Retrospective Review

Comparison of the Efficacy of a Gabapentinoid with an Opioid Versus an Opioid Alone in Patients with Spinal Cord Stimulation

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Background: Combination therapy with a gabapentinoid and an opioid improves the quality of life (QOL) of patients with chronic pain. However, the role of combination therapy in patients with spinal cord stimulation (SCS) has not been evaluated.

Objective: Our primary objective was to evaluate the clinical outcomes of combination therapy consisting of a gabapentinoid and an opioid in patients undergoing SCS.

Study Design: Retrospective evaluation.

Setting: Veterans Health Service Medical Center, Seoul, Korea.

Methods: We retrospectively reviewed 100 military veteran patients who underwent SCS implantation. Forty-eight of 100 patients had been maintained on SCS for 2 years. Patients were divided into 2 groups by analgesic type: group A (opioid only, n = 20) and group B (opioid + gabapentinoids, n = 28). Pre-implantation information included the numeric rating scale (NRS) pain score, quality of life scale (QOLS) score, and oral morphine equivalents (OMEs). Post-implantation data were obtained at 1, 6, 12, and 24 months.

Results: Group B had higher QOLS scores at 1, 6, 12, and 24 months than those of group A ($P < 0.05$). There were no statistically significant differences in the NRS pain score or OMEs at 1, 6, 12, or 24 months between the 2 groups.

Limitation: Retrospective design, relatively short follow up period (2 years).

Conclusion: This study indicated that the addition of a gabapentinoid to an opioid is superior to an opioid alone in terms of QOL in military veteran patients with SCS for 2 years. Combination therapy consisting of a gabapentinoid added to an opioid can be a good modality to improve QOL in patients with SCS.

Key words: Combination, drug therapy, gabapentin, multimodal analgesia, opioid, pain, pregabalin, spinal cord stimulation

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Chronic pain is a common and important problem, which has negative psychological and social effects and adverse effects on quality of life (QOL) (1). It is now argued that QOL is more important than conventional treatment goals that have simply focused on pain control.

Gabapentinoids, including gabapentin and pregabalin, are effective for pain and sleep disorders, mood and emotions, and QOL associated with diabetic peripheral neuropathy and postherpetic neuralgia (2-7). Opioids also improve the QOL of patients with cancer and chronic neuropathic pain (8). In addition, studies have shown that SCS reduces pain and improves QOL in patients with painful diabetic polyneuropathy (9).

Taking QOL into consideration, multidisciplinary treatment, such as multimodal analgesia, is now used to

care for patients with chronic pain. Combination therapy consisting of gabapentin and an opioid (oral morphine, oral tramadol or transdermal fenanyl) has been shown to reduce neuropathic pain in cancer patients to a greater extent than opioid therapy alone (10). Although there have been reports regarding combination therapy consisting of gabapentinoids and opioids, to our knowledge, there have been no previous studies of such combination therapy in patients undergoing SCS. This retrospective study was performed to evaluate the clinical outcomes of combination therapy consisting of a gabapentinoid and an opioid in patients maintained on SCS for 2 years in terms of pain control, QOL, and opioid requirement.

Methods

Study design and patient selection

After Institutional Review Board (BOHUN 2016-10-008) approval, the charts of all patients receiving SCS between October 2008 and December 2014 were reviewed retrospectively. During this period, 100 patients underwent SCS trial implantation for management of chronic pain. Patients were included if they underwent permanent SCS implantation that had been maintained for 2 years and had been taking an opioid or opioid with gabapentinoid (gabapentin or pregabalin) as oral analgesics. Patients were excluded if they lacked follow-up data or if SCS was not maintained for 2 years. After exclusion, 48 patients were included in the study. Patients were divided into 2 groups according to analgesic type: group A (opioid only, n = 20) and group B (opioid + gabapentinoid, n = 28). In group B, 14 patients had been taking gabapentin as the gabapentinoid and the remaining 14 patients pregabalin. Figure 1 shows the patients included in this study.

Agents (Opioids and Gabapentinoids)

The opioids used in this study included oral morphine (MS CONTIN; Mundipharma International,

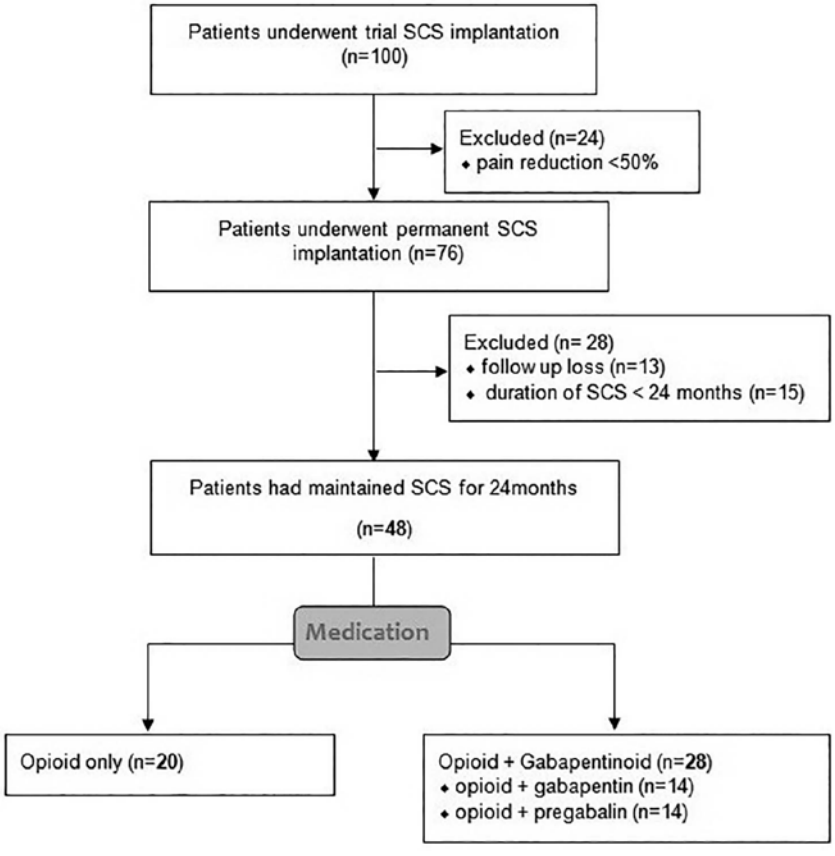

Fig. 1. *Flow chart of patient enrollment.*

Ltd., Cambridge, UK), oral oxycodone (Oxycontin; Mundipharma International, Ltd., Cambridge, UK), and transdermal fentanyl (Duragesic® matrix fentanyl patch; Janssen Pharmaceuticals, Beerse, Belgium). The gabapentinoids included oral gabapentin (Neurontin®; Pfizer, Inc., New York, NY, USA) and oral pregabalin (LYRICA®; Pfizer, Inc.). These pharmacological agents were used in accordance with the manufacturers' prescription information and the patients' requirements according to their condition. The maximum daily doses of oral morphine and oral oxycodone were 360 mg and 440 mg, respectively. The maximum daily release rate of transdermal fentanyl was 125 μg/h. The maximum daily doses of oral gabapentin and pregabalin were 2,400 mg and 600 mg, respectively.

SCS implantation

All patients included in our study underwent a trial prior to permanent SCS implantation, and the duration of trial stimulation was approximately 1 week. In all implantation cases, the Genesis IPG (Octrode lead; Advanced Neuromodulation Systems, Plano, TX, USA) was placed for both the trial and permanent SCS system.

Outcome Measurement

The numeric rating scale (NRS) pain score, quality of life scale (QOLS) score, and opioid medication dose were checked before SCS implantation. The NRS pain score was based on a scale from 0 to 10, where 0 indicated no pain and 10 the worst pain imaginable (11). The QOLS score, developed by the American Chronic Pain Association, was also based on a scale from 0 to 10, where 0 indicated non-functioning and 10 indicated normal QOL (12). Non-functioning is defined as staying in bed all day or feeling hopeless and helpless about life, while normal QOL is defined as going to work or volunteering each day, having normal daily activities, having a social life outside of work, or taking an active part in family life. The opioid medication dose was recorded in oral morphine equivalents (OMEs) for each patient through medication records (13). Post-implantation data for the NRS pain score, QOLS score, and OMEs were obtained at 1, 6, 12, and 24 months.

Statistical Analysis

Statistical analyses were performed using SPSS18.0 (SPSS Inc., Chicago, IL). The normally distributed data between groups were analyzed using Student's t test. Otherwise, the Mann–Whitney U test was used to analyze variables without a normal distribution. In each group, the NRS pain score, QOLS score, and OMEs before SCS implantation were compared with those obtained at 1, 6, 12, and 24 months after SCS implantation using Wilcoxon's signed-rank test. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Results

Patient characteristics

Demographic data, such as age, BMI, diagnosis, and duration of SCS maintenance were not significantly different between the groups (Table 1). In

Table 1. *Demographic data of both group.*

	Group A (Opioid only)	Group B (Opioid + Gabapentinoid)	*P*-value
Number	20	28	
Age (years)	60.5 ± 15.5	63.5 ± 17.1	0.530
Height (cm)	167.7 ± 7.9	167.5 ± 7.4	0.924
Weight (kg)	71.9 ± 7.9	70.1 ± 13.5	0.556
BMI	25.6 ± 2.48	24.86 ± 3.84	0.427
Diagnosis [N (%)]			0.815
Complex regional pain syndrome I	8 (40.0%)	9 (32.1%)	
Complex regional pain syndrome II	3 (15.0%)	2 (7.1%)	
Failed back surgery syndrome	5 (25.0%)	9 (32.1%)	
Postherpetic neuralgia	1 (5.0%)	4 (14.3%)	
Painful diabetic polyneuropathy	2 (10.0%)	2 (7.1%)	
Raynaud disease	0 (0.0%)	1 (3.6%)	
Chronic back pain	1 (5.0%)	1 (3.6%)	
Duration of maintaining SCS (months)	46.7 ± 16.0	43.1 ± 15.2	0.438

This above analysis was performed using Mann-Whitney U test or t test for indifferent samples according to the normality of data to evaluate the differences between the values of the group A and group B. $P < 0.05$

Table 2. *Pre and post-implantation data of NRS in both groups. Group A (opioid only), Group B (opioid + gabapentinoid)*

Time (month)	NRS, mean ± SD		
	Group A	Group B	*P*-value
Pre-implantation	8.4 ± 0.75	8.25 ± 0.8	0.535
Post-implantation 1	3.7 ± 0.86	3.54 ± 0.64	0.453
Post-implantation 6	4.75 ± 2.21	3.89 ± 1.03	0.251
Post-implantation 12	5.15 ± 2.16	4.46 ± 1.4	0.351
Post-implantation 24	5.55 ± 2.21	5.14 ± 1.32	0.595

NRS, numerical rating scale; QOLS, quality of life scale; OME, oral morphine equivalent. This above analysis was performed using t test for indifferent samples according to the normality of data to evaluate the differences between the values of the group A and group B. Normal distribution was checked by Kolmogorov-Smirnov test. The P < 0.05 were considered statistically significant.

Table 3. *Pre and post-implantation data of OMEs in both groups. Group A (opioid only), Group B (opioid + gabapentinoid).*

Time (month)	OMEs, median (minimum-maximum)		
	Group A	Group B	*P*-value
Pre-implantation	80 (20-630)	80 (0-400)	0.659
Post-implantation 1	40 (0-590)	40 (0-270)	0.975
Post-implantation 6	50 (0-550)	40 (0-370)	0.341
Post-implantation 12	40 (0-420)	35 (0-100)	0.941
Post-implantation 24	40 (0-200)	40 (0-100)	0.339

NRS, numerical rating scale; QOLS, quality of life scale; OME, oral morphine equivalent. This above analysis was performed using Mann-Whitney U test for indifferent samples according to the normality of data to evaluate the differences between the values of the group A and group B. Normal distribution was checked by Kolmogorov-Smirnov test. The P < 0.05 were considered statistically significant.

addition, there were no significant differences in pre-implantation data, including the NRS pain score, QOLS score, and OMEs, between the 2 groups (Tables 2 and 3 and Fig. 2).

Clinical outcomes

Group B had significantly higher QOLS scores at 1, 6, 12, and 24 months than those of group A ($P = 0.02$, 0.004, 0.005, and 0.012, respectively) (Fig. 2). There were no significant differences in the NRS pain score ($P = 0.453$, 0.251, 0.351, and 0.595, respectively) or OMEs ($P = 0.747$, 0.649, 0.851, and 0.240, respectively) at 1, 6, 12, or 24 months between the 2 groups (Tables 2 and 3). For both groups, there were statistically significant increases in QOL ($P < 0.05$) and decreases in the NRS pain score and OMEs (both $P < 0.05$) at 1, 6, 12, and 24 months compared with the respective pre-implantation scores.

Discussion

Chronic pain is a major social and economic problem, which has an estimated prevalence ranging from 11% to 64% (14,15). Chronic pain has a significant impact on the patient's QOL, with low QOL observed in patients with chronic pain caused by any medical condition (16). In addition, chronic neuropathic pain has a significant effect on QOL and places high economic burdens on both the individual and society (17). Therefore, patients with chronic pain should be managed by combination analgesic pharmacotherapy to improve QOL and reduce social and economic burdens.

SCS is the most effective way to improve QOL in

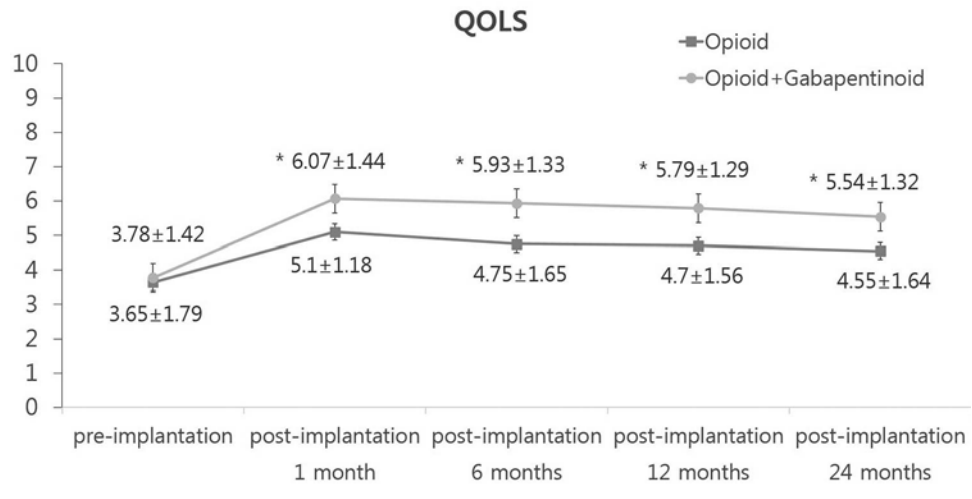

Fig. 2. *Pre- and post-implantation QOLS score in both groups. *P < 0.05.*

patients with chronic pain reported to date (18). Pluijms et al (9) reported that SCS was associated with improvements in QOL, neuropathic pain characteristics, and sleep, as well as with clinically relevant pain relief in two-thirds of patients with painful diabetic polyneuropathy. Many studies have demonstrated the efficacy of SCS; however; these studies also reported that patients who initially respond well to SCS do not always maintain their initial response over the subsequent years (18-21). Thus, patients may continue to take oral medication, such as opioids or gabapentinoids, after receiving SCS. In the present study, 48 patients were taking oral medication while maintaining SCS for 2 years. All 48 were taking opioids, of whom 28 were taking a gabapentinoid in addition to the opioid. Therefore, chronic pain management requires multimodal treatments, with interventional procedures and drug therapy playing especially important roles in a clinical setting.

Gabapentinoids and opioids are among the few drugs that have demonstrated efficacy in the pain management of patients with chronic pain (22-24). Although single-drug studies have demonstrated the efficacy of gabapentinoids and opioids, some patients participating in these studies still had significant residual pain and discontinued treatment because of severe adverse events. Therefore, combination drug therapy is needed for chronic neuropathic pain, because each of these monotherapies only partially relieves pain.

Moreover, the use of combination drug therapy has been advocated as a means of improving analgesia and QOL through synergistic or additive effects. Gilron et al (25) demonstrated that the combination of gabapentinoid and opioid is important, and reported that the combination of gabapentins and opioids showed better control of neuropathic pain at lower doses of each drug, compared with placebo or either agent alone. Furthermore, Wang et al (26) reported that combination therapy of pregabalin and morphine resulted in a marked improvement in QOL from baseline compared with patients receiving either morphine or pregabalin monotherapy. In addition, several studies demonstrated that the combination of gabapentinoids and opioids reduced pain and improved QOL compared with monotherapy (10,27,28). However, care should be taken when using pregabalin and opioids together because pregabalin has been classified as a Schedule V controlled substance and has the potential for abuse and dependence based on its ability to induce benzodiazepine-like euphoria and enhance the effects of opioids (29). In the present study, the patients treated with both a gabapentinoid and opioid showed improvements in QOL at 1, 6, 12, and 24 months compared with those receiving the opioid alone, although there were no statistically significant differences in pain reduction or opioid consumption at any of these time points between the gabapentinoid + opioid group and opioid monotherapy group. Furthermore, the side effects of the gabapentinoid and opioid combination therapy were mostly mild, and no severe side effects such as seizure, muscle spasm, decreased level of consciousness, or respiratory depression occurred.

Our study had several limitations. First, it was a retrospective case review and not a randomized controlled trial. Second, this study was performed in patients with maintenance of SCS for only 2 years, representing a relatively short follow-up period. Third, patients undergoing SCS may take a gabapentinoid only, but no such patients were included in our study.

Conclusion

In conclusion, this study indicated that a gabapentinoid added to an opioid is superior to an opioid alone in terms of improving QOL in military veteran patients with SCS for 2 years. Therefore, combination therapy consisting of a gabapentinoid added to an opioid represents a good modality to improve QOL in patients with SCS.

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