Gabapentin versus Naproxen in the Management of Failed Back Surgery Syndrome; A Randomized Controlled Trial

M. B. KHOSRAVI, S. AZEMATI and M. A. SAHMEDDINI

**Abstract** : Gabapentin is an analogue of the gamma amino butyric acid (GABA), which regulates the conductance of calcium channels. In this study, we compared the efficacy of gabapentin the one of naproxen in the treatment of failed lumbar discectomy syndrome. In this controlled trial, patients who had had elective lumbar discectomy or spinal fusion surgery more than one year ago, and complaining about leg and back pain in spite of different medical therapy were randomly assigned to receive naproxen (control group) or gabapentin. Gabapentin was started at a daily dose of 300 mg. This dose was increased by 300 mg at the end of each week up to a maximum dose of 1800 mg. Naproxen, which was administered at an initial daily dose of 250 mg, was increased similarly to the maximum 1500 mg. Patients were then followed up for the next 6 consecutive months. Back and leg pains were compared between the two groups at 9 consecutive time points, namely 0, 2, 4, 6, 8, 12, 16, 20 and 32 weeks after starting the treatment. The Visual Analog Scale (VAS) score of the back pain was significantly reduced when a 600 mg daily dose of gabapentin was reached ($P < 0.001$). At a dose of 1800 mg, the decrease in back pain amounted 20.5%. Naproxen-treated patients did not show significant improvement in back pain. Leg pain as similarly assessed by a VAS significantly decreased when a 1200 mg dose of gabapentin was attained ($P < 0.008$). At 1800 mg, the reduction in VAS was 39.2%. Naproxen-treated patients had a 7.7% pain reduction at 6th week, when using the maximum daily dose of 1500 mg ($P < 0.04$), but the pain increased thereafter. We conclude that Gabapentin, at a maximum daily dose of 1800 mg, is significantly more efficent than naproxen at treating persistent pain after spinal surgeries.

**Key words** : gabapentin ; naproxen ; failed back surgery syndrome.

**INTRODUCTION**

Failed back surgery syndrome or “failed lumbar discectomy syndrome” is the continuation of pain after spinal surgery. It is characterized by chronic pain, which is often disabling. Its incidence is estimated to range between 10 and 40% of lumbosacral spinal surgeries (1, 2). One of the most common causes of this syndrome is epidural fibrosis (20 to 36%) (3). The success rate of a new surgery in patients with fibrosis is 15%, while such success rate reaches 31% when no fibrosis is present (4). Fifteen to twenty percent of patients submitted to supplementary surgery complain of symptoms worsening (5).

Pain after spinal surgery has two components: leg and back pain. Neuropathic leg pain is described as a burning, tingling, or electrical type pain. It is usually severe, slow to resolve, and extremely distressing. Like other forms of chronic pain, it may have a devastating effect on the patient’s psychological health, social function, and other aspects of health-related quality of life (6).

Gabapentin is an analogue of the gamma amino butyric acid (GABA). This endogenous neurotransmitter regulates the conductance of voltage dependent Ca$^{2+}$ channels (VDCCs). Pre-synaptically, it reduces excitatory neurotransmitter release in the dorsal horn (7). Gabapentin has initially been used as an anticonvulsant medication, and was first approved for that use in 1994. Since then, it has been reported to be efficient at treating neuropathic pain (8, 9), diabetic neuropathy (10, 11), postherpetic neuralgia (12, 13), multiple sclerosis (14) and reflex sympathetic dystrophy (15). Gabapentin has been used for reducing the postoperative pain in spinal surgery (16), vaginal hysterectomy (17), abdominal hysterectomy (18), and laparoscopic cholecystectomy (19, 20).
In this study, we aimed at comparing the efficacy of gabapentin with the one of naproxen at releasing persistent leg and back pain after spinal surgery during a 2-year period.

METHODS

The protocol of this randomized controlled trial was approved by the Ethics Committee of Shiraz University of Medical Sciences, Shiraz, Iran. Patients admitted to the pain clinic of the University teaching hospital were recruited. All of them had undergone elective lumbar discectomy or spinal fusion surgery more than one year before, and were complaining about chronic leg and back pain. Upon admission, they already had received several treatments such as non-steroidal anti-inflammatory drugs (NSAIDs) and/or antidepressants.

Patients were visited by a single anesthesiologist. After recording of complete history and performing physical examination, patients were informed about the aims and protocol of the study. A written informed consent for inclusion into the study was then obtained. The exclusion criteria for inclusion were pregnancy, lactation, impaired renal function, clinically significant hepatic, respiratory, hematologic, or cardiovascular illness, history of allergic reaction to the two study drugs, significant psychiatric disorder, opium addiction, and previous treatment with gabapentin or naproxen.

The study started with a baseline period of one week, during which patients were asked to discontinue any analgesic medication or antidepressant. In case of a >4 pain score, they were allowed having acetaminophen and codeine (300 mg/20 mg), up to five tablets per day. After one week, a baseline visual analogue scale (VAS) score ranging from no pain to the worst imaginable pain (0-10 cm) was recorded (time 0). Using a computer-generated randomization list, patients were then randomized into two groups. The first group was scheduled to receive gabapentin (G group, 20 patients), and the second one to receive naproxen (N group, 20 patients).

Gabapentin was started at a daily dose of 300 mg. This dose was increased at the end of each week by 300 mg up to a maximum dose of 1800 mg that was achieved on the 6th week. This dose was continued for 6 consecutive months. Naproxen was started at a daily dose of 250 mg, with incremental regimens of 250 mg at the end of each week up to a maximum daily dose of 1500 mg. This dose was also achieved at the end of the 6th week, and continued for the next 6 months. Patients were asked to come back to the pain clinic for a VAS assessment every two weeks, until the 8th week. Thereafter, patients were evaluated every 4 weeks. A final assessment was performed after 6 months of using 1800 mg gabapentin or 1500 mg naproxen, that is at the 32nd week. The amount of acetaminophen and codein used as a rescue medication was compared between groups at the same time points.

STATISTICAL ANALYSIS

Statistical analysis was performed using the SPSS software (version 15, IBM). Repeated measurement design using Fisher’s least significant difference was used to compare back and leg pain VAS between the two groups at the different time points. Age, time from spinal surgery, and duration of pain were compared using two sample t-tests. A decrease in pain score of more than 50% was defined as a positive response to treatment. The amount of rescue medication used was compared using independent t-tests. A P value < 0.05 was considered statistically significant.

RESULTS

In total, 44 patients were referred to our pain clinic. One of them was pregnant, one had a psychiatric disorder, and two had hepatic and renal diseases. They were excluded from the study. The remaining 40 patients had grade I or II ASA physical status (Fig. 1). The patients in the two groups were similar with regard to age (47 ± 8 and 49 ± 8 years in gabapentin and naproxen group, respectively), weight (68 ± 3 and 67 ± 4 kg), male to female ratio (9/11 and 8/12), time elapsed since spinal surgery (29 ± 10 and 29 ± 9 months), and duration of pain (16 ± 9 and 17 ± 9 months) (Table 1).

The baseline VAS score for leg pain, which was determined after one week of discontinuing all analgesic medications, was comparable in the two groups (5.6 ± 1.7 in the gabapentin group, and 5.8 ± 1.5 in the naproxen group, P = 0.32). The corresponding baseline VAS for back pain were 6.8 ± 1.4 and 6.5 ± 1.3 in the gabapentin and naproxen group, respectively (P = 0.74).

Back pain showed a significant response to gabapentin at a daily dose of 600 mg (P < 0.001). The naproxen-treated patients did not show any response to the drug for back pain. After 6 weeks, when the daily dose of gabapentin was 1800 mg, back pain VAS reached a 20.5% decrease as compared to
**Table 1**

Characteristics of patients in the gabapentin and naproxen group

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Naproxen Group (n:20)</th>
<th>Gabapentin Group (n:20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>49±8.3</td>
<td>47±8.3</td>
<td>0.45</td>
</tr>
<tr>
<td>Time from spinal surgery (month)</td>
<td>29±9.4</td>
<td>29±10</td>
<td>0.99</td>
</tr>
<tr>
<td>Duration of pain (month)</td>
<td>17±8.8</td>
<td>16±9.4</td>
<td>0.46</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>8/12</td>
<td>9/11</td>
<td>0.74</td>
</tr>
<tr>
<td>Baseline VAS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leg</td>
<td>5.8±1.5</td>
<td>5.6±1.7</td>
<td>0.32</td>
</tr>
<tr>
<td>Back</td>
<td>6.55±1.3</td>
<td>6.8±1.4</td>
<td>0.74</td>
</tr>
</tbody>
</table>

Data presented as mean (±SD)

VAS: Visual Analog Scale

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Fig. 1. — CONSORT Flow Diagram

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baseline (from 6.8 to 5.4). At the end of the study, this reduction in VAS amounted 27.2% (from 6.8 to 4.9, P < 0.001) (Fig. 2). In the naproxen group, at a daily dose of 1500 mg, back pain increased by 9.7% (from 6.55 to 7.15), while, at the end of the study (6 months follow up), this increment reached 22% increment (from 6.55 to 8, Fig. 3).

Leg pain VAS scores in the gabapentin group significantly decreased after 4 treatment weeks, at a daily dose of 1200 mg (P < 0.008). After 6 weeks, when the dose of gabapentin was 1800 mg, the VAS decrease reached 39.2% as compared to baseline (from 5.6 to 3.4). At the end of the study, the leg pain VAS score decreased to 1.55 (73.3% decrease) (P < 0.001, Fig. 3). In the naproxen group, increasing the dose of naproxen to a maximum of 1500 mg caused a 7.7% decrease in leg pain VAS as compared to baseline (from 5.8 to 5.3, P < 0.04). This effect was also observed at the 8th and 12th treatment weeks (P < 0.001 and < 0.005, respectively). Thereafter, the VAS score increased and reached 6.35 at the end of the study.

At the end of the study period, a 50% reduction in pain score from baseline was considered indicative of a positive response to treatment. In the gabapentin group, 95% and 15% of patients were responders with regard to leg and back pain, respectively. Contrarily, none of the naproxen-treated patients could be considered as responders.

Regarding acetaminophen and codeine rescue consumption, it was significantly lower in the gabapentin group (P < 0.05) (Fig. 4).

**DISCUSSION**

We compared the effect of gabapentin (up to 1800 mg a day) and naproxen (up to 1500 mg a day) on the two components of failed laminectomy syndrome, leg and back pain. Our findings indicate that gabapentin, at a daily dose of 1800 mg is more efficient than naproxen 1500 mg at reducing leg and back pain.

Failed back surgery syndrome or failed laminectomy syndrome concerns 10 to 40% of lumbo-sacral spine surgery patients (1, 2). In that case, leg pain is a neuropathic, radicular pain. It is usually caused by a compression or injury of the nerve roots. Back pain might be of a mixed nociceptive and neuropathic nature (21). Eldabe and colleagues reported moderate low back pain (VAS = 4.98 ± 2.4) but severe leg pain (VAS = 7.47 ± 1.35) in failed back surgery syndrome patients (22). This contrasts with our findings where back pain was more intense than
One of the most frequent causes of failed back surgery syndrome is epidural fibrosis (20 to 36%) (3). Other causes such as wrong level of surgery, inadequate surgical techniques, vertebral instability, recurrent disc herniation, improper patient selection, pseudomeningocele, arachnoiditis, and infection (5, 23) are possible. Reoperation for recurrent disc herniation has results that are comparable.

Fig. 3. — Visual analog scale (VAS) score of leg pain at 8 different time points in the two groups (Values are mean ± SD)

Fig. 4. — Number of acetaminophen codeine used as rescue drug at 8 different times in two groups (values are mean ± SD)
to the first intervention, whereas repeated surgery for fibrosis has a 30-35% success rate only. In that case, 15 to 20% of patients complain of symptoms worsening (5). It is believed that nerve root mobility can be restricted by scar tissue, causing recurrent radicular pain after lumbar sacral surgery (24), but this is debated. Other authors assert that there is no difference between symptomatic and asymptomatic patients in terms of fibrosis presence and extent, as evidence by contrast-enhanced magnetic resonance imaging MRI (25) or computed tomography (26).

Considering the poor surgical success rate (less than 10% when 4 or more spinal surgeries are performed at the same level), there is a need for alternative therapeutic modalities. One of these modalities is pharmacological treatment.

Gabapentin is an anticonvulsant drug that is currently being prescribed for patients suffering from chronic pain such as diabetic neuropathy (10,11) and post-herpetic neuralgia (12, 13). It is also used in neuropathic pain (8, 9), and reflex sympathetic dystrophy (15), as well as for pain after vaginal hysterectomy (17), abdominal hysterectomy (18,20), and laparoscopic cholecystectomy (19). Gabapentin neither interact with GABA receptors nor undergoes GABA metabolism. It binds to the α2 GABA-subunit, which regulates the conductance of voltage dependent Ca\(^{2+}\) channels (VDCCs) (7). It has been shown that GBP pre-synaptically reduces excitatory neurotransmitter release in the dorsal horn via VDCC inhibition (27).

There are some reports of using daily doses of gabapentin up to 3600 mg for chronic radiculopathy (28), with significant results. In other reports, gabapentin has been used up to 2400 mg a day in neuropathic pain syndrome (9). Gabapentin could reduce pain by 21% as compared 14% in the placebo group. In our study, the maximum dose of gabapentin was 1800 mg. It induced a 73.3% reduction of leg pain, and a 21% decrease in back pain. The component of leg pain is a neuropathic type. This may explain why gabapentin was more efficient at reducing leg pain than back pain. In our study, the maximum pain relief was attained at a dose of 1800 mg a day. Progressively increasing the drug posology was associated with a progressive decrease in leg and back pain. When considering a 50% pain decrease as indicative of treatment efficiency, we can conclude that gabapentin has been efficient at relieving leg pain in patients with failed back surgery syndrome, but less effective at relieving low back pain.

Burgest and colleagues recommended using NSAIDs to relieve pain associated with various failed back surgery syndrome components, such as discogenic pain, facet arthropathy, and arthritis (29). However, we found that naproxen was not efficient at relieving back and leg pain. In a systematic review published in 2011 by Kuijpers and co-workers, four clinical trials in which NSAIDs had been used for back pain were analyzed. The researchers reported that NSAIDs could be efficient in non-specific chronic low back pain. However, they were less efficient when used during a long period of time (30). We also found that naproxen was not efficient at relieving low back pain in patients with failed back surgery, either on a short or long term basis. This finding is consistent with the recommendation by Van Buyten who does not recommend NSAIDs in the treatment algorithm of failed back surgery. For this author, the first line treatment in that case can be either anticonvulsants or antidepressant, accompanied by transcutaneous electrical nerve stimulation (TENS) (31). In our study, back pain increased in the naproxen group at a maximum dose of 1500 mg. Leg pain had a shorter response period (6 weeks-3 months), after which it increased to higher values than the baseline value.

Few side effects have been reported after using gabapentin. They include dizziness, confusion, nausea, ataxia, and somnolence (16). Such side effects did not occur in our study.

We did not use and evaluate the concomitant use of naproxen and GBP, which can be considered as a limitation of our study. Use of such a combination can be considered in future studies.

Conclusion

Gabapentin at a daily dose of 1800 mg is significantly more efficient than 1500 mg of naproxen at treating persistent pain after spinal surgeries. The therapeutic effect of gabapentin more pronounced for leg pain than for back pain.

References

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