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Research Article

Preoperative use of gabapentin decreases the anesthetic and analgesic requirements in patients undergoing radical mastectomy

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Abstract *Background/aim:* Gabapentin is an anticonvulsant drug that is safe and effective for the treatment of neuropathic pain syndrome, as well as postoperative pain with good results. This prospective randomized study was done to evaluate the effects of preoperative administration of oral gabapentin (1200 mg) on the intraoperative fentanyl and isoflurane consumption, postoperative analgesic requirements and postoperative pain in patients undergoing radical mastectomy.
Methods: Sixty ASA I and II patients were randomly allocated into two equal groups to receive oral gabapentin 1200 mg, 2 h before surgery (G group) or control (C group). General anesthesia was induced and maintained at bispectral index value between 40 and 60. During surgery the end-tidal isoflurane concentrations required to maintain adequate depth of anesthesia and the required incremental doses of intraoperative fentanyl were recorded. Postoperative pain was assessed using visual analogue scale (VAS) at rest for 24 h. Postoperatively, whenever visual analogue scale (VAS) was more than 5 or on patients' demand, analgesia in both groups was provided with diclofenac sodium (1 mg/kg IM) or tramadol hydrochloride (1 mg/kg IV) as needed. VAS, analgesics requirements, and side-effects were assessed for 24 h postoperatively.
Results: Intraoperative fentanyl and postoperative analgesic consumption were significantly lower in G group than C group ($P < 0.001$). Patients in the G group had significantly lower end-tidal

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concentrations of isoflurane required to maintain adequate depth of anesthesia ($P < 0.05$). VAS was significantly lower in G group than C group at the first three measurement times ($P < 0.01$). The incidence of postoperative nausea and vomiting was significantly lower in G group than C group (30% versus 60% of patients, respectively, $P < 0.05$). The incidence of dizziness was significantly higher in the G group than C group (26% versus 3.3% of patients, respectively, $P < 0.05$). *Conclusion:* Gabapentin (1200 mg) administered orally 2 h before surgery decreased the intraoperative fentanyl and isoflurane consumption, postoperative analgesic requirements, postoperative pain, and the incidence of postoperative nausea and vomiting, but increased dizziness.

1. Introduction

A number of analgesic regimens can be used for pain relief during surgery. These regimens include the use of opioids, local anesthetics, nonsteroidal anti-inflammatory drugs (NSAIDs), α_2-agonists, and cyclooxygenase-2 inhibitors. The multiplicity of mechanisms involved in pain requires a multimodal analgesia regimen, suggesting that a combination of opioid and non-opioid analgesic drugs may improve analgesic efficacy and reduce opioid requirements and side-effects after surgery [1].

Gabapentin is a structural analogue of γ-aminobutyric acid, which was first developed as an anticonvulsant drug [2]. It is safe and effective for the treatment of neuropathic pain syndrome [3], as well as for the prevention of postoperative pain [4]. In animal models of inflammatory pain [5], gabapentin was shown to reduce hyperalgesia and inhibit C-fibre responses to noxious stimuli [6] by modulating both central and peripheral nociceptive responses [7]. After a single oral dose of 300 mg, mean maximum plasma concentrations were attained in 2–3 h. It does not bind with plasma proteins and is not metabolized in humans. Absorption kinetics of gabapentin is dose-dependent, possibly due to a saturable transport system [8]. The bio-availability of a single 300 mg oral dose of gabapentin is 60% and decreases with increasing dose. Elimination of gabapentin is by renal clearance and the elimination half-life is about 5–7 h after a single oral dose of 200–400 mg [9].

As gabapentin has a substantial inhibitory effect on the development and establishment of allodynia and hyperalgesia [10], we investigated whether the use of gabapentin could reduce intraoperative fentanyl and isoflurane consumption, postoperative analgesics consumption and postoperative pain in the initial 24 h in patients undergoing radical mastectomy.

2. Material and methods

After acceptance of the Medical Ethics Committee of Al Monofia University Hospital and obtaining a patient informed consent, 60 patients of ASA physical status I and II, scheduled for radical mastectomy surgery were included in this study. Patients were excluded from the study if they had known allergy to any of the study drugs, epilepsy, previous treatment with gabapentin, chronic pain syndrome, psychiatric disorder, substance abuse, analgesic intake within 48 h before surgery or inability to understand the visual analogue scale after explanation (a scale for pain assessment in which 0 = no pain and 10 = worst pain).

Patients were randomly allocated (using a computer generated table) to one of two equal groups, the study group (G group; $n = 30$) and the control group (C group; $n = 30$). Two hours before surgery G group received oral gabapentin 1200 mg (Gabapentine 400 mg, Neurontine, Pfizer®). In both groups patients were premedicated with IV midazolam 0.05 mg/kg, 45 min before the scheduled time of surgery. After the patients had been taken to the operation room, crystalloid infusion (6–8 ml/kg) was started through a 20-gauge IV cannula and mean arterial blood pressure, heart rate, electrocardiogram and peripheral oxygen saturation were monitored. In both groups anesthesia was induced with thiopental sodium 5–7 mg/kg IV and fentanyl 2 μg/kg IV, and intubation of trachea was facilitated with atracurium besylate 0.5 mg/kg. Anesthesia was maintained with isoflurane 1–1.5% in 50% oxygen/air. Respiratory frequency and tidal volume were adjusted to maintain the end-tidal carbon dioxide level at 35–40 mm Hg. End-tidal isoflurane concentrations were monitored continuously and recorded at 10 min (time 1), 30 min after induction of anesthesia (time 2), 30 min after skin incision (time 3), and at the end of the surgical procedure (time 4). Isoflurane was titrated guided by bispectral index (BIS = 40–50) and hemodynamic endpoints (mean arterial pressure and heart rate within 20% of the preinduction value). Because isoflurane titrated using BIS alone might provide hypnosis but insufficient analgesia, the protocol allowed to increase the inspired isoflurane concentration if BIS exceeded 5 (maximum allowable increase of isoflurane was 2% for 5 min), if this did not achieve the targeted values of blood pressure and heart rate, analgesia in the form of 0.5–1 μg/kg boluses of fentanyl were used as required. Monitoring during anesthesia comprised continuous electrocardiogram and heart rate, pulse oximetry, non-invasive arterial blood pressure, measurement of end-tidal CO_2 and end-tidal isoflurane concentration. All parameters were recorded at 5-min intervals. After completion of surgery, neuromuscular blockade was reversed with atropine 0.02 mg/kg and neostigmine 0.04 mg/kg and patients were extubated when adequate spontaneous ventilation was established. Patients were transferred first to the recovery room and then to the surgical ward.

Postoperative pain assessment was monitored by anesthetist in the following times; on arrival to postanesthesia care unit (time 1~), 2 h after skin closure (time 2~), 6 h after skin closure (time 3~), 10 h after skin closure (time 4~) and in the first postoperative morning (time 5~). Postoperative analgesia was provided in both groups based on VAS scores. When VAS values were $\leqslant 5$, diclofenac sodium 1 mg/kg IM was administered and recorded, if VAS > 5 tramadol 1 mg/kg was administered. The time to first postoperative analgesic dose and the total amount of analgesic used (mg/24 h) by each group were recorded.

Any side-effect, such as dizziness, nausea and vomiting, diarrhea, epigastric discomfort, peripheral edema or headache

Table 1 Demographic data and perioperative characteristics.

	G group (n = 30)	C group (n = 29)	P value
Age (yr)	47 ± 6	45 ± 8	0.080
Weight (kg)	82 ± 12	79 ± 10	0.161
Height (cm)	164 ± 9	162 ± 10	0.069
Duration of surgery (min)	73 ± 21	71 ± 17	0.680
Duration of anesthesia (min)	80 ± 15	84 ± 14	0.352
Intraoperative fentanyl consumption (μg)	122 ± 40	148 ± 33	0.001*
Diclofenac consumption (mg)	55 ± 24	95 ± 37	0.000*
Tramadol consumption	103 ± 33	145 ± 45	0.000*
Time to first analgesic request (h)	8 ± 6	3 ± 4	0.000*

Values are presented as mean ± SD.
* $P < 0.05$ denotes statistical significance.

were recorded if present. If nausea and vomiting occurred, ondansetron 4 mg IV was administered.

Statistical analysis was performed on a personal computer using SPSS version 16.0. Data were presented as mean ± standard deviation (SD) or number (percentage) as appropriate. VAS scores and end-tidal isoflurane concentrations were analyzed with two-factor ANOVA for repeated measures. The total amount of intraoperative fentanyl and postoperative analgesics consumed in each group in 24 h was compared using an unpaired t test. Chi-square test was used for comparison of proportions and frequencies between both groups. A value of $P < 0.05$ was considered statistically significant.

3. Results

One patient in the C group was excluded from statistical analysis because of surgical complications. The patient's characteristics, the mean duration of surgery and the mean duration of anesthesia were comparable between both groups (Table 1). Intraoperative fentanyl consumption and postoperative analgesic consumption during the first 24 h, were significantly lower in the G group than the C group (Table 1). In addition to the time to first analgesic dose was significantly longer in G group than the C group (Table 1).

Table 2 End-tidal isoflurane concentrations at times of measurement.

Parameter	G group (n = 30)	C group (n = 29)	P value
Time 1 (5 min after induction)	1.5 ± 0.52	1.6 ± 0.57	0.101
Time 2 (15 min after induction)	1.2 ± 0.2	1.4 ± 0.4	0.013*
Time 3 (30 min after induction)	1.1 ± 0.3	1.3 ± 04	0.030*
Time 4 (45 min after induction)	0.9 ± 0.3	1.1 ± 0.3	0.014*
Time 5 (at the end of the surgery)	0.8 ± 0.2	1.0 ± 0.4	0.010*

Data are mean ± SD.
* $P < 0.05$ denotes statistical significance.

Except for time 1, where there were no difference between the two groups, the end-tidal isoflurane was higher in the C group than the G group at all other times of measurement (Table 2 and Fig. 1).

Heart rate and blood pressure did not significantly differ between the two groups throughout the perioperative period. Indeed hypotension was recorded in 4 patients (13.3%) in G group and in 6 patients (20%) in C group but this was statistically insignificant ($P > 0.05$), and it was corrected by increasing the rate of intravenous fluid infusion. Visual analogue scale was significantly lower in G group than in C group at time 1, time 2, time 3 and at time 4 but there was no significant difference between both groups at time 5, $P > 0.05$ (Table 3).

4. Discussion

The present study showed that the preoperative administration of oral gabapentin 1200 mg significantly reduced the intraoperative fentanyl requirements and end-tidal isoflurane concentrations required to maintain adequate depth of anesthesia. Importantly, we used an objective, qualitative measure of anaesthetic state (BIS) to guide anaesthetic requirements [11,12].

Our study is the first to show that preoperative gabapentin reduces the intraoperative end-tidal isoflurane concentrations required to maintain adequate depth of anesthesia. However the effect of preoperative dose of gabapentine on intraoperative anesthetic consumption has been previously reported

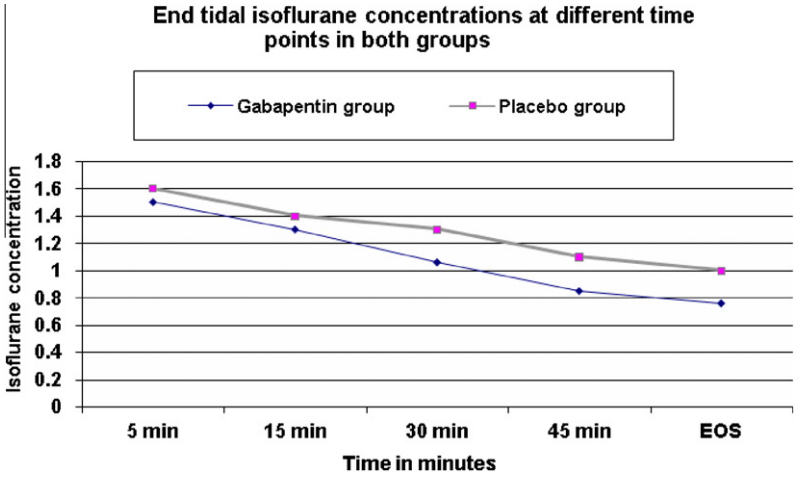

Figure 1 Intraoperative end-tidal isoflurane concentrations. EOS = End of surgery.

Table 3 Postoperative visual analogue scale in both groups.

	G group (n = 30)	C group (n = 29)	P value
Time 1~ (arrival to post anesthesia care unit)	3.5 ± 2.3	6.1 ± 1.7	0.000*
Time 2~ (2 h after skin closure)	3.2 ± 2.1	4.4 ± 1.2	0.003*
Time 3~ (6 h after skin closure)	1.8 ± 1.7	3.3 ± 1.1	0.001*
Time 4~ (10 h after skin closure)	2.2 ± 1.3	2.9 ± 1.2	0.034*
Time 5~ (first postoperative morning)	2.1 ± 1.9	2.4 ± 1.6	0.079

Data are mean ± SD.
* $P < 0.05$ denotes statistical significance.

[13–15]. Hatice et al. [13] reported significant decrease in the total propofol and remifentanil consumption in gabapentin group compared with phenytoin group in patients undergoing craniotomy for supratentorial tumor resection. The same finding has also previously shown by Alparslan et al. [14] who reported reduction in intraoperative fentanyl consumption in gabapentin group compared with placebo in patients undergoing ear, nose and throat surgery. In disagreement with us and the others Prabhakar et al. [15], who reported no difference in propofol consumption in patients received preoperative gabapentin or placebo but this might be because of the smaller dose used in their study as they used 800 mg but we used 1200 mg. The analgesic efficacy of preoperative gabapentin has been previously reported [16–18]. In the present study a significant reduction in total dose of postoperative analgesics with a significant lower pain scores in most times of measurement.

The choice to give gabapentine 2 h before the operation appears rational in order to attain maximal plasma concentration at the time of surgical stimuli. Gabapentin crosses rapidly the blood–brain barrier and consequently, it concentrates in brain tissue, where it exhibits its effect [19]. Gabapentin has been reported as an anxiolytic drug in previous studies [20,21]. Reducing preoperative anxiety with gabapentin may have contributed to the improved postoperative analgesia and to reduced analgesic requirements because there is a possible association between preoperative anxiety and postoperative pain [22].

A possible mechanism for gabapentin-mediated analgesia is the modulation of glutamate receptors (NMDA and AMPA/kainate). Gabapentin seems to decrease both NMDA and non-NMDA-mediated glutamate currents in the superficial lamina of the rat spinal cord [23] and also inhibits nociceptive responses to intrathecal NMDA and AMPA in vivo [24]. Furthermore, the analgesic effects of gabapentin are antagonized by the NMDA/glycine receptor agonist serine [25]. Suarez et al. [26], suggest that sodium entry through presynaptic NMDA-R channels facilitates axon excitability and the interaction of gabapentin with this mechanism might contribute to its analgesic benefits. Gabapentin has no direct GABA action and does not block GABA uptake or metabolism [27]. Another suggested mechanism for gabapentin is that it binds to the voltage-dependent calcium channels [28]. All, or any, of the suggested mechanisms may be responsible for the analgesic action of gabapentin.

Postoperative nausea and vomiting (PONV) during the first 24 h was significantly lower in gabapentin group. In agreement with Pandey et al. [29] and Saeed et al. [30] who conclude that 600 mg gabapentin 2 h before surgery effectively suppresses nausea and vomiting after cholecystectomy .The etiology of PONV following surgery remains unclear. Factors like age and gender of patient, obesity, technique of anesthesia employed, presence of post-operative pain, use of opioids for pain management and elective surgical procedures also influence the incidence of PONV. Gabapentin has been reported to be effective in the treatment of emesis in patients receiving cytotoxic drugs [31]. The precise mechanism of action is not known but mitigation of tachykinin neurotransmitter activity has been postulated to be useful [32]. There is evidence that tachykinin activity is part of the pathogenesis of chemotherapy-induced emesis in ferrets, and a selective tachykinin-receptor antagonist improves both acute and delayed nausea and emesis induced by chemotherapy [33]. The etiology of PONV in patients undergoing surgical operation is not identical to that in patients receiving cytotoxic drugs but the present study assume that it may be one probable mechanism for prevention of PONV by gabapentin.

The present study showed that total diclofenac requirements were significantly less in the gabapentin group. NSAIDs are commonly used analgesics in surgical procedures for decreasing pain and opioid requirements [34]. They are well established, effective, and inexpensive; however, inadequate analgesia and adverse renal, gastrointestinal, and hemostatic effects may limit their use in some groups of patients [35,36]. Gabapentin is less well established and is likely to be quite expensive. For it to have a useful place, it may ultimately need to be shown to provide better opioid-sparing and/or improved pain relief compared with the NSAIDs and to be associated with fewer adverse events. However, in our study, we determined that 26% of patients encountered dizziness, which may limit the use of gabapentin in ambulatory patients.

5. Conclusion

Gabapentin 1200 mg administered orally 2 h before surgery significantly decreased the intraoperative fentanyl and isoflurane consumption, postoperative analgesic requirements, postoperative pain score, incidence of postoperative nausea and vomiting but increased incidence of dizziness.

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