

## Evaluation of the Effect of a Preoperative Single Dose of Gabapentin on Emergence Agitation in Patients Undergoing Breast Cancer Surgery

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### Abstract

**Background:** Emergence agitation is a transient confusional state that usually occurs within 10 to 30 minutes of recovery from general anesthesia. It may lead to serious consequences and increasing hospital costs. This study evaluates the effect of gabapentin on emergence agitation in patients undergoing breast cancer surgery.

**Methods:** This randomized, double blind controlled trial enrolled 100 female patients with American Society of Anesthesiologists' classifications I and II who were candidates for breast cancer surgery. Patients were randomly assigned into two groups (n=50) that received either oral gabapentin 600 mg or placebo. Induction and maintenance of anesthesia were similar in both groups. At the end of surgery, patient's agitation score, pain score, and presence of nausea or vomiting were reported. In the ward, the presence of headache or dizziness was checked during the first 8 h. Mann-Whitney test was used for comparison of agitation and pain scores between two groups. Chi-square test was used for comparing occurrence of nausea, vomiting and qualitative. The qualitative demographic variable and t-test compared quantitative demographic variables.

**Results:** There was a significantly lower incidence of emergence agitation in the gabapentin group before ( $P<0.001$ ) and after ( $P=0.029$ ) extubation. There were significantly lower mean agitation scores before ( $P<0.001$ ) and after ( $P=0.006$ ) extubation and in the pain score ( $P=0.005$ ) in the gabapentin group. The need for remifentanyl infusion ( $P<0.05$ ) during surgery was significantly lower in the gabapentin group compared with the placebo group. Occurrence of nausea and vomiting and gabapentin side effects that included headache or dizziness did not significantly differ between two groups ( $P=0.126$ ,  $P=1$ ,  $P=0.629$  respectively).

**Conclusion:** Gabapentin not only decreased postoperative pain but also effectively reduced emergence agitation without any significant side effects in patients undergoing breast cancer surgery.

**Keywords:** Gabapentin, Emergence agitation, Postoperative pain, Nausea and vomiting, Headache, Dizziness

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## Introduction

Emergence agitation (EA) is a transient confusional state associated with recovery from general anesthesia which should not be confused with persistent postoperative delirium. It usually occurs within the first 10 to 30 minutes of recovery time, although prolonged episodes of agitation that last for up to 2 days have been reported.<sup>1-4</sup> Emergence agitation is common in children and most frequently associated with rapid awakening from inhalational anesthesia. There is no definitive explanation for EA, but many different causes have been suggested such as age, rapid return of consciousness in an unfamiliar environment, the presence of pain (wounds, sore throat, bladder distension, etc.), stressful induction, airway obstructions, noisy environment, the child's personality, anesthetic premedication and the anesthetic technique (sevoflurane more than halothane).<sup>1,5-10</sup>

For adult patients there is little data on EA in the medical literature, but possible risk factors for agitation include patients under stress, breast or abdominal surgery, medical therapy with benzodiazepines, arterial hypoxemia or hypercarbia and, to a lesser extent, length of surgery.<sup>4, 11, 12</sup>

Regardless of pathophysiology and causal factors, EA is associated with adverse events such as increased bleeding from the surgical site, damage to the surgical repair, forceful removal of a surgical drain or an intravenous access, severe pain at the operative site and finally, prolongation of recovery room stay and increased hospital cost.<sup>3,10</sup> To reduce the occurrence and consequences of agitation after general anesthesia, some medications such as midazolam, clonidine, dexmedetomidine, fentanyl, ketorolac, propofol, morphine and physostigmine have been used.<sup>1,13-18</sup>

Gabapentin is a structural analogue of the neurotransmitter gamma-aminobutyric acid. This medicine was initially introduced as a spasmolytic agent and adjuvant anticonvulsant drug for the treatment of refractory generalized or partial seizures.<sup>19,20</sup> Subsequently, it has been shown to be effective in treating a variety of chronic pain conditions, including post-herpetic neuralgia,

diabetic neuropathy, complex regional pain syndrome, inflammatory pain, central pain, malignant pain, trigeminal neuralgia, HIV-related neuropathy, and headaches.<sup>21,22</sup> Some clinical studies have found gabapentin to be effective in reducing or treating postoperative pain in patients who underwent thyroid or spinal surgery, radical mastectomy, arthroscopy with block and cholecystectomy.<sup>22-30</sup> The efficacy of gabapentin in reducing postoperative pain and analgesic consumption has been also shown in a number of meta-analyses and a systematic review.<sup>31, 32</sup>

It has been shown that gabapentin attenuates the pressor response associated with laryngoscopy and tracheal intubation<sup>33,34</sup> and decreases postoperative nausea and vomiting.<sup>10,29</sup> Taking the above into consideration it seems reasonable that gabapentin with its anxiolytic and analgesic properties in adults, which also decreases delirium,<sup>19,21</sup> can control postoperative agitation.

However, according to our knowledge, there is no study that has investigated the effects of gabapentin on agitation in adults. The results of a study by Salman et al. in a small patient population series have demonstrated that preoperative oral gabapentin did not have a significant benefit on EA in children.<sup>19</sup>

The aim of the present study therefore, was to determine the efficacy of a preoperative single dose of gabapentin in reducing postoperative agitation in patients undergoing breast cancer surgery.

## Materials and Methods

This double-blind, randomized, placebo-controlled study was approved by the Institutional Review Board of the Shiraz University of Medical Sciences. Its purpose and methods were explained to patients prior to surgery and informed consents were obtained from all patients. A sample size of 50 patients in each group was determined to be sufficient to detect a 36% difference in the incidence of EA between study groups, assuming a power of 80% and a significance level of 5% (power=80%,  $\alpha=0.05$ ). The study enrolled 100 adult patients aged 20-60 years who were

**Table 1.** Demographic data and perioperative times.

	<b>Gabapentin group</b>	<b>Control group</b>	<b>P-value</b>
Age (years)	48.72±9.21	45.62±8.11	0.217
Weight (kg)	65.30±11.34	61.42±10.67	0.176
Duration of operation(min)	100.66±15.2	103.33±16.24	0.128
Duration of intubation(min)	7.70±4.06	8.80±04.11	0.182
Duration of recovery(min)	60.10±17.06	63.0±17.92	0.409

American Society of Anesthesiologists (ASA) classifications 1 or 2 and were scheduled for either modified radical mastectomy (MRM) or quadrantectomy and axillary node dissection (AND). Patients with severe preoperative anxiety, history of impaired kidney or liver functions, history of diabetes mellitus, chronic pain, and those who took antianxiety, neuroleptic, antidepressant or benzodiazepine medications for a long duration were excluded. We used the block randomization method to randomly assign patients into two groups of 50 each. Group A received two gabapentin (300 mg) capsules for a total of 600 mg and group B received two identical-looking capsules (placebo), orally, with sips of water one-half hour before induction of anesthesia. Gabapentin and placebo were prepared as identical capsules. At the pre-anesthetic visit, patients were instructed about the use of the Numeric Rating Scale (NRS) that ranges from 0 (no pain) to 10 (unimaginably severe pain).

Before going to the operating room, all patients completed a prepared form that included identification data (age, sex, body weight, etc.), previous medical conditions, type and duration of drug usage, history of drug allergy, history of previous surgery and presence of severe anxiety. After patients were transported to the operating room, routine monitoring devices that included continuous electrocardiography, noninvasive blood pressure (BP) and pulse oximetry monitors were attached to all patients.

Patients' heart rate (HR), BP and blood oxygen saturation (SpO<sub>2</sub>) were recorded. After monitoring and pre-oxygenation, all patients received midazolam (0.03 mg/kg) and fentanyl (2 µg/kg) by intravenous injection as premedications. Anesthesia was induced with thiopental (3-5 mg/kg) and 1-1.5 mg/kg of succinylcholine was

used to facilitate orotracheal intubation. After intubation and the onset of controlled ventilation, end-tidal CO<sub>2</sub> (ETCO<sub>2</sub>) monitoring was used. Respiratory rate and tidal volume were adjusted to maintain normocarbida. General anesthesia was maintained with isoflurane (1%-2%) and 50% nitrous oxide in oxygen. All patients received injections of morphine (0.1mg/kg) for pain control during surgery and the postoperative period.

The concentration of medications was adjusted to maintain an adequate depth of anesthesia (stable HR and BP) according to routine practice. Additional analgesics such as remifentanyl (0.03 µg/kg/min) were administered during surgery for patients who needed additional relaxation or analgesia. Fluid and blood losses were replaced according to standard practice.

At 5 to 10 min before completion of surgery, isoflurane was discontinued; 2 min prior to completion of surgery, N<sub>2</sub>O was discontinued and 100% oxygen administered to all patients with spontaneous ventilation.

Immediately after the end of surgery and each 5 min until the time of extubation, patient's degree of EA according to the Riker sedation-agitation scale (RSAS), as well as patient's HR, SpO<sub>2</sub>, BP and ETCO<sub>2</sub> levels were measured and recorded by two trained nurse anesthetists .

Extubation was performed when patients exhibited spontaneous respiration and adequate muscle strength recovery. An anesthesiologist resident who was unaware of the patient's study treatment assignment was responsible for observing the recovery state of each patient and assessing their level of agitation.

In the recovery room, following extubation, two trained nurse anesthetists monitored patients each 5min up to 15 min and then each 15 min thereafter and recorded the degree of EA using RSAS,

**Table 2.** Incidence of agitation in the two study groups.

	<b>Gabapentin group</b>	<b>Control group</b>	<b>P-value</b>
Incidence of agitation during intubation	10(20%)	33(66%)	<0.001
Incidence of agitation during recovery	5(10%)	15(30%)	0.023
Mean agitation number during intubation	3.72±0.99	4.78±1.08	<0.001
Mean agitation number during recovery	4.08±0.44	4.40±0.67	0.006

HR, SpO<sub>2</sub>, BP, ETCO<sub>2</sub>, the degree of pain through the NRS, and the degree of nausea and vomiting. Patients received pethidine (25 mg) and then apotel (1 g) if their NRS number was more than 3 and continued for 20 min. In cases of nausea and vomiting, patients received intravenous odansetron (4 mg). When the agitation score was more than 4, midazolam (0.02 mg/kg) was injected intravenous after controlling for the treatable causes of agitation such as a distended urinary bladder. The total amount of all drugs administered was recorded. When the recovery discharge score of patients, according to the Aldrete and Kroulik Score, reached an acceptable level, patients were discharged and transferred to the ward. For the first 8 h in the ward, patients were observed for the probable occurrence of gabapentin complications or side effects such as headache and dizziness. Side effects were recorded on a special form by a trained nurse.

Demographic data such as age and weight were presented as mean±SD. Agitation and pain score were analyzed by the Mann-Whitney test. Chi-square tests were used to compare categorical data and the incidence of nausea and vomiting. The independent t-test was used for quantitative demographic data. *P*-values of ≤0.05 were considered statistically significant.

## Results

Data from 100 patients who met the inclusion criteria and completed the study were analyzed. Demographic and perioperative data are presented in Table 1. No statistically significant differences were identified between demographic and perioperative data of the two study groups.

There was a higher incidence of EA as evidenced by an agitation score of >4 in the placebo group compared to the gabapentin group

both during the intubation period and recovery time (Table 2).

As seen in Table 1, the two groups were similar with regards to mean intubation time after completion of surgery (7.7±4.06 versus 8.8±4.11, *P*=0.182) and mean recovery time (60.10±17.06 versus 63.0±17.92, *P*=0.409).

Patients' BP, HR, SpO<sub>2</sub>, ETCO<sub>2</sub> and respiratory rate were checked numerous times, all of which were maintained within normal ranges for both groups.

Postoperative pain score and the number of patients who needed intraoperative infusions of remifentanyl were higher in the placebo group compared with the gabapentin group (Table 3).

The incidence of common adverse effects such as nausea and vomiting (*P*=0.126), dizziness (*P*=1.00) and headache (*P*=0.629) did not significantly differ between study groups (Table 3).

## Discussion

This study demonstrated that oral premedication with 600mg gabapentin reduced postoperative EA and mean pain score. Despite the results of previous study,<sup>20, 23</sup> postoperative nausea and vomiting in the gabapentin group was not statistically different compared to the placebo group.

The incidence of agitation in the placebo (control) group was 30% during recovery and 66% during intubation. This was similar (62%) to a study by Lankinen et al. with small children.<sup>16</sup> The reported incidence of EA in most previous studies was between 10% to 67% in children,<sup>1, 2, 5</sup> and 2%-23% in adults.<sup>1, 10, 11</sup> This disparity was partially attributed to the use of different agitation scales in these studies. Although different agitation scales have been created for adults in the ICU, no specific scales exist to evaluate patients with EA



**Table 3.** Mean pain score and postoperative side effects.

	<b>Gabapentin group</b>	<b>Control group</b>	<b>P-value</b>
Mean pain score	3.82±2.52	5.20±2.41	0.005
Patients who needed remifentanyl	13(26%)	25(50%)	0.023
Nausea and vomiting	11(22%)	19(38%)	0.126
Dizziness	14(31.1%)	14(31.1%)	1.00
Headache	13(28.9%)	10(22.2%)	0.629

in the recovery room.<sup>11</sup> However because of its ease of use, even in emergency situations, and more precise evaluation of agitation and inter-rater reliability this study used the RSAS which was developed to assess the level of agitation and sedation in intensive-care patients. RSAS ranges from level 1 (unarousable) to 7(dangerously agitated). In this scale, patients at level 4 are considered to be non-agitated calm and cooperative.<sup>11</sup>

We used a dose of 600mg of gabapentin because recent dose-response studies defined this dose as the optimal preemptive dose for postoperative analgesia. Increasing the dose beyond 600 mg does not improve analgesia, however it increases the risk of side effects.<sup>30</sup>

Little research has been undertaken on adult postoperative agitation. Although the incidence of EA in adults is less than children, it can be associated with a greater possibility of uncontrolled behavior and injury.<sup>10</sup> Emergence agitation is a clinical condition in which the underlying cause is unknown, but multiple factors such as preoperative anxiety, existence of a tracheal tube, bladder distension, pain and site of surgery (abdomen and breast) have been shown to be correlated with agitation.<sup>13,15</sup> In contrast, a history of previous illness and treatment by antidepressants were found to be protective factors. Thus if predisposing factors are avoided, postoperative agitation can be reduced.<sup>13</sup>

According to one theory, EA occurs due to changes and the relationship of gamma-aminobutyric acid (GABA) A receptors in the central nervous system.<sup>10</sup> However a number of agents including fentanyl, clonidine, oxycodone, dexmedetomidine and midazolam have been administered for prevention or treatment of EA

with variable success.<sup>13</sup> It has been shown that EA can be prevented by using ketamine in patients who underwent propofol anesthesia and by midazolam in patients under sevoflurane anesthesia.<sup>13,17</sup> Gabapentin is a structural analogue of the neurotransmitter GABA that is generally well tolerated with favorable side effects. This medicine was initially introduced as treatment for refractory seizures. Later it was shown to be effective in treating a variety of acute and chronic pain conditions,<sup>21-28</sup> and in attenuating the pressor response associated with a laryngoscopy and intubation.<sup>33</sup> It has been shown to decrease preoperative anxiety<sup>21</sup> and postoperative nausea and vomiting<sup>10, 29</sup>.

To the best of our knowledge, there was only one published study that evaluated the effect of gabapentin on EA in children. That study reported that preoperative oral gabapentin did not have significant benefit on EA.<sup>19</sup> However, in the current study gabapentin decreased the incidence of EA without an increase in the occurrence of this drug's common side effects. This might be due to its effects on GABA receptors or decreased preoperative anxiety and/or postoperative pain. In conclusion gabapentin decreased postoperative pain and effectively reduced EA without any significant side effects in adult patients who underwent breast cancer surgery.

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