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Efficacy of tapentadol prolonged release for pre- and post-operative low back pain: a prospective observational study

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Abstract. – OBJECTIVE: Low back pain (LBP) is a highly prevalent chronic pain condition with a neuropathic component of pain that limits the benefits of classical opioids. Tapentadol is an innovative drug for the treatment of chronic severe pain, with a dual mechanism of action combining μ-opioid receptors agonism and noradrenaline re-uptake inhibition (NRI). Its efficacy is equal to that of strong opioids, with a better tolerability profile and a consequently lower risk of treatment discontinuation. The aim of this study was to evaluate the analgesic efficacy and tolerability of tapentadol prolonged release (PR) *vs.* other analgesics in patients with moderate-to-severe neuropathic low back pain, before and after back surgery.

PATIENTS AND METHODS: The primary endpoints of the study were the rate of response to treatment, measured as ≥30% reduction in pain intensity on the Numeric Rating Scale (NRS), and tapentadol PR efficacy for pain relief. The secondary endpoints were the improvements of the neuropathic component of pain and of sleep quality.

RESULTS: A total of 40 patients were enrolled in the study, receiving either tapentadol PR (n=21, 52.5%) or other analgesics (n=19, 47.5%), both before and after surgery. The rate of response to treatment was statistically in favor of tapentadol PR ($p<0.01$). The reduction in pain intensity was statistically significant in the group treated with tapentadol PR, both before and after surgery ($p<0.01$), with a complete resolution of pain 90 days after surgery. The quality of sleep after surgery improved more in patients treated with tapentadol PR than in the comparator group ($p<0.01$), with 100% of the patients reporting a "good" sleep quality 2 months after surgery.

CONCLUSIONS: Tapentadol PR was well tolerated by all patients, and its efficacy for pain relief was also confirmed in our small group of "real-life" patients with chronic, severe low back pain. Overall, the tolerability of this treatment may help to improve patients' quality of life, which is frequently compromised because of pain and its related comorbidities.

Key Words:
Tapentadol, Low back pain, Neuropathic pain.

Introduction

Low back pain (LBP) is a highly prevalent chronic pain condition[1,2], and a leading cause of disability worldwide, frequently associated with several comorbid conditions such as depression, panic and anxiety disorders, and sleep disturbances[3].

Persistent back pain results in central sensitization, when plastic alterations occur within the involved structures, determining an imbalance between ascending and descending pathways, massive spinal release of glutamates, and neuro-modulating peptides that ultimately modify the spino-thalamic neurons and interneurons with the transition to chronic pain and a neuropathic component in the majority of cases (>90%)[4]. Thus, the benefits of classical opioids for LBP are limited, given the low efficacy on the neuropathic component of pain, and on the central sensitization and poorer long-term outcomes[5].

Tapentadol is an innovative drug for the treatment of chronic severe pain, with a dual mechanism of action combining μ-opioid receptor agonism (MOR) and noradrenaline re-uptake inhibition (NRI)[6]; these two mechanisms contribute in a complementary and synergistic way to the broad spectrum of analgesic efficacy of tapentadol on nociceptive and neuropathic pain. The efficacy of tapentadol prolonged release (PR)

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is equal or superior to that of strong opioids, because of a partly shared mechanism. However, a better tolerability profile of tapentadol results in a significantly lower risk of treatment discontinuation and, thus, an improved quality of life[7]. Specifically, the MOR component of tapentadol activity acts against nociceptive pain, whereas the NRI component of tapentadol is effective against neuropathic pain. The reduced μ-load of tapentadol, which is ≤40% relative to classical MOR agonists, determines a lower opioid activity for a comparable level of analgesia, with fewer gastrointestinal, respiratory, and endocrinological adverse events[7]. Furthermore, tapentadol shows minimal serotoninergic activity, with potential safety advantages over the long term in terms of risk of emesis[8].

In addition, tapentadol shows a higher safety profile in relation to the lower risk of drug interactions: noteworthy, tapentadol shows reduced binding to plasma proteins, no impact on CYP450 enzymes, no active metabolites, and its main metabolic pathway is glucuronidation. For these reasons, tapentadol may represent a valuable first choice option in the treatment of chronic, neuropathic, and mixed pain[9]. However, few data are available regarding the safety and efficacy of tapentadol in high-risk patients, who are rarely enrolled in clinical trials.

The aim of this study was to evaluate the analgesic efficacy and tolerability of tapentadol PR monotherapy *vs.* other analgesic therapies (paracetamol and non-steroidal anti-inflammatory drugs [NSAIDs]) in patients with moderate-to-severe neuropathic LBP, before and after back surgery.

Patients and Methods

Patients of either gender, older than 18 years old, suffering from moderate-to-severe chronic low back pain, and/or with pain intensity ≥4 on the Numeric Rating Scale (NRS), were included in this observational, prospective study. The presence of a major systemic illness was an exclusion criterion.

The study visits were scheduled as follows: the initial enrollment visit (V0) occurred 3 months before actual date of surgery; visit 1 (V1) occurred 2 months before surgery; visit 2 (V2) occurred 1 month before surgery; visits 3 and 4 (V3 and V4) were performed 7 days and 21 days after surgery, respectively; visits 5 and 6 (V5 and V6) were performed 2 months and 3 months after surgery, respectively. The last follow-up visit (V7) occurred 6 months after surgery. During the pre-operative period, analgesic therapy was carried out either with tapentadol or with paracetamol/NSAIDs. Tapentadol PR (Grunenthal, Aachen, Germany) was started at a dose of 100 mg daily and uptitrated, if necessary, to a maximum dose of 150 mg twice daily (Table I). In the post-operative period and during follow-up for 6 months, patients were allowed to use as painkillers either tapentadol PR or paracetamol/NSAIDs.

The primary endpoints of the study were the analgesic efficacy of tapentadol PR assessed as pain relief on the NRS, and the proportion of patients responding to therapy. In the pre-operative phase, the responders were defined as patients who experienced a reduction in pain intensity ≥30% on the NRS scale at V1 and V2, compared

Table I. Daily tapentadol dosage in mg/die before and after surgery.

Visit	Daily dosage										Total		
	0 mg		50 mg		100 mg		200 mg		300 mg				
	n	%	n	%	n	%	n	%	n	%	n	Mean	SD
V0	0	0.0	0	0.0	18	85.7	3	14.3	0	0.0	21	114.3	35.9
V1	0	0.0	0	0.0	0	0.0	17	81.0	4	19.0	21	219.0	40.2
V2	0	0.0	0	0.0	2	9.5	11	52.4	8	38.1	21	228.6	64.4
V3	0	0.0	0	0.0	12	57.1	9	42.9	0	0.0	21	142.9	50.7
V4	0	0.0	0	0.0	20	95.2	1	4.8	0	0.0	21	104.8	21.8
V5	18	85.7	1	4.8	2	9.5	0	0.0	0	0.0	21	11.9	31.2
V6	20	95.2	1	4.8	0	0.0	0	0.0	0	0.0	21	2.4	10.9
V7	21	100.0	0	0.0	0	0.0	0	0.0	0	0.0	21	0.0	0.0

with V0. Similarly, in the post-operative phase responders were patients with a ≥30% reduction in NRS pain intensity compared with V3 (7 days after surgery). The secondary endpoints were the results of the DN4 questionnaire assessing the neuropathic component of pain, and sleep quality, which was graded on a scale from "almost poor" to "poor", "almost good", and "good". Tapentadol PR tolerability was assessed by measuring the incidence of adverse events.

Statistical Analysis

Statistical analysis was performed with the Statistical Analysis System (SAS) 9.4 statistical software (SAS Institute, Cary, NC, USA). Data were analyzed by descriptive statistics; statistical comparisons were performed by the Student's *t*-test, the ANOVA test or the χ^2-test, as appropriate. A *p*-value of <0.05 was considered statistically significant.

Results

In total, 40 patients were enrolled in the study, of which 24 were males (60%), mean age 56 years old, with an age range of 20-79 years old. The most frequent diagnosis responsible for LBP were herniated lumbar disc (n=25), stenosis of the spinal canal (n=7), and post-laminectomy syndrome (n=2).

Patients received either tapentadol PR (n=21, 52.5%) or other analgesics (n=19, 47.5%), both before and after surgery. Baseline characteristics of patients in both groups, ASA score, type and duration of anesthesia, as well as the duration of surgery and overall duration of the peri-operative period, did not differ significantly between the two groups.

The surgical procedure was mainly herniotomy (n=31), with few different operations such as arthrodesis (n=1), re-opening of a previous laminectomy (n=1), and hip arthroplasty (n=1). No adverse events were reported in both groups during the follow-up.

At V1, the responders to tapentadol PR were 42.9%, which is at the limit of statistical significance (p=0.0533, χ^2-test with Yates correction). At V2, there were 95,2% responders to tapentadol PR, with a statistically significant difference compared to the rate of responders to other analgesic (42.1%, p=0.0009; at the χ^2-test with Yates correction). This statistical difference persisted in the post-operative period up to V4 (p<0.01).

The mean NRS scores at V0 did not differ between the two groups: pain intensity at V0 was similar for all patients, with a mean NRS of 9.8 in the group treated with tapentadol and a mean NRS of 9.6 in the comparison group (p=0.4231). The reduction in pain intensity was statistically significant in the group treated with tapentadol PR both before and after surgery (p<0.01) (Figures 1A and B). Furthermore, the reduction of pain intensity was more pronounced and statistically different between tapentadol PR and the control group (p<0.0001) (Figure 1B): from V4 to V7, mean NRS was 2.7, 0.2, 0.0, and 0.0, respectively, in the tapentadol group, *vs.* a mean NRS of 4.3, 3.1, 2.5, and 1.8, respectively, in patients treated with paracetamol/NSAIDs. Thus, tapentadol PR was significantly more effective than comparators, with a complete resolution of pain 90 days after surgery.

According to the scores of the DN4 questionnaire, all patients reported neuropathic pain at V0 and at V1. At V2, the complete resolution of neuropathic pain was reported by five patients (23.8%) treated with tapentadol PR, and none of the patients treated by other analgesics (p=0.0726, NS). At V3, 85.7% of patients treated with tapentadol PR reported neuropathic pain, *vs.* all patients (100.0%) in the control group (p=0.2662). After surgery, neuropathic pain improved more in patients treated with tapentadol PR compared with patients treated with paracetamol/NSAIDs (Figure 2). Moreover, at V4, neuropathic pain persisted in only 14.3% of patients treated with tapentadol PR *vs.* 100.0% patients in the control group (p<0.01). The complete resolution of neuropathic pain was reported by all patients treated with tapentadol PR from V5 onwards, whereas 84.2%, 63.2%, and 15.8% of patients treated with paracetamol/NSAIDs reported persistent neuropathic pain at V5, V6, and V7, respectively (p=0.0001 for V5 and V6 and p=0.1963 for V7).

The quality of sleep at V0 was "poor" in 38 patients, and "almost poor" in two patients. During the treatment period, no statistically significant differences were found in changes in the sleep quality between the two treatment groups, either at V1 or at V2 (p=0.0754). However, the McNemar test revealed a statistically significant improvement of sleep quality at both V1 and V2 compared with V0, within both groups. After surgery, the sleep quality improved more in patients treated with tapentadol PR than in the comparator group (all p<0.01), with 90.5% of patients in the tapentadol PR group reporting "almost good" sleep quality already at visit 3 (7 days after surgery), and 100% with a "good" sleep quality from V5 onwards. Conversely, patients treated with

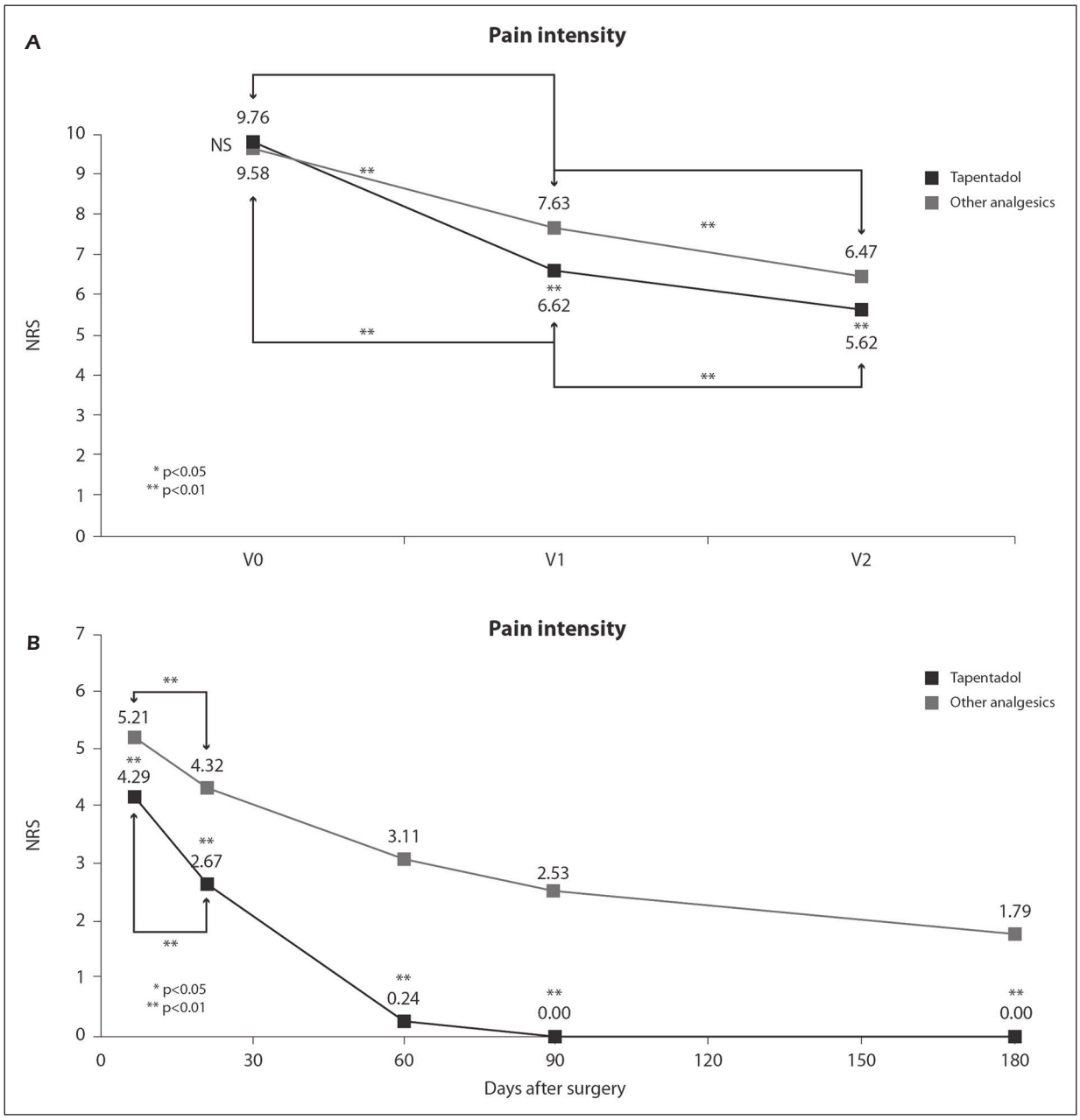

Figure 1. Pain intensity measured with NRS before **(A)** and after **(B)** surgery.

paracetamol/NSAIDs, reported an "almost poor" sleep quality in 68.4% of cases at V3, with only a slight improvement of sleep quality during follow-up: at V7 only six patients (31.6%) rated their sleep quality as "good" (p<0.0001).

Discussion

Chronic LBP is characterized by both nociceptive and neuropathic pain[3] with the latter connected to injuries of the lower limbs nerve roots and pathologically damaged lumbar discs.

Tapentadol PR provides a strong analgesic effect derived from its synergic MOR and NRI action[10-12], which is also reflected in a limited incidence of adverse effects[13] and in a significant improvement in quality of life[14], placing tapentadol PR as a particularly suitable option in patients with chronic LBP, especially for the treatment of its neuropathic component, given the NRI activity of the molecule. Several studies[15-23] have

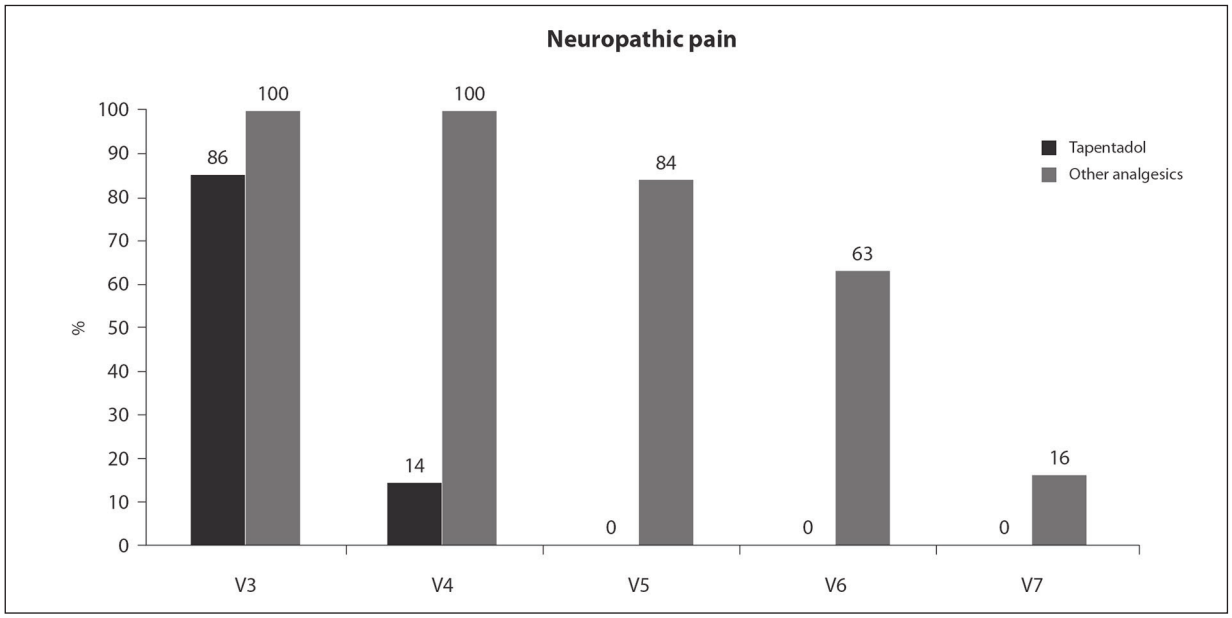

Figure 2. Frequency of neuropathic pain after surgery.

investigated this issue, showing that tapentadol PR provides comparable or even superior analgesia to strong opioids in patients with severe, chronic LBP, with a better tolerability.

Moreover, the impact of tapentadol PR on the quality of life and functional recovery has been tested over oxycodone controlled release (CR) in pooled analyses of randomized trials of non-oncological pain, with consistent results for tapentadol PR in improving all dimensions of quality of life (for instance, in terms of sleep quality), with a significant advantage over oxycodone CR.

The results of our study show that tapentadol PR was significantly more effective than the comparators for pain relief during both the pre-operative and the post-operative period. Of note, only few studies have compared tapentadol PR to paracetamol and NSAIDs, and thus our experience may open the way for further investigations of this type. Noteworthy, a complete resolution of pain was achieved in the tapentadol PR group 90 days after surgery, compared with a low but persistent LBP up to 6 months after surgery in patients treated with conventional analgesics. Furthermore, a similar benefit was noted for tapentadol PR on neuropathic pain, as assessed with the DN4 questionnaire: in this case, complete resolution of neuropathic pain occurred as early as 2 months after surgery.

Although sleep quality between the two treatment groups did not differ significantly, the improvements in the sleep quality compared with baseline were noted both in the tapentadol PR and in the comparator group, suggesting that the use of tapentadol PR may contribute to improve the overall patients' quality of life, as already reported elsewhere[7,14].

Conclusions

The results of our study confirm the efficacy of tapentadol PR for pain relief in a population of patients with chronic severe LBP. Pain reduction is effective from the beginning of treatment, with complete resolution of pain occurring 90 days after surgery. Noteworthy, the reduction in pain intensity correlates with the reduction in the neuropathic component of pain. Moreover, tapentadol lPR treatment improves sleep quality, which is linked to the overall patients' quality of life and functional recovery and affects patients' productivity and well-being.

Key Points

- Tapentadol is an innovative molecule with a dual mechanism of action, combining μ-opioid receptor agonism and norepinephrine re-uptake inhibition. It is effective both

on the nociceptive and neuropathic components of pain, representing an effective option in the treatment of chronic back pain.

- The rate of response to tapentadol PR in our study was higher than the rate of response to other analgesics, with a statistically significant difference both before and after surgery ($p<0.01$).
- The reduction in pain intensity was statistically significant in the group treated with tapentadol PR both before and after surgery ($p<0.01$). Tapentadol PR was significantly more effective than comparators, with a complete resolution of pain 90 days after surgery.
- Neuropathic pain improved more in patients treated with tapentadol PR than in patients treated with paracetamol/NSAIDs 21 days after surgery ($p<0.01$), with complete resolution of neuropathic pain in all patients treated with tapentadol 2 months after surgery.
- The quality of sleep improved earlier and more in the tapentadol PR group, whereas only a minority of patients in the control group reported a "good" at the end of the follow-up ($p<0.0001$).

Conflict of interest

TB has received personal fees from Grunenthal. The other authors have no conflict of interest.

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