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Efficacy and tolerability of tapentadol prolonged release during rehabilitation: a prospective, observational study

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Abstract. – OBJECTIVE: The treatment of chronic pain frequently combines pharmacologic and non-pharmacological options, and analgesia after surgery is of major importance. Tapentadol is both μ-opioid receptor agonist (with a 40% agonism on these receptors) and noradrenaline reuptake inhibitor, with similar analgesic efficacy to strong opioids, but fewer adverse effects. For these reasons, tapentadol may represent a valuable first choice option in the treatment of chronic, neuropathic, and mixed pain.

PATIENTS AND METHODS: The primary endpoint of the present study was the proportion of responder patients, with ≥30% reduction in pain intensity during loading on the NRS; several additional endpoints were also evaluated.

RESULTS: Twenty-five adult patients were enrolled, with a rate of response to treatment of 100%. Moreover, pain reduction was as high as 50% in 23/25 patients (92%). The average NRS at rest at V0 was 7.2 ± 1.0, whereas the average NRS at loading was 7.7 ± 0.9; this score significantly decreased at all visits. The score of the Roland-Morris questionnaire, a score of disability, improved significantly throughout the study ($p<0.0001$), as well as the Barthel Index ($p<0.0005$), and the neuropathic component of pain, which was significantly reduced during the study, from 88% at V0 to 12% at V3. Sleep quality improved throughout the study, and the treatment was rated as good (91% of patients) or optimal (9%).

CONCLUSIONS: Our findings show that tapentadol PR may contribute to improve patients' quality of life, especially during rehabilitation after back surgery, when tapentadol PR treatment is effective and well tolerated.

Key Words:
Tapentadol, Chronic pain, Post-laminectomy.

Introduction

Frequently, back pain is a chronic condition[1,2] with several complications in the overall health status, including sleep disturbances, depression, and anxiety disorders[3].

Analgesic treatment and interventional procedures are usually associated in order to obtain better pain control. Moreover, analgesia after surgery is of major importance.

Tapentadol is indicated for the treatment of chronic severe pain. Its dual mechanism of action consists of a 40% μ-opioid receptor agonism (MOR) associated to noradrenaline reuptake inhibition (NRI)[4]. Tapentadol prolonged release (PR) demonstrated a similar or superior efficacy for pain control compared with strong opioids, but the reduced μ-load carries out a lower incidence of adverse effects and an overall better tolerability profile with a lower risk of treatment discontinuation and improved patients' quality of life[5]. In addition, tapentadol PR 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 glucoronidation[6]. For these reasons, tapentadol PR may represent a valuable first choice option in the treatment of chronic, neuropathic, and mixed pain[7]. Moreover, tapentadol PR is very effective in controlling low back pain and neck pain[8,9].

The aim of this study was to evaluate the analgesic efficacy and tolerability of tapentadol PR (Grunenthal, Aachen, Germany) in patients during rehabilitation post-laminectomy or spinal stabilization surgery.

Patients and Methods

This is a prospective, open-label, observational study, enrolling all adult patients (≥18 years), with chronic pain higher than 5 on the Numeric Rating Scale (NRS), post-laminectomy or vertebral

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stabilization, during post-operative rehabilitation. Systemic illnesses constituted the most important exclusion criterion.

All patients received tapentadol PR at a starting dose of 25 mg twice daily (BID), which could be gradually increased according to clinical needs by 25 mg BID or 50 mg BID every 3 days up to a maximum dose of 500 mg/day, in order to obtain a pain intensity during loading ≤3 on the NRS and maintaining a good tolerability. In case of persisting pain, rescue analgesia was carried out with paracetamol.

The primary endpoint of the study was the proportion of responder patients, defined as subjects who experienced a ≥30% reduction in pain intensity during loading on the NRS by the end of the study compared with baseline. Secondary endpoints were: any change in pain intensity both at rest and during loading on the NRS score; the presence of the neuropathic component of pain, assessed with the DN4 questionnaire; improvements in quality of daily life assessed with through Barthel index questionnaire; the degree of disability measured with the Roland-Morris questionnaire; subjective therapy effectiveness based on a 4-point verbal scale (3 = very effective, 2 = effective, 1 = not very effective, 0 = ineffective); sleep quality on a 4-point scale (1 = very disturbed; 2 = with frequent awakenings; 3 = good; 4 = restful sleep); tolerability of tapentadol PR on a 4-point verbal scale (0 = not tolerated; 1 = poorly tolerated; 2 = well tolerated; 3 = very well tolerated); and the incidence of adverse events and treatment discontinuation. All evaluations were performed at baseline (V0), after 3 days (V1), after 14 days (V2) and after 40 days of treatment (V3), or earlier in case of treatment discontinuation.

Statistical Analysis

Statistical analysis was performed with 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

As per scheduled protocol, a total of 50 patients would have been enrolled in the study. However, only 25 patients formed the final population (12 males, mean age: 66.25 years, age range: 55-73 years). Two patients discontinued treatment due to nausea of moderate intensity. Chronic pain was caused by post-laminectomy syndrome (seven patients, 28%) or vertebral stabilization (18 patients, 72%), with the most frequent diagnosis being disc herniation (eight patients, 32%), arthrodesis (seven patients, 28%), lumbar stenosis (six patients, 24%), and spondylarthrosis (four patients, 16%). Pain was nociceptive in 14 patients (56%) and mixed in 11 patients (44%), with none of the patients reporting isolated neuropathic pain. Most patients reported continuous pain (16 subjects, 64%), whereas pain was intermittent for seven subjects (28%). Before enrollment in this study, analgesia was achieved with paracetamol (13 patients, 52%), NSAIDs (six patients, 24%), opioids (six patients, 24%) and adjuvant therapies (three patients, 12%), and was considered effective by six patients (24%). Conversely, most patients considered previous analgesia either very bad (three patients, 12%) or bad (16 patients, 64%). Tolerability of previous treatments was low in ten patients (4%), with seven (28%) and eight (32%) patients grading the tolerability of previous analgesia as good or very good, respectively.

The average dosage of tapentadol PR at baseline was 130 mg/day, and it increased at approximately 200 mg/day during follow-up, with a maximum dose of 300 mg/day.

The rate of response to treatment was 100%: all 25 patients obtained at least a 30% reduction in pain intensity during loading compared with baseline. Moreover, pain reduction was as high as 50% in 23/25 patients (92%).

Pain intensity assessed with the NRS improved throughout the study period ($p<0.0001$). The average NRS at rest at V0 was 7.2±1.0, whereas the average NRS at loading was 7.7±0.9; this score decreased statistically significantly at all visits (Table I, Figures 1A and 1B). The score of the Roland-Morris questionnaire, a score of disability, was 14.6±1.5 at V0, and became 11.3±1.2 at V2 and 8.2±0.8 at V3, respectively ($p<0.0001$, Figure 2). Similarly, the Barthel index improved from an average 80.2±12.4 at V0, to an average 85.0 ± 9.5 at V2, and an average 91.7 ± 6.5 at V3 ($p<0.0005$, Figure 3). The neuropathic component of pain was significantly reduced during the study from 88% at V0 to 12% at V3 (three patients). Paracetamol 1000 mg was necessary in four patients as a rescue medication to improve pain control. Sleep quality improved throughout the study,

Table I. Pain intensity at rest and during loading over the study period, with mean and standard deviation.

NRS score	V0	V1	V2	V3
Rest	7.2±1.0	6.0*±1.1	3.7*±1.1	2.4*±0.6
Loading	7.7±0.9	6.4*±1.1	3.8*±1.0	2.4*±0.5

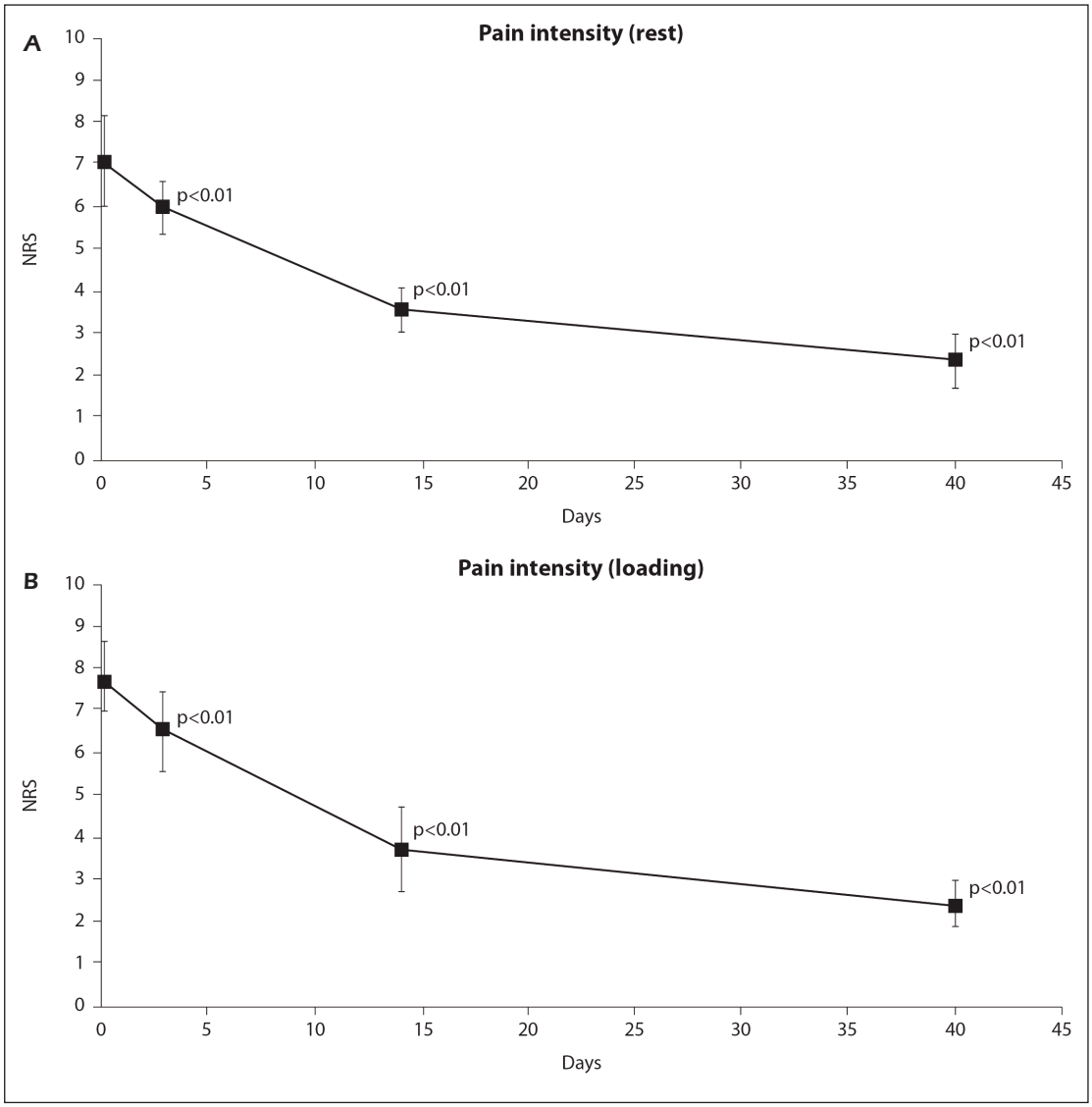

Figure 1. Pain intensity at rest **(A)** and during loading **(B)**, assessed on the NRS, throughout the study.

with all patients reporting a good quality of sleep at V3 compared with only 12.5% at baseline (Figure 4). Overall tolerability of tapentadol PR treatment was good (91% of patients), with some patients (9%) grading tapentadol PR tolerability as optimal.

Discussion

Frequently, chronic pain shows a double nature, with both the nociceptive and the neuropathic component[3], which need to be addressed. The best approach to treat this painful

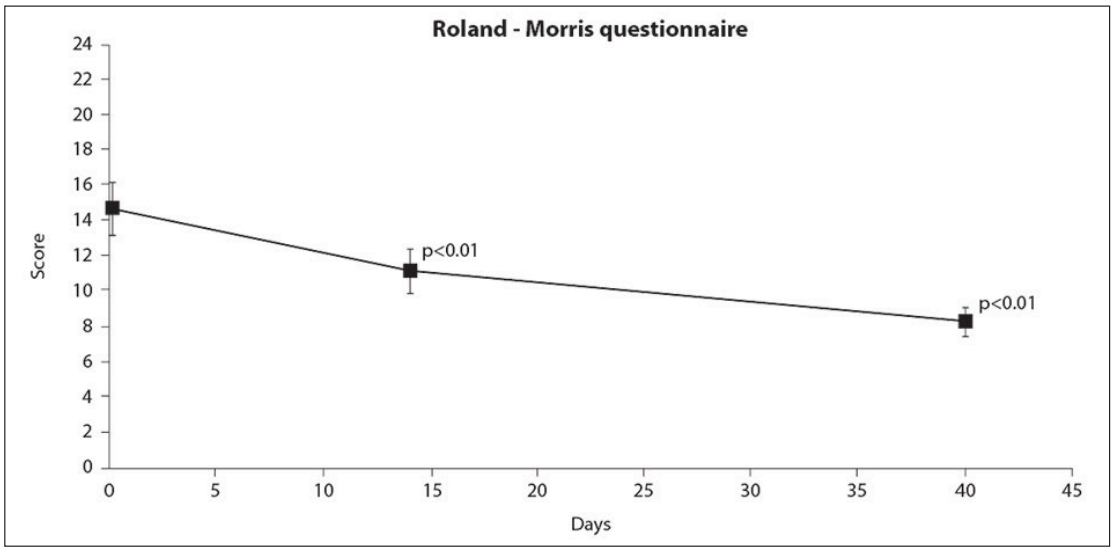

Figure 2. The score of the Roland-Morris questionnaire throughout the study.

condition is based on the combination of pharmacological and non-pharmacological therapies[10-13], with particular attention to the neuropathic component of pain. An effective level of analgesia can be achieved with tapentadol, a synthetic molecule with a synergic action on MOR and NRI[14-16]. Although tapentadol maintains the same analgesic efficacy of opioids, the reduced μ-load allows reducing the rate of adverse effects[17] and the rate of treatment discontinuation, with a significant improvement in quality of life[16]. This is translated to all dimensions of quality of life, such as sleep quality, functional capacity, and mobility/improved disability.

The results of the present study show that tapentadol PR was significantly effective in reducing pain intensity during loading (we obtained a 100% response rate with a pre-specified NRS reduction of 30%, and a 92% response rate when considering a 50% reduction in NRS). These results were achieved as early as 3 days after the beginning of tapentadol PR treatment and were accompanied by a signifi-

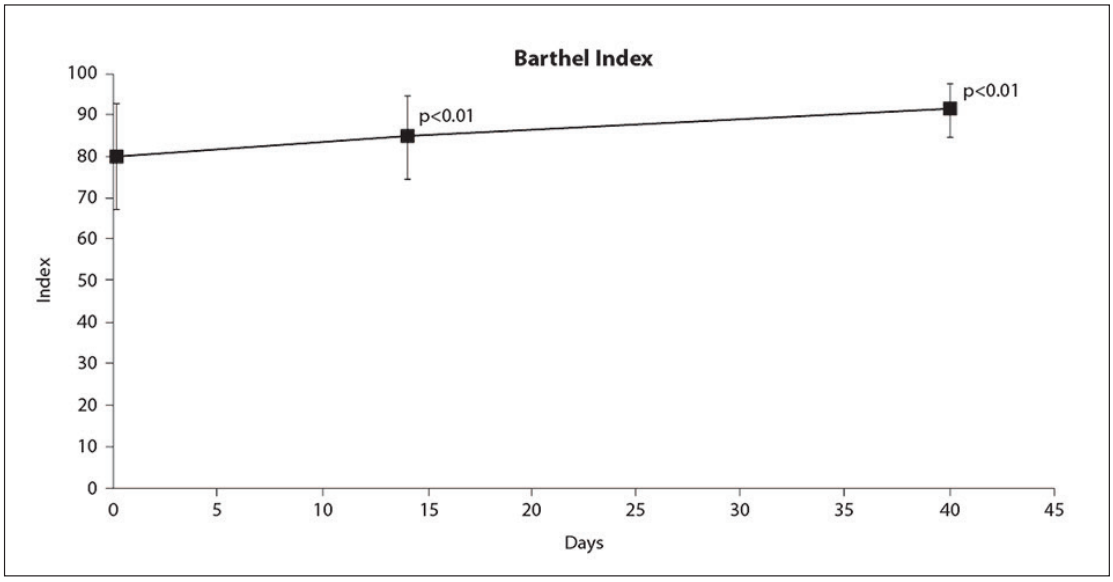

Figure 3. The Barthel Index throughout the study.

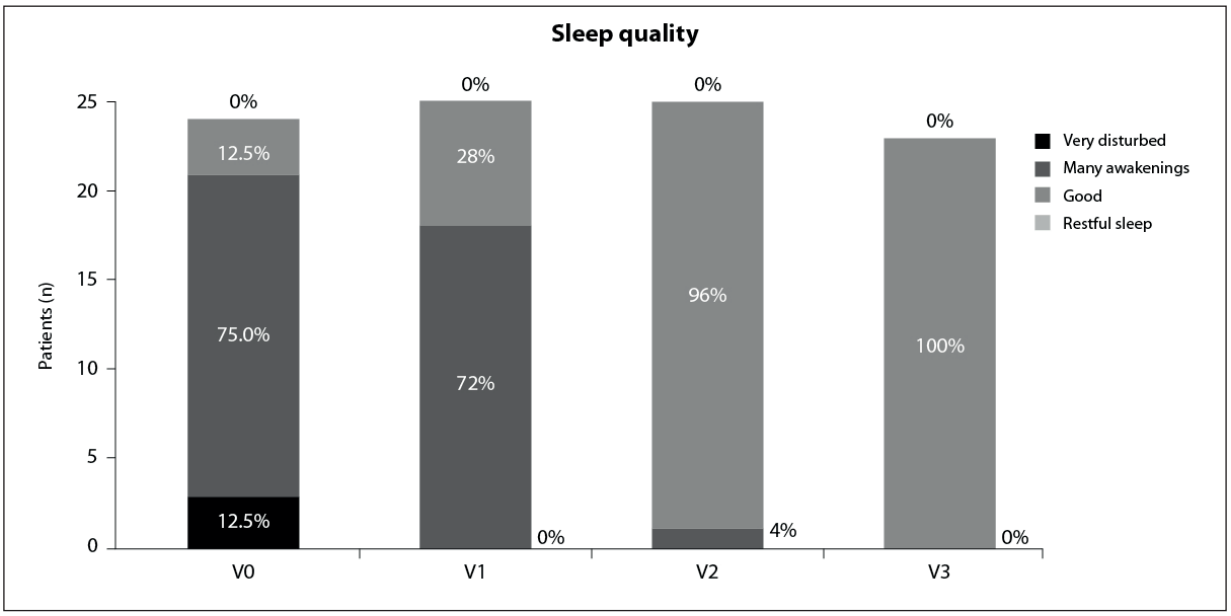

Figure 4. Sleep quality throughout the study.

cant reduction in the neuropathic component of pain, a reduced score of disability, an improved quality of life and sleep quality. These findings suggest that the use of tapentadol PR may contribute to improve patients' quality of life, as already reported elsewhere[5,18] and that during rehabilitation after back surgery, tapentadol PR treatment is effective and well tolerated.

Conclusions

Back pain is a chronic condition usually requiring both strong pharmacological analgesia and interventional procedures. Tapentadol PR shows a favorable profile and is less prone to therapy abuse; it also carries on a low incidence of adverse effects, thus representing a valid option for the treatment of chronic pain. Our study confirms the safety, efficacy, and tolerability of tapentadol PR during rehabilitation post-laminectomy and spinal stabilization, with pain control reached as early as three days after the beginning of treatment.

Key Points

- Tapentadol is effective both on the nociceptive and neuropathic components of pain due to its dual mechanism of action: μ-opioid receptor agonism and norepinephrine reuptake inhibition.
- A high percentage of patients achieved a reduction of pain intensity with tapentadol PR (100% of patients with at least 30% NRS reduction, and 92% of patients with 50% NRS reduction).
- The scores of the Roland-Morris and Barthel questionnaires, as well as of the DN4 questionnaire and the verbal assessment of sleep quality, were improved during the study (all $p < 0.05$).
- Only two patients discontinued tapentadol PR, due to nausea of moderate intensity with a very high overall tapentadol tolerability.

Conflict of Interests

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

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