Evaluation of the safety and effects of pregabalin premedication on sleep quality, haemodynamic changes and pain in elderly patients with comorbidities undergoing spinal stenosis

Ebru Tarıkçı Kılıç¹ A-F

¹ Training and Research Hospital, Umraniye, Turkey

INTRODUCTION

In industrialized countries, more than 10% of the elderly population are over the age of 85. Aging causes an increase in the number of physiological changes in the systems and diseases. More than 35% of elderly inpatients and 55% of patients aged 65 and over undergo surgery. Geriatric premedication, therefore, becomes increasingly important in modern anaesthesia practice [1].

Stress and anxiety due to possible elective surgery cause a series of metabolic and hormonal changes in elderly patients (the pituitary-hypothalamic-adrenocortical system is stimulated, and the sympato-adrenal pathway is activated) [2], resulting in an increase (up to 40%) in the level of adrenaline [3]. Increased blood pressure and heart rate mean anaesthesia errors. Preoperative psychological status affects both intraoperative period and increases the need for a postoperative analgesic agent. Physiological changes with aging affect patients’ response to anaesthesia. The doses of anaesthetic drugs for elderly patients should be carefully adjusted and even reduced when possible. Researchers are still looking for the best premedication agent for elderly patients and ways of administering it [3].

An ideal premedication agent should provide sedation, analgesia, and anxiolysis, increase the quality of induction, maintenance, and recovery, be administered orally, minimize the side-effects of the induction agent, and should not cause nausea, impair cardiovascular stability and suppress respiration [4]. Today, benzodiazepines, opioids, antihistamines, anticholinergics, alpha-2 adrenergics, antacids, and H₂ antagonists are commonly used for premedication. New agents are expected to prevent anxiolytic, sedative, and amnestic effects and increase reflex activity, especially in elderly patients with a large number of comorbidities.

Postoperative pain varies according to the site and complexity of the surgical operation, causes physiopathological changes regardless of the surgical site and source, and delays recovery, and increases hospital stay and costs. The correct analgesic improves postoperative recovery and reduces hospital stay.
and medical costs. Woolf et al. (1913) were the first to argue that postoperative pain is a manageable acute pain that accompanies the inflammatory response to surgical trauma and becomes less intense with tissue recovery. Woolf laid groundwork for the emergence of the concept of ‘preemptive analgesia’ by using antinociceptive treatment that blocks the conduction of afferent signals. This technique is used to identify pain mechanisms to reduce pain due to incision and inflammation damage [5, 6].

Pregabalin is a GABA analog with no direct effect on GABA-like mechanisms. The analgesic actions of pregabalin establish an alpha-2 subunit to inhibit voltage-gated calcium channels, preventing neuronal depolarization and thereby reducing the release of excitatory neurotransmitters, resulting in pain control. Pregabalin has anticonvulsant, anxiolytic, and analgesic activity, and in recent years there has been an increase in the number of studies addressing its use for premedication [7].

This is the first study to investigate the safety of premedication pregabalin and its effect on preoperative sleep, intraoperative haemodynamic parameters, anaesthesia consumption, blood loss, and postoperative pain control in patients over 65 years of age who had undergone surgery for spinal stenosis, and also to compare its effects with those of diazepam.

MATERIALS AND METHOD

The sample consisted of 95 patients over 65 years of age, with an American Society of Anesthesiologists (ASA) physical status of I–III in a private single center in 2015–16. The study was approved by the local Ethics Committee. A retrospective chart review design was used. Data were collected from anaesthesia registration forms, service nurse observation files, and the medical information system of the hospital. Preoperative records were used to collect data on participants' demographic characteristics, ASA scores, comorbidities, sleep quality measurements and indications for an operation. Intraoperative records were used to collect data on type of monitoring, total intraoperative anaesthesia consumption, haemodynamic parameters, blood loss, duration of surgery, and Aldrete scores. Postoperative records were used to collect data on VAS scores, postoperative analgesia consumption, additional opioid demand, first mobilization, first oral intake, and complications, if any.

The exclusion criteria were: 1) having an ASA score > III, 2) being followed-up in the postoperative intensive care unit, 3) allergic to the medications in question, 4) having renal and liver failure, (5) acute pancreatitis, (6) a history of spinal stenosis, and also to compare its effects with those of diazepam.

Statistical analysis. Frequency was used for nominal and ordinal data while means and standard deviations were used for scale data. The Kolmogorov-Smirnov test was used for normality testing. An independent samples t-test was used for normally distributed data while the Mann Whitney U test was used for non-normally distributed data. Data were analyzed using the Statistical Package for Social Sciences (SPSS for Windows, version 17) at a significance level of 0.05.

RESULTS

Table 1 shows the participants’ demographic characteristics, ASA scores, and comorbidities. There was no significant difference in age and body mass index (BMI) between the 2 groups.
There was also no significant differences in duration of surgery between the 2 groups. The PG group PG significantly lower intraoperative anaesthesia consumption (total propofol and remifentanil) and total bleeding compared with group D (p < 0.000). Disc extrusion was the most common indication for both groups. (Tab. 2). Comparison of the total blood loss is presented in Figure 1. Significantly total blood loss was lower in the PG group.

### Table 2. Comparison of intraoperative findings and indications for operation

<table>
<thead>
<tr>
<th></th>
<th>Pregabalin (n=45)</th>
<th>Diazepam (n=51)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of surgery (min)</td>
<td>144.55±25.31</td>
<td>143.43±23.14</td>
<td>0.821</td>
</tr>
<tr>
<td>Propofol consumption (mg)</td>
<td>5.04±0.56</td>
<td>5.35±0.52</td>
<td>0.090</td>
</tr>
<tr>
<td>Remifentanil consumption (mg)</td>
<td>9.82±0.39</td>
<td>10.25±0.59</td>
<td>0.000</td>
</tr>
<tr>
<td>Intraoperative blood loss (ml)</td>
<td>391.00±172.45</td>
<td>571.67±204.40</td>
<td>0.000</td>
</tr>
<tr>
<td>Operation indications, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neurodegenerative diseases</td>
<td>5 (11.1)</td>
<td>4 (7.8)</td>
<td>0.842</td>
</tr>
<tr>
<td>Extruding disc</td>
<td>17 (37.8)</td>
<td>23 (45.1)</td>
<td></td>
</tr>
<tr>
<td>Scoliosis</td>
<td>2 (4.4)</td>
<td>4 (7.8)</td>
<td></td>
</tr>
<tr>
<td>Tumour</td>
<td>15 (33.3)</td>
<td>15 (29.4)</td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>6 (13.3)</td>
<td>5 (9.8)</td>
<td></td>
</tr>
</tbody>
</table>

A - Mann Whitney U Test; b - Independent Samples T Test; c - Chi-Square Test (Likelihood ratio);
BMI - Body Mass Index; ASA - American Society of Anesthesiologist; HT - Hypertension, COPD: Chronic obstructive pulmonary diseases.

Table 3 shows the participants’ pre- and post-induction systolic blood pressure, diastolic blood pressure, and maximum heart rate values (30 min, 1 h, and 2 h) and VAS scores. The group PG had significantly lower scores in all measurements than the group D (p < 0.05) (Fig. 2).

In the postoperative period, the recorded total fentanyl consumption from PCA was found to be higher in the D group, although it was not statistically significant. Aldrete score, which was the most important criteria in terms of discharge to the service, was higher in the PG group. Sleep quality was better in the PG group and anxiety was found to be lower which we believed seconder to the sleep quality. In addition to these finding, early mobilization and first oral intake were significantly faster in the PG group (Tab. 4).

### Table 3. Comparison of time-dependent measurements and difference analysis results

<table>
<thead>
<tr>
<th></th>
<th>Pregabalin (n=45)</th>
<th>Diazepam (n=51)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-induction SBP</td>
<td>138.78±13.12</td>
<td>158.98±21.33</td>
<td>0.000</td>
</tr>
<tr>
<td>Pre-induction DBP</td>
<td>68.56±9.03</td>
<td>75.65±13.19</td>
<td>0.013</td>
</tr>
<tr>
<td>Post-induction SBP</td>
<td>99.80±9.21</td>
<td>143.94±20.21</td>
<td>0.000</td>
</tr>
<tr>
<td>Post-induction DBP</td>
<td>56.42±5.55</td>
<td>68.39±11.20</td>
<td>0.000</td>
</tr>
<tr>
<td>Systolic 30 min</td>
<td>108.02±10.49</td>
<td>131.69±18.28</td>
<td>0.000</td>
</tr>
<tr>
<td>Diastolic 30 min</td>
<td>61.60±6.72</td>
<td>63.75±9.85</td>
<td>0.211</td>
</tr>
<tr>
<td>Systolic 1 h</td>
<td>105.07±13.21</td>
<td>125.96±16.12</td>
<td>0.000</td>
</tr>
<tr>
<td>Diastolic 1 h</td>
<td>59.04±8.06</td>
<td>61.82±9.17</td>
<td>0.120</td>
</tr>
<tr>
<td>Systolic 2 h</td>
<td>105.91±11.97</td>
<td>122.61±14.47</td>
<td>0.000</td>
</tr>
<tr>
<td>Diastolic 2 h</td>
<td>58.40±6.08</td>
<td>59.20±6.61</td>
<td>0.573</td>
</tr>
<tr>
<td>Pre-HR</td>
<td>76.63±12.47</td>
<td>76.87±10.24</td>
<td>0.659</td>
</tr>
<tr>
<td>Post-HR</td>
<td>72.38±7.08</td>
<td>75.53±10.38</td>
<td>0.083</td>
</tr>
<tr>
<td>HR 30 min</td>
<td>72.42±6.79</td>
<td>76.86±10.95</td>
<td>0.095</td>
</tr>
<tr>
<td>HR 1 h</td>
<td>71.80±5.03</td>
<td>76.45±9.53</td>
<td>0.003</td>
</tr>
<tr>
<td>HR 2 h</td>
<td>74.53±5.19</td>
<td>76.92±9.03</td>
<td>0.111</td>
</tr>
<tr>
<td>VAS pre</td>
<td>4.44±1.06</td>
<td>5.67±0.93</td>
<td>0.000</td>
</tr>
<tr>
<td>VAS 2h</td>
<td>3.24±0.74</td>
<td>3.98±0.99</td>
<td>0.000</td>
</tr>
<tr>
<td>VAS 6h</td>
<td>2.62±0.65</td>
<td>3.08±1.00</td>
<td>0.019</td>
</tr>
<tr>
<td>VAS 12h</td>
<td>2.16±0.71</td>
<td>2.86±0.95</td>
<td>0.000</td>
</tr>
<tr>
<td>VAS 24h</td>
<td>1.96±0.60</td>
<td>2.25±0.66</td>
<td>0.031</td>
</tr>
</tbody>
</table>

A - Independent Samples T Test; b - Mann Whitney U Test; SBP - Systolic Blood Pressure; DBP - Diastolic Blood Pressure; HR - Heart rate; VAS - Visual Analog scale.

Additional opioid requirement was found to be higher in the D group. When the side- effects were checked, nausea vomiting dizziness were observed more frequently in the D group during the postoperative period (Tab. 5).

### DISCUSSION

Pregabalin is a new generation antiepileptic that reduces the release of neurotransmitters such as glutamate, noradrenaline, and substance P. A daily 150–600 mg dose of pregabalin has been approved in Turkey as an additional treatment for adult patients with peripheral neuropathic pain,
in anxiety reduction. Administration of 300 mg pregabalin
(p.o) on the morning of the surgery enabled the PG group
to have more stable haemodynamic values and less bleeding,
which is secondary to persistent balanced hypotensive
anaesthesia throughout the surgery than the D group. In the
postoperative period, the PG group had lower VAS scores and
opioid consumption, earlier mobilization (with the reduction
of pain), lower urgent demand for opioid than the group
D. Adult patients with increased preoperative anxiety had
significantly more postoperative pain and a higher demand
for analgesic and a sedative drug. Moreover, the less the
anxiety in the preoperative period, the faster the recovery.

Although a large number of premedication drugs has
been developed in recent years, more than 80% of patient
still report postoperative anxiety and pain. Gonano et al.
[11] preoperatively administered 300 mg pregabalin to 40
patients and reported low anxiety in patients after orthopedic
surgical interventions. Polat et al. (8) found that 150 mg
pregabalin reduced post abdominal hysterectomy anxiety
in patients, and therefore recommend it as an alternative
premedication. Omara AF et al. [12] reported that 150 mg
preemptive pregabalin significantly reduced the demand
for urgent postoperative analgesics and improved the sleep
quality of patients on the first night after femur fixation.
Luo et al. [13] reported that patients with preoperative sleep
quality had less severe postoperative pain.

Singh et al., [14] who compared pregabalin premedication
and placebo, found that pregabalin inhibited stress response
to laryngoscopy and intubation, resulting in stable
perioperative haemodynamic parameters. Eren et al. [15]
showed that 50 patients who underwent elective lumbar
microdiscectomy surgery and received pregabalin had lower
mean arterial pressure and heart rate values, and lower post-
intubation tachycardia and hypertension. Chakraborty [16]
and Sundar [17] conducted research on pregabalin at different
times and obtained similar results for 150 mg. Saxena et al.
[18] compared 150 and 300 mg doses of pregabalin, and
reported no difference in laryngoscopy and intraoperative
haemodynamic parameters between the 2 groups. Reuben
et al. [19] divided patients scheduled for lumbar laminectomy
into 4 groups; 1) placebo, 2) 400 mg celecoxib, (3) 150 mg
pregabalin, and 4) 150 mg pregabalin + 400 mg celecoxib
one hour before and 12 hours after surgery. They concluded
that pre- and postoperative pregabalin was as effective in
pain relief and morphine consumption as celecoxib, and
that the combination of both drugs was the most effective
treatment. Spreng et al. [20] divided 50 patients scheduled
for discectomy into 2 groups; 1) 150 mg oral pregabalin one
hour before surgery and 2) placebo. They concluded that the
pregabalin group had significantly lower pain scores and
opioid consumption than the placebo group. Kim et al. [21]
sought an effective dose of preoperative oral pregabalin for
the multi-model analgesia regimen in lumbar spinal fusion
surgery and concluded that the 150 mg pregabalin group
had less opioid consumption and demand for it. Researchers
have used different doses of preemptive pregabalin for
hysterectomy, spinal surgery, orthopedic surgery, and
laparoscopic surgery. Baloyiannis et al.[22] investigated the
effects of 300 mg pregabalin administered before laparoscopic
colorectal surgery on postoperative morphine consumption
and concluded that those who received pregabalin had
significantly lower morphine consumption on 8, 24 and 48
hours than the placebo group.

**Figure 2. Mean VAS values**

**Table 4. Group outcomes and difference analysis results**

<table>
<thead>
<tr>
<th>Group</th>
<th>Pregabalin (n=45)</th>
<th>Diazepam (n=51)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total fentanyl consumption PCA</td>
<td>17.47±0.73</td>
<td>17.51±0.86</td>
<td>0.691*</td>
</tr>
<tr>
<td>Aldrete scores</td>
<td>11.41±1.99</td>
<td>6.71±1.27</td>
<td>0.000*</td>
</tr>
<tr>
<td>Sleep Quality</td>
<td>1.24±0.57</td>
<td>2.45±0.73</td>
<td>0.000*</td>
</tr>
<tr>
<td>RSS at 2 h</td>
<td>2.07±0.25</td>
<td>2.14±0.35</td>
<td>0.261</td>
</tr>
<tr>
<td>Additional opioid demand, n (%)</td>
<td>9 (20.0)</td>
<td>41 (80.4)</td>
<td>0.000*</td>
</tr>
<tr>
<td>Preop anxiety</td>
<td>46.20±3.98</td>
<td>46.65±5.74</td>
<td>0.041*</td>
</tr>
<tr>
<td>First mobilization</td>
<td>8.62±0.49</td>
<td>9.84±0.97</td>
<td>0.000*</td>
</tr>
<tr>
<td>First oral intake</td>
<td>5.20±0.99</td>
<td>6.98±1.14</td>
<td>0.000*</td>
</tr>
</tbody>
</table>

* – Mann Whitney U Test; * – Chi-Square Test

**Table 5. Postoperative side effects or complications**

<table>
<thead>
<tr>
<th>Group</th>
<th>Pregabalin (n=45)</th>
<th>Diazepam (n=51)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea, n (%)</td>
<td>7 (15.6)</td>
<td>9 (17.6)</td>
<td>0.764*</td>
</tr>
<tr>
<td>Vomiting, n (%)</td>
<td>4 (8.9)</td>
<td>9 (17.6)</td>
<td>0.211*</td>
</tr>
<tr>
<td>Dizziness, n (%)</td>
<td>2 (3.9)</td>
<td>11 (24.4)</td>
<td>0.764*</td>
</tr>
</tbody>
</table>

* Chi-Square Test

diffuse anxiety disorder, fibromyalgia, and partial epilepsy.
It is a rapid-acting anxiolytic and analgesic that achieves
maximum plasma concentration approximately one hour
after oral intake. Preemptive administration of pregabalin
results in the blockage of the neuropathic component of
acute nociceptive surgical pain, thereby reducing chronic
neuropathic pain, opioid demand, pre- and postoperative
anxiety and stress [8, 9]. Pregabalin may also play a significant
role in postoperative pain management because it reduces
excessive excitability of dorsal horn neurons induced by tissue
damage, and inhibits hyperalgesia and central sensitivity [10].
There are few studies that investigate the effects of preemptive
pregabalin on pain and analgesic consumption. What is
more, they report conflicting results due to differences in
dosage regimen and type of surgery. Therefore, further
research is warranted.

In the current study, administration of 300 mg pregabalin
(p.o) the night before the surgery enabled the participants to
have better sleep, which is considered to play a secondary role
In 2017, Hu Jiai conducted a literature research on studies about pregabalin and gabapentin premedication and included 79 randomized controlled trials with 6,201 patients who received single dose premedication. The conclusion was that there was a dose response relationship between opioid consumption and postoperative pain (24). A similar study was designed by Gupta et al. to evaluate the effect of pregabalin as premedication on the perioperative anesthetic requirement and analgesia. They recommended premedication with 75 mg of pregabalin the night before and 300 mg an hour before surgery as this decreased analgesic consumption in the postoperative period without causing any adverse effects (25). Rajappa conducted a randomized controlled study on 135 patients under spinal anaesthesia and concluded that premedication with 150 mg of pregabalin provided postoperative pain relief (26).

**RESULTS**

Massive bleeding during spinal stenosis surgeries adversely affects intraoperative and postoperative haemodynamics, especially in elderly patients (vision in the surgical field, difficulty of intervention, hemodynamic problems). In the current study, balanced and controlled hypotensive anaesthesia resulted in reduced intraoperative bleeding in the participants.

The PG group had significantly earlier mobilization than the D group, which may have been due to low VAS scores. Warner FM et al. [23] employed an experimental animal model and reported that pregabalin improved motor recovery on months 1, 3, 6, and 12 in spinal cord injury. Considering this study, further research on spinal surgeries is therefore warranted.

The incidence of nausea and vomiting was significantly lower in the PG group participants, who had an earlier oral intake than group D participants. This is an important result because early oral feeding promotes recovery. Due to the residual effect of pregabalin, the PG group also had lesser anaesthesia recovery and higher postoperative RRS than the D group. Long early postoperative sedoanalgesia and lack of stable hemodynamics and respiratory depression deficiency is, in a sense, ideal.

Pregabalin is a drug with a low frequency of side-effects, little interaction with other drugs, and good oral intake tolerance, although there are research reports on side-effects such as drowsiness, dizziness, dry mouth, and somnolence. In the current study, participants reported dizziness and dry mouth. Previous studies have also reported an increase in dose-related side-effects. The results obtained in this study show that 300 mg preemptive pregabalin is safe for elderly patients.

**CONCLUSIONS**

Two doses of 300 mg of premedication pregabalin for spinal stenosis surgery resulted in high sleep quality, low intraoperative anaesthesia and analgesic consumption, low postoperative pain score, low demand for emergency rescuing analgesics, early mobilization and early oral intake, which are parameters that play a significant role in recovery. Premedication pregabalin did not cause any serious side-effects in patients over 65 years of age.

This study has one limitation: it was based on a retrospective design. Further randomized controlled studies with larger sample sizes are needed to provide more evidence regarding the effects of premedication pregabalin. In conclusion, it is believed that premedication pregabalin is a good alternative adjuvant in the elderly.

**Compliance with ethical standards**

All procedures were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments.

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**Conflict of interest**

The authors declare that they have no conflicts of interest.

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16. Chakraborty R, Jain R, Sharma R. Evaluation of the efficacy of preoperative oral pregabalin in attenuating hemodynamic response to...


