NSAIDs) in patients with vertebral fractures.

Methods: A total of 78 patients (17 males and 61 females) with a mean age of 69.5 years were included. The major inclusion criterion was an osteoporotic vertebral fracture between T7 and L3. The exclusion criteria included fractures above T7 and below L3; and other bone disorders such as disc herniation, spondylolisthesis, an infection, or a tumour. Pain intensity was assessed with the aid of a 10-point visual analogue scale (VAS). Bone mineral density (BMD) data, delay in reunion, and any other matter of significance, were discussed with the treating doctors and cross-checked with independent doctors. The NSAIDs given were non-selective cyclooxygenase (COX) inhibitors (naproxen, indomethacin and flurbiprofen) and selective COX 2 inhibitors (piroxicam, celecoxib, and rofecoxib). All data were compiled and appropriately analysed.

Results: Some NSAIDs interfered with bone healing. No male required surgery, but two females taking naproxen, one taking flurbiprofen, and another taking celecoxib, required surgery. In terms of bone healing, non-union and delay in reunion were more evident in those taking naproxen, indomethacin or flurbiprofen than in those taking piroxicam, celecoxib, or rofecoxib. All T scores were lower than -2.5, indicating that all the patients were osteoporotic. Positive changes in T scores after 12 weeks were evident only in those taking rofecoxib, celecoxib, or piroxicam. VAS scores were also better in these patients.

Conclusions: Celecoxib seems to be the best of the six NSAIDs in terms of both analgesia and bone health. The study recommends the use of celecoxib in patients with vertebral fractures.

Keywords: Orthopaedic, NSAID, COX, Bone reunion, Analgesic activity, Pain management, T score

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are prescribed very frequently to patients with lumbar or intervertebral disc disorders for the effective management of pain and inflammation [1,2]. Chronic use of NSAIDs often causes one or more side-effects including gastric irritation, stomach ulcers, gastrointestinal bleeding, renal failure, cardiac arrest, and stroke [3-6]. Relief from the severe pain associated with lumbar disorders requires high doses of NSAIDs for prolonged periods of time. NSAIDs inhibit cyclooxygenase (COX) enzymes. COX-1 is involved in physiological functions including haemostasis and gastric protection. COX-2 (which is inducible) mediates pain, inflammation, and fever, in turn inhibiting the synthesis of prostaglandins from...
arachidonic acid. NSAIDs affect bone destruction and bone formation by the pathway mediated by COX-2 only [7,8].

Decades-long investigations have explored the roles played by NSAIDs in bone healing, pain, and management of inflammation. Several studies have suggested that NSAIDs interfere with bone healing; many other studies instead found NSAIDs to be safe and effective [7,8].

Effective analgesia is not an issue, but safety profiles have always been of concern [9,10]. Older patients often have bone diseases such as osteoporosis which is a systemic skeletal disease characterised by reductions in bone mass and bone tissue. The bones become fragile and prone to fracture. Bone mineral density (BMD) is reduced in osteoporotic patients. Osteoporosis is very common in post-menopausal women, caused principally by oestrogen deficiency. The bones (particularly the femora, vertebrae, and radii) become fragile and porous. Aging and androgen deficiency cause osteoporosis in males. Treatment seeks to reduce bone resorption and increase bone formation, either by inhibiting osteoclasts and/or stimulating osteoblasts [11,12]. Vertebral fractures are the most common fractures in osteoporotic patients. In the present work, we studied the effectiveness of various NSAIDs in patients with vertebral fractures.

**EXPERIMENTAL**

**Methods**

The study was performed in the Department of Orthopaedics, Jining No.2 People’s Hospital, Jining City, from January 2014 to December 2015. Patient data were collected from hospital records, with permission.

**Study protocols**

The study was carried out in accordance with the guidelines of the Declaration of Helsinki of 1975 [13], and received the prior approval of the institutional Review Board of Jining No. 2 People’s Hospital, Jining City (approval no. JPH/ortho/2014/12-e02; 04/12/14). Prior consent was given by each patient and the hospital administration for sharing of (anonymous) medical records. Patients were divided into six groups depending on the type of NSAID administered (Table 1).

A total of 78 patients (17 males and 61 females) with an average age of 69.5 years were included. The major inclusion criterion was an osteoporotic vertebral fracture between T7 and L3. The exclusion criteria included fractures above T7 and below L3; and other bone disorders such as disc herniation, spondylolisthesis, infection, or tumour. Pain intensity was assessed by a 10-point visual analogue scale (VAS). The BMD data, any delay in reunion, and any other matter of significance, were discussed with the treating doctors and cross-checked with independent doctors.

Patients were given different NSAIDs. The non-selective COX inhibitors were naproxen, indomethacin, and flurbiprofen; the selective COX 2 inhibitors were piroxicam, celecoxib, and rofecoxib. Patients were blinded to their drugs until study completion at 12 weeks.

From 6 weeks onward, the effects of NSAIDs on bone health were evaluated on the basis of any need for surgery, bone non-union, and any delay in reunion. All parameters were evaluated on a BMD basis (derived using dual energy X-ray absorptiometry [DXA]); we calculated T-scores for all patients. Routine check-ups covered other qualitative factors; these were evaluated by all three independent experts in terms of final outcomes.

**Clinical analgesic performance: Pain score study**

VAS pain scores in 78 subjects were recorded weekly. Pain was assessed prior to treatment (baseline), and weekly up to 6 weeks after treatment, using a 10-cm VAS (ranging from 0 [no pain] to 10 [worst pain imaginable]). All patients were taking NSAIDs regularly.

### Table 1: Study groups and treatment applied

<table>
<thead>
<tr>
<th>Group code</th>
<th>NSAID</th>
<th>Dose (p.o.)</th>
<th>Number of patients (male/female)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>Naproxen</td>
<td>250 mg qid</td>
<td>13 (2/11)</td>
</tr>
<tr>
<td>I</td>
<td>Indomethacin</td>
<td>25 mg qid</td>
<td>14 (3/13)</td>
</tr>
<tr>
<td>F</td>
<td>Flurbiprofen</td>
<td>50 mg tid/ qid</td>
<td>11 (1/10)</td>
</tr>
<tr>
<td>P</td>
<td>Piroxicam</td>
<td>20 mg OD for 4 weeks</td>
<td>13 (3/10)</td>
</tr>
<tr>
<td>C</td>
<td>Celecoxib</td>
<td>200 mg bd</td>
<td>12 (3/9)</td>
</tr>
<tr>
<td>R</td>
<td>Rofecoxib</td>
<td>25 mg od</td>
<td>15 (5/10)</td>
</tr>
</tbody>
</table>

NSAID = non-steroidal anti-inflammatory drug
Statistical analysis

All data are expressed as mean ± standard deviation. Statistical analysis featured two-way analysis of variance (ANOVA) performed using SPSS for Windows software (SPSS Inc, Chicago, IL, USA). \( P < 0.05 \) was considered to reflect significance.

RESULTS

VAS pain scores were recorded weekly. BMDs were derived in weeks 1 and 12. Any delay in reunion, non-union, or surgical requirement was assessed by three independent experts.

Table 2 compares the effectiveness of various NSAIDs in patients with vertebral fractures. We observed that some NSAIDs interfered with bone healing. No male required bone surgery, but two females taking naproxen, one taking flurbiprofen, and one taking celecoxib, required surgery (Table 2).

In terms of bone healing, non-union and delay in reunion were more common in those taking naproxen, indomethacin, or flurbiprofen than in those taking piroxicam, celecoxib, or rofecoxib (Figure 1 and Figure 2).

Table 2: Effect of NSAIDs on various parameters of bone health

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Need for surgery (M/F)</th>
<th>Non-union (M/F)</th>
<th>Delay in reunion (M/F)</th>
<th>T-score (week 1)(M/F)</th>
<th>T-score (week 12)(M/F)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naproxen</td>
<td>2 (0/2)</td>
<td>6 (1/5)</td>
<td>7 (2/5)</td>
<td>-2.67</td>
<td>-2.70</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>0</td>
<td>3 (1/2)</td>
<td>4 (0/4)</td>
<td>-2.60</td>
<td>-2.64</td>
</tr>
<tr>
<td>Flurbiprofen</td>
<td>1 (0/1)</td>
<td>5 (1/4)</td>
<td>4 (1/3)</td>
<td>-2.59</td>
<td>-2.70</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>0</td>
<td>5 (1/4)</td>
<td>3 (1/2)</td>
<td>-2.70</td>
<td>-2.68</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>1 (0/1)</td>
<td>2 (0,2)</td>
<td>1 (0/1)</td>
<td>-2.66</td>
<td>-2.45</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>0</td>
<td>1 (0,1)</td>
<td>2 (0/2)</td>
<td>-2.57</td>
<td>-2.50</td>
</tr>
</tbody>
</table>

NSAID = non-steroidal anti-inflammatory drug

T-scores were used to assess bone health. Bone healing was evaluated using DXA. The T-scores were all lower than -2.5, indicating that all patients were osteoporotic. The T-scores improved after 12 weeks only in those taking rofecoxib, celecoxib, and piroxicam (Table 2).

VAS pain scores were also lower in those taking rofecoxib, celecoxib, and piroxicam (Table 3).

DISCUSSION

Patients were asked to give pain scores (from 0 [no pain] to 10 [worst pain imaginable]). VAS scores have been studied in postoperative patients suffering from strong pain (scores of ≥ 9) [14]. The VAS is quite reliable, showing high test and retest repeatability; it is also very sensitive and can measure multiple dimensions of pain.

The T-score is a parameter derived from BMD; the BMD of a subject is compared to that of a healthy 30-year-old: ideally, the score should be zero. According to National Institutes of Health (NIH) guidelines, a score from 1 to -1 indicates a normal BMD; as core from -1 to -2.5indicates low bone mass and a score of -2.5 or lower indicates severe osteoporosis with bone fractures [15].
Table 3: Clinical analgesia experienced by patients with vertebral fractures receiving different NSAIDs

<table>
<thead>
<tr>
<th>Time (weeks)</th>
<th>Naproxen</th>
<th>Indomethacin</th>
<th>Flurbiprofen</th>
<th>Piroxicam</th>
<th>Celecoxib</th>
<th>Rofecoxib</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>9.90±0.02</td>
<td>9.99±0.20</td>
<td>8.87±0.01</td>
<td>9.90±0.10</td>
<td>9.90±0.01</td>
<td>9.80±0.01</td>
</tr>
<tr>
<td>1</td>
<td>8.01±0.20</td>
<td>9.01±0.07</td>
<td>7.69±1.01</td>
<td>8.01±0.10</td>
<td>8.98±0.01</td>
<td>8.60±0.40</td>
</tr>
<tr>
<td>2</td>
<td>7.50±0.12</td>
<td>8.80±0.40</td>
<td>5.86±0.22</td>
<td>7.87±0.04</td>
<td>6.90±0.32</td>
<td>7.06±0.54</td>
</tr>
<tr>
<td>4</td>
<td>7.00±0.25</td>
<td>7.96±0.24</td>
<td>4.96±1.20</td>
<td>7.01±0.41</td>
<td>6.02±0.04</td>
<td>6.06±0.60</td>
</tr>
<tr>
<td>6</td>
<td>6.00±0.10</td>
<td>7.20±0.25</td>
<td>6.01±0.02</td>
<td>6.01±1.04</td>
<td>5.69±0.25</td>
<td>4.26±1.42</td>
</tr>
<tr>
<td>8</td>
<td>6.75±0.15</td>
<td>6.50±1.15</td>
<td>5.22±1.20</td>
<td>4.22±1.01</td>
<td>4.90±1.02</td>
<td>3.02±1.22</td>
</tr>
<tr>
<td>12</td>
<td>5.50±1.02</td>
<td>5.00±1.20</td>
<td>4.58±1.50</td>
<td>4.20±1.02</td>
<td>4.06±1.02</td>
<td>2.20±1.62</td>
</tr>
</tbody>
</table>

All study data were derived from racially homogenous patients.

One large study concluded that patients treated with celecoxib (200 to 800 mg/day) enjoyed better outcomes than those treated with nonselective NSAIDs such as diclofenac, ibuprofen, naproxen, ketoprofen, and loxoprofen [16]. We also found that the selective COX2 inhibitors afforded the best analgesia [17].

We found that the various NSAIDs affected bone health differently. Although COX2 inhibitors are safer, their possible effects on delay in bone union and non-union required study. Various reports on drug dose-dependent effects on bone health have appeared, although in the present study, we did not administer different doses of NSAIDs [18-20]. The COX-selectivity of an NSAID governs the efficacy of analgesia as well as bone health.

Limitations of the study

Response to drugs may vary with age; we did not consider the age effect. Moreover, pain perception may differ slightly from subject to subject. A study including a larger number of subjects with similar kinds of fracture would yield more accurate results.

CONCLUSION

NSAIDs that selectively inhibit COX2 enzyme effectively alleviate pain but their effects on bone health required analysis. In general, prolonged use of non-selective inhibitors is no safer than selective inhibitors for patients with vertebral fractures. However, further dose and time studies are required. We found that celecoxib was the best of the six NSAIDs, both in terms of analgesia and bone health.

DECLARATIONS

Acknowledgement

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Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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