Original Article

Effects of Preoperative Low-Dose Gabapentin on Postoperative Pain and Sedation of Patients Undergoing General Anesthesia

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Objective: To study the drug interaction between gabapentin and morphine in surgical patients under general anesthesia.

Materials and Methods: Two hundred sixty patients undergoing surgery under general anesthesia were randomized into two groups, A with 130 patients receiving gabapentin 2.0 to 3.5 mg/kg orally for premedication add-on, and B with 130 patients getting morphine 0.1 to 0.2 mg/kg intravenously. After surgery, a co-researcher assessed patients using Ramsay sedation scale (RSS) and pain numeric rating scale (NRS) at 2, 4, 8, 12, 16, and 24-hour intervals.

Results: Two hundred thirty-two patients were included the present study without procedural adverse events. There were 120 and 112 patients in gabapentin and morphine group, respectively. The administration dosage of gabapentin and morphine between the two groups showed statistically significant differences (p=0.031). During the emergence, the RSS on the sedation, agitation, drowsiness, and pain scores of gabapentin (1.8±0.4) and morphine (1.7±0.5) appeared statistically significant differences (p=0.032); however, the RSS on that in the post-anesthetic care unit (PACU) were 2.0±0.1and 2.0±0.2, respectively, which showed insignificant differences (p-value 0.283).

Conclusion: A small, single oral dose of gabapentin as premedication showed a synergistic effect on intraoperative morphine administration. However, this additive effect was not long lasting through the PACU and might not be suitable for an extended surgery.

Keywords: Drug interaction; Gabapentin; Morphine; Anesthesia

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Anesthesia has been developed parallel to surgery for decades. It is divergent in knowledge and applications in physics, as well as anatomy, pharmacology, physiology, and pathology of organs system. In addition, it involves the treatments and objectives in many surgical fields such as obstetrician, neurologist, orthopedist, general surgeon, or ophthalmologist regarding pathophysiology of the underlying diseases, surgical incision, operative duration, and perioperative patients' vital changes. Briefly, anesthesia personnel are vigilant in four principles, anesthesia or unconsciousness, analgesia or painless, relaxation or immobility, and a-reflexia or attenuation of autonomic responses[1,2].

An anesthesiologist must administer many kinds of drugs to anesthetize a patient during general anesthesia. Anesthetics including sedatives, analgesics, and muscle relaxants play important roles in pharmacodynamics and pharmacokinetics[3]. Thus, it results in physiologic alteration of an unconscious patient. Interestingly, after administration, some drugs have anaphylactic or anaphylactoid reaction, while some are additive, synergistic, agonist or antagonist to the others. This is known as drug interaction[4-6].

Prior to admission, patient's drugs consumption known as medical reconciliation helps to be aware of peri-operative drug interaction. For example, propofol, sufentanyl, or alfentanil, which are widely used in anesthesia, are metabolized by cytochrome P450 enzymes in the liver. As such, it has the potential to interact with other drugs metabolized by the same system[7-9]. Patients suffering from alcoholism interferes the metabolism of barbiturate intra-operatively[10]. Aminoglycosides such as

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gentamicin, neomycin, or streptomycin can prevent the presynaptic release of acetylcholine resulting in the potentiation of non-depolarizing muscle relaxants. On the other hand, patients with chronic antiepileptic therapy such as phenytoin or carbamazepine can decrease the sensitivity of the post-junctional membrane to acetylcholine resulting in the resistance to non-depolarizers[11-13]. Diazepam and Chloral hydrate have additive effect (1+1 = 2) as insomnia and depression, while antihistamine and muscle relaxant produce synergistic action (1+1 > 2) as drowsiness on central nervous system[14,15].

Gabapentin is an anti-epileptic drug, also called an anticonvulsant. It affects chemicals and nerves in the body involved in the cause of seizures and some types of pain such as neuropathic pain or post-herpetic neuralgia. However, its adverse effects can affect many parts of the body such as mood or behavior changes, anxiety, panic attacks, trouble sleeping, agitated, hostile, aggressive, restless, mentally or physically hyperactive, depressed, or having suicidal ideation[16,17]. Currently, it is widely used for preemptive analgesia. Accordingly, taking gabapentin with other drugs particularly opioids that make patient sleepy can worsen these effects. As a result, investigators would like to study the drug interaction between gabapentin and opioids in patients under general anesthesia[18].

Materials and Methods

The present study was a prospective cohort study approved by the Siriraj Institutional Review Board (COA Si701/2019) and registered via Thai Clinical Trial Registry (TCTR20191020001), written inform consents were obtained from all subjects.

The sample size was calculated from a previous observational in 20 cases as follows, standard deviation of 5.98 was equal to 123 and 95% confidence level with allowable error of 0.5, then the sample size to achieve the objective was 246 by the method of Randomized Complete Block Design (estimation for single mean)[19].

After the 10% drop-out was added, 260 patients undergoing surgery under general anesthesia were enrolled in the present study between November 2019 and December 2020. Inclusion criteria were elective patients aged 18 to 65, body mass index (BMI) of less than 30 kg/sq.m, and the American Society of Anesthesiologists (ASA) I-III. The exclusion criterion was patients with a high risk of severe medical diseases, for example, end-stage renal disease, or impending heart failure. Withdrawal or termination criteria were patients dissatisfied to continue the study or had severe intraoperative complications.

Before the day of surgery, the project was explained in detail to all participants. Two hundred sixty volunteered patients were randomized into two groups, group A with 130 patients receiving gabapentin 2.0 to 3.5 mg/kg orally for premedication add on and group B with 130 patients getting morphine 0.1 to 0.2 mg/kg intravenously.

In the operating theatre, patients were monitored with standard anesthesia care, including non-invasive blood pressure (IBP), electrocardiography (EKG), percutaneous oxygen saturation (SpO_2), pulse rate (RR), and end tidal carbon dioxide ($ETCO_2$). An anesthesiologist administered 6 LPM of oxygen for preoxygenation. Morphine 0.1 to 0.2 mg/kg after propofol 1.5 to 2.5 mg/kg was given intravenously for induction. Then atracurium 0.6 mg/kg was dispensed for intubation and maintenance of anesthesia with sevoflurane in air and oxygen.

After surgery, a co-researcher assessed patients using Ramsay sedation scale (RSS) and pain numeric rating scale (NRS) at 2, 4, 8, 12, 16, and 24-hour intervals.

Statistical analysis

Data were expressed as median (min, max) and mean ± standard deviation (SD) using IBM SPSS Statistics software, version 21.0 (IBM Corp., Armonk, NY, USA). Categorical and non-parametric data were analyzed by chi-square test. Comparison between the two groups would be analyzed by independent t-test. A p-value of less than 0.05 was considered statistical significance at 95% confidence interval (CI).

Results

Two hundred thirty-two patients completed the study, due to 11 having prolonged operation, 21 being cancelled, and seven taking non-premedication. There were 120 and 112 patients in the gabapentin and the morphine group, respectively. They all expressed no procedural adverse events during the study. Demographic characteristics between the two groups were 77 (33.2%) males, 155 (66.8%) females, ASA I 35 (14.8%), II 124 (52.5%), and III 73 (32.6%), with an average age of 55.4±9.8 years, a body weight of 55±6.5 kg, and an operation time of 2.5±4.5 hours (Table 1).

The administration dosage of gabapentin at 2.0 to 3.5 mg/kg and morphine at 0.1 to 0.2 mg/kg, between the two groups showed statistically significant differences (p=0.031). During the emergence, the

Table 1. Patients' characteristics

Variables	n (%)
Sex	
Female	155 (66.8)
Male	77 (33.2)
Age (years); mean±SD	55.4±9.8
ASA	
I	35 (15.1)
II	124 (53.4)
III	73 (31.5)
Operation time (hour); median (IQR)	1.5 (0.5 to 3.0)

ASA=American Society of Anesthesiologists; SD=standard deviation; IQR=interquartile range

Table 2. The Ramsay sedation and pain numeric rating scale during the emergence and in the post-anesthetic care unit

Variables	Administration dosage (mg/kg)		
	Gabapentin (2.0 to 3.5)	Morphine (0.1 to 0.2)	p-value
RSS in emergence			
Sedation	2	1	
Agitation	1	1	
Drowsiness	2	1	
Pain	1	2	
Mean±SD	1.8±0.4	1.7±0.5	0.032*
RSS in PACU			
Sedation	2	1	
Agitation	1	1	
Drowsiness	2	1	
Pain	2	3	
Mean±SD	2.0±0.1	2.0±0.2	0.283

RSS=Ramsay sedation scale; PACU=post-anesthetic care unit; SD=standard deviation

Significance at p=0.05

RSS on the sedation, agitation, drowsiness, and pain scores of gabapentin (1.8±0.4) and morphine (1.7±0.5) appeared statistically significant differences (p=0.032). However, the RSS on that in the post-anesthetic care unit (PACU) were 2.0±0.1 and 2.0±0.2, respectively, which showed insignificant differences (p=0.283) (Table 2).

Discussion

Patients having morphine with gabapentin showed significant synergistic effect on sedation, agitation, drowsiness, and pain scores during the emergence. Thus, a low, single oral dose of gabapentin ordered as premedication implied enough additive result on intraoperative morphine administration. This was supported by Eckhardt et al (2000)[20] in a randomized, placebo-controlled, double-blinded study on gabapentin that enhanced the analgesic effect of morphine in 12 healthy male volunteers. They concluded that pharmacodynamics and pharmacokinetic interaction between morphine and gabapentin, leads to an increased analgesic effect of morphine for treating severe pain.

Normally, both gabapentin and morphine are intricate by the same enzymes. In human, morphine is metabolized by cytochrome P450 pathway, which mainly involves the CYP3A4 and partly the CYP2D6. However, gabapentin potential inhibits the CYP3A4 in vitro. As a result, morphine is supposed to yield a longer analgesic effect after gabapentin administration and shows some possibility of drug interaction by Zhou et al (2007)[9]. In addition, as sedation is the most common side effect of gabapentin administration, the inactivation of CYP3A4 by drug can cause unfavorable and long-lasting drowsiness and probably toxicity of morphine. Clinically, the low dose of gabapentin might be beneficial to minimize adverse effects and enough for intraoperative pain relief to the patients. This was supported by Quintero (2017)[21] in a review about gabapentin misuse, interactions, contraindications, and side effects, which stated that gabapentin could interact with morphine and induce side effects such as hypoventilation, respiratory failure, deficits in visual field, myopathy, somnolence, and dizziness. These can be related to the route of administration.

However, this additive effect of gabapentin on morphine was not long lasting through the PACU. Since gabapentin bioavailability is not dose proportional, when the dose is increased the bioavailability decreases. The metabolism of gabapentin is approximately 60%, 34%, and 27% following 900, 2,400, and 4,800 mg/day given in three divided doses, respectively[22]. Therefore, a small dose of gabapentin might have a short elimination half-life, which average 5 to 7 hours, and may not be suitable for the extended surgery[23].

Nevertheless, the study could not confirm whether the higher dose of both gabapentin and morphine would produce postoperative additive analgesia as stated in some previous studies regarding the dose-dependent effect. Peng et al (2017)[15] in a meta-analysis of randomized controlled trials titled gabapentin could decrease acute pain and morphine consumption in spinal surgery patients, summarized that gabapentin was efficacious in the reduction of

postoperative pain, total morphine consumption, and morphine related complications following spine surgery. A high dose of 900 or more mg/day of gabapentin was more effective than a low dose of less than 900 mg/day. Papathanasiou et al (2015)[24] in a study on a co-administration of morphine and gabapentin led to dose dependent synergistic effects in a rat model of postoperative pain, summarized that the combination of morphine and gabapentin resulted in synergistic anti-hyperalgesic effects. This dose-dependent effect indicated benefit of high doses of gabapentin as adjuvant to morphine.

Moreover, Salama et al (2018)[25] in a prospective randomized study on the effect of preemptive gabapentin on anesthetic and analgesic requirements in 70 patients undergoing rhinoplasty concluded that pre-operative oral gabapentin significantly reduced intra-operative remifentanil and sevoflurane requirements during hypotensive anesthesia along with decreased post-operative analgesic requirement. Mahoori et al (2014)[18] in a study on the effect of pre-operative administration of gabapentin on post-operative pain relief after herniorrhaphy, stated that prophylactic administration of gabapentin decreased pain scores and analgesic consumption in the first 24 hour after repair of inguinal hernia. Parikh et al (2010)[26] studied the effect of oral gabapentin used as preemptive analgesia to attenuate post-operative pain in patients undergoing abdominal surgery under general anesthesia stated that a single oral dose of gabapentin given pre-operatively enhanced the analgesic effect of Tramadol as it also reduced the requirement of rescue analgesia with Diclofenac. Additionally, Hurley et al (2006)[27] in a meta-analysis on the analgesic effect of perioperative gabapentin on post-operative pain, summarized that oral gabapentin was a useful adjunct for the management of postoperative pain that provided analgesic through a different mechanism than opioids and other analgesic agent and would make a reasonable addition to a multimodal analgesic treatment plan.

Limitation

This present study was performed in a single center. The small dosage of gabapentin was limited by the routine prescription of the attending surgeons.

Conclusion

A small, single oral dose of gabapentin ordered as premedication showed a synergistic effect on intraoperative morphine administration. However, this additive effect was not long lasting through the PACU and might not be suitable for an extended surgery.

What already known in this topic?

Most anesthetics are metabolized by cytochrome P450 enzymes in the liver. As such, it has the potential to interact with other drugs metabolized by the same system such as gabapentin. Gabapentin, an anti-epileptic drug, is widely used for preemptive analgesia and would have drug interaction with opioids in patients under general anesthesia.

What this study added?

This present study revealed that a small, single oral dose of gabapentin ordered as premedication showed a synergistic effect on intraoperative morphine administration. However, the effect did not last long, through the PACU.

Conflicts of interest

The authors declare no conflict of interest.

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