The Comparative Preemptive Analgesic Efficacy of Addition of vitamin B Complex to Gabapentin versus Gabapentin alone in Orthopedic Surgery under Spinal Anesthesia

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Abstract

Background: development of new multimodal analgesic regimens have led to substantial improvement in postoperative pain relief. **Aim of the work**: we designed this study to compare the effect of combined vitamin B complex-gabapentin versus gabapentin alone on postoperative pain in orthopedic surgery under spinal anesthesia. **Methods:** 80 patients who underwent elective orthopedic surgery under spinal anesthesia were randomized to receive orally 300mg gabapentin (Group G) or 300mg of gabapentin plus 2 vitamin B complex (Group GB) tablets 30minutes before surgery. Postoperative pain intensity and total analgesic consumption during 12 hours after surgery, vomiting, and drowsiness during recovery were assessed. **Results:** the pain intensity in the gabapentin plus vitamin B complex group was lower than gabapentin group during 12hours after surgery (p-value <0.001*)*. Meanwhile, the total analgesic consumption in this group was less than gabapentin alone (p-value <0.05). The incidence of vomiting in patients who received combined gabapentin—vitamin B complex group was similar to gabapentin alone (p-value >0.05). **Conclusion:** combination of vitamin B complex to gabapentin reduced intensity of postoperative pain and also the total amount of analgesic consumption within the first 12hours postoperative following orthopedic surgery under spinal anesthesia.

Keywords: orthopedic surgery, gabapentin, pain, vitamin B complex

Introduction

Pain is defined by International Association for Study of Pain (IASP) as an unpleasant sensory and emotional experience associated with actual or potential tissue damage. The relief of postoperative pain is a subject, which has been receiving an increasing amount of attention in the past few years. Postoperative pain due to surgical trauma and tissue injury is associated with neuroendocrine stress responses, catecholamine and inflammatory mediator release, and the central sensitization, which is considered to be one of the mechanisms responsible for the persistence of postoperative pain [1].The noxious stimuli may cause the expression of new genes (Which are resp0nsible for neuronal sensitization) in the dorsal horn of the spinal cord within 1hour after tissue injury due to surgical trauma. Hence, the traditional separation between the acute and chronic pain is unproven because the acute pain may quickly turn into chronic pain. Also, the intensity of acute postoperative pain is a significant predictor of chronic postoperative [2,3] . Prevention of central sensitization with multimodal analgesic interventions could reduce the intensity or even eliminate acute postoperative pain hyperalgesia and chronic pain after surgery [3,4]. Furthermore, pain control after cesarean delivery improved the general condition of the patient and infant rooming in times breastfeeding [5]. Nowadays, opioids are widely used for pain relief but, they often provide suboptimal analgesia with occasional serious side effects [5]. Furthermore, it is reported that a single administration of an opioid may induce a long lasting increase of threshold pain sensitivity, leading to delayed hyperalgesia [5,6]. Therefore, the search for a new drug to decrease the severity of postoperative pain with minimal side effects is necessary. Some clinical trials for using gabapentin as preemptive analgesia, given before a variety of surgical intervention producing visceral and somatic injury, have found significant reduction in postoperative analgesic requirements and others have found a reduction in early and late postoperative pain [7–10]. Furthermore it is reported that pretreatment with gabapentin prevents the occurrence of hyperalgesia[11] with no effect on platelets, gastric mucosa, renal function and renal function respiratory system [12]. The analgesic

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effect of gabapentin may be due to the inhibition of neurotransmitters released from sensory neurons, via a calcium-dependent process [13,14]. Although, recently a few studies reported a statistically significant but clinically unimportant difference in pain scores with movement during 24 hours after surgery for gabapentin[15,16].On the other hand, results of the recent studies have been demonstrated a beneficial effects for neurotropic vitamins (vitamins B1, B6, and B12) in alleviating acute pain [15–22]. Vitamins B (thiamine, pyridoxine and cyanocobalamine) were given alone or in combination with acetaminophen, diclofenac, or other non-steroidal anti-inflammatory drugs for relief of pain in various diseases such as degenerative diseases of the spine, back pain, rheumatic diseases, and also postoperative pain [18–23].There was an evidence that thiamine (vitamin B1) and cobalamine (Vitamin B12) play an important role in nerve conduction and excitability [17] .There was an evidence that folate and the 3 related B-vitamins have a fundamental role of in brain health across the lifecycle [24] .A literature review found no clinical trials based on the combination of gabapentin plus neurotropic vitamins in orthopedic surgery under spinal anesthesia. The safety of premedication of patients with gabapentin has been reported in humans, and orthopedic anesthesia in previous studies [25].
We hypothesized that using of two drugs with different action may provide a better analgesia with a lower side effects. In order to test this hypothesis, we designed this randomized, placebo-controlled study to compare the postoperative analgesic effects of gabapentin alone and gabapentin plus vitamin B complex.

Methods

The present study was randomized, placebo-controlled study in which the patients were fully informed about the study protocol and provided written informed consent. **The study was approved by the Ethics Board of Al-Azhar University.**

Exclusion criteria included significant coexisting complications such as hepatic, renal, cardiovascular diseases, and any contraindication to regional anesthesia such as local infection or bleeding disorders, opioid dependence, psychotic and other analgesic drugs use and a history of chronic pain. 80 patients were recruited of whom 5 excluded from the study groups due to failed spinal anesthesia or other factors violating the study protocol. A total of 80 patients aged between 18 and 60 years in the American Society of Anesthesiologists (ASA) physical I or II posted for elective orthopedic surgery under spinal anesthesia. All patients were randomized to receive orally 300 mg gabapentin plus two placebo tablets (group G) or 300 mg of gabapentin plus two vitamin B complex tablets contains 125 mg vitamin B1 (thiamine), 125 mg of vitamin B6 (pyridoxine), 125ug vitamin B12 (Cobalamin) and 0.5 mg folic acid (Group GB) 30 minutes before surgery. The study data were recorded by a blinded observer. All patients were given an intravenous preload of lactated Ringer's solution at 5 to 7 mL/kg before the subarachnoid block. Under an aseptic technique, a 22-gauge Quincke needle was inserted intrathecally via a midline approach at the L4–5 interspace by the same anesthetist, who was unaware of patient assignment, while the patient was in the sitting position. Following a successful dural puncture, the anesthetic solution (0.25mg/kg bupivacaine 0.5%) was injected.The primary outcomes of the present study were to evaluate the time to the first requirement of analgesia supplement and the total analgesic consumption in the first 12 postoperative hours. In the present study, postoperative analgesia was defined as the time from the intrathecal injection of anesthetic solution to the first requirement of analgesic supplement.The pain intensity of patients was evaluated at the end of anesthesia in the recovery room, then at 2, 4, 8, and 12 hours after surgery. Patients were trained preoperatively to use of the visual analog scale (VAS) of pain from zero to 10 (0 no pain, 10 maximum imaginable pain) for pain assessment. If the VAS exceeded 4 and the patient requested a supplement analgesic, according to the hospital's protocol of pain management, diclofenac Na 75 mg ampule was given as postoperative pain relief. If the time of administration from diclofenac Na to patients' request was less than 8 hours, intravenous pethidine 25 mg was given for breakthrough pain (VAS>4) relief. Other sedative or analgesic agents were not used. The secondary outcome of this study included the assessment of BP and HR level, and the incidence of complication. Recorded data were analyzed by using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as

mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

Results

One hundred fifty patients were recruited of whom 5 excluded from the study groups due to failed spinal anesthesia or other factors violating the study protocol. There were no significant differences between the 2 groups regarding the demographic properties (age, gender, body weight, height, and duration of surgery (Table1)

Table 1: comparison between the groups according to demographic data

Demographic data	Group G (n=37)	Group GB (n=38)	t/x2#	p-value
Age (years) Range Mean±SD	 18-60 28.99±6.38	 18-60 29.70±6.53	0.186	0.905
Sex Male Female	 24 (64.9%) 13 (35.1%)	 27 (71.1%) 11 (28.9%)	1.103#	0.776
Weight (kg) Range Mean±SD	 40-95 38.89±8.56	 40-95 37.48±8.24	0.036	0.991
Height (cm) Range Mean±SD	 150-185 25.46±5.60	 150-185 26.16±5.76	0.209	0.699
ASA I II	 30 (81.1%) 7 (18.9%)	 33 (86.8%) 5 (13.2%)	0.439#	0.769
Duration surgery (min) Range Mean±SD	 70-210 102.53±22.56	 70-210 106.07±23.33	0.922	0.846

t-Independent Sample t-test; #x^2: Chi-square test
p-value >0.05 NS

This table showed no statistically a significant difference between groups according to demographic data.

The difference of the mean time to the first analgesic request in group GB (5.45±0.76hours) versus group G (4.36±1.21hours) was significant. As shown in table2, total amount of pethidine consumption within 12hours following surgery was significantly lower in group GB as compared with the group G. In other words, 94.7% of patients in group GB did not require pethidine and the intensity of their pain was low (VAS≤4) or reduced by administering diclofenac NA alone, while 18.9% of patients in group G requested analgesia in addition to diclofenac NA Figure 3 and heart rate was significantly lower in the (GB) group than (Table 2 showed total the analgesic consumption by patients was significantly lower in group GB as compared with group G . Table 3 showed the pain intensity in the gabapentin plus B complex group was lower than gabapentin group during 12hours (Figure 2). The blood pressure of group G was shown in table 4.

Table 2: comparison between groups according to analgesic

Analgesic	Group G (n=37)	Group GB (n=38)	x2	p-value
Pethidine (mg)	7 (18.9%)	2 (5.3%)	5.531	0.037*
Total doses pethidine	175mg	50mg		
Diclofenac Na (mg)	26 (70.3%)	21 (55.3%)	6.114	0.012*
Total doses diclofenac	1950mg	1575mg		

x^2: Chi-square test; *p-value <0.05 S
This table showed statistically significant difference between groups according to time of analgesic.

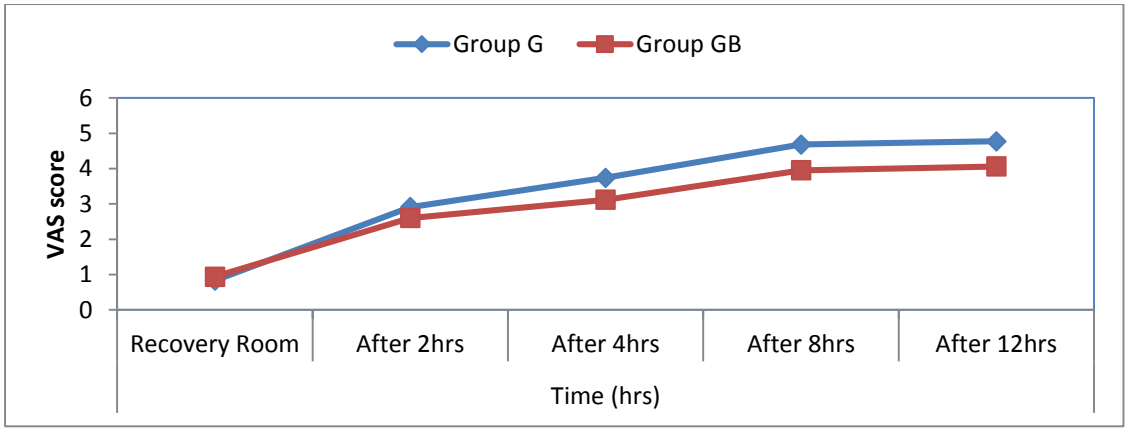

Fig. 1: line chart between groups according to VAS score

Table 4: comparison between groups according to MABP (mmHg)

MABP (mmHg)	Group G (n=37)	Group GB (n=38)	t-test	p-value
Baseline	82.42±3.21	82.19±3.21	0.211	0.498
Postoperative 1hr	82.66±3.22	81.12±3.16	0.475	0.606
Postoperative 2hrs	84.08±3.24	81.36±3.17	3.682	0.013*
Postoperative 4hrs	84.74±3.30	81.61±3.18	4.931	0.011*
Postoperative 8hrs	85.58±3.34	81.85±3.19	6.366	<0.001**
Postoperative 12hrs	86.44±3.37	82.1±3.20	7.003	<0.001**

t-Independent Sample t-test;
p-value >0.05 NS; *p-value <0.05 S; **p-value <0.001 HS

This table shows statistically significant difference between groups according to MABP postoperative after 2hrs to after 12hrs.

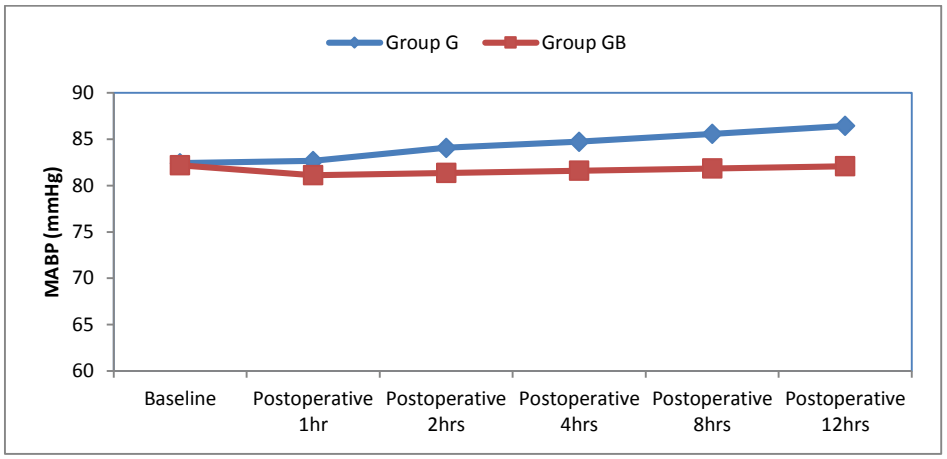

Fig. 2: line chart between groups according to MABP (mmHg)

Discussion

Based on the data found in our study, we concluded that premedication of patients with combined gabapentin—vitamin B complex (GB) group reduced the total consumption of analgesic in the first 12hours postoperatively compared to the gabapentin alone (G) group. Meanwhile, patients experienced pain at lower intensity in the first 12hours postoperatively compared to the other group. Some recent studies since the aforementioned review indicate that the gabapentin and vitamin B complex group is effective in reducing the pain scores after various surgical procedures [7–11,18–22] .But, the authors found no clinical trials based on the combination of gabapentin B complex vitamins in orthopedic under spinal anesthesia . However, our finding concerning the effect of adding vitamin B complex to gabapentin regimen for postoperative pain after orthopedic indirectly are supported by another

study [25].The auhors reported that some of the vitamins B (B1, B6 and B12) can be used alone or in combination with diclofenac or other nonsteroidal anti-inflammatory drugs for relief of acute pain of the lumbar vertebrae [17,18]. Furthermore, there was evidence that thiamine (vitamin B1) plays an important role in nerve conduction and excitability [17,18,22,26].In a study of **Terán *et al*.** [22], it was reported that the analgesic efficacy of acetaminophen is increased when neurotropic vitamins were added to acetaminophen. The results of present study is also in harmony with the findings of the clinical studies by **Bruggemann *et al*.**[17] and **Mibielli *et al*.** [18] which declared that analgesic effect of combined Diclofenac-B vitamins was more pronounced compared to Diclofenac alone. **Beltrán-Montoya *et al*.** [26] also reported that statistical difference between the control (ketorolac 30mg) compared to ketorolac 15mg plus vitamin B complex groups was insignificant. These results are in agreement with our findings. Results of the present study assumed that using the 2 agents would allow a reduction in dose for both agents and therefore limit incidence of unt**0**ward effects while improving efficacy. However, the analgesic effect of gabapentin probably due to decreasing the release of neurotransmitters from sensory neurons, via a calcium-dependent process [12,13]. While, vitamin B complex especially thiamine (vitamin B1), pyridoxine (vitamin B6) plays an important role in nerve conduction and excitability [17].In agreement with another studies we empirically chose to use the single dose (300mg) of gabapentin and 2 tablet vitamin B complex as a reasonable compromise between the efficacy and toxicity [9,11,12,15].The next observation of this study was that the incidence of nausea and vomiting was similar to the gabapentin plus B complex group. Some studies suggested that using gabapentin (an anticonvulsant) before surgery significantly reduced the incidence of postoperative nausea and vomiting after open cholecystectomy [27–30]. This antiemetic effect of gabapentin may be caused by reducing the activity of tachykinin neurotransmitter [2,9]. Furthermore, vitamin B6 has been known to possess antiemetic effects since 1942. Hypotheses to describe the antiemetic effects of pyridoxine include prevention and treatment of vitamin B6 deficiency, intrinsic anti-nausea properties, or augmentation the anti-nausea properties of antihistamines [30].

Conclusion

Based on the results found in our study, we concluded that the total analgesic requirement within the first 12hours postoperative in patients who received gabapentin and vitamin B complex (GB) was smaller than patients who received gabapentin alone. The side-effects were similar in both the groups. Thus, the combination of these drugs as safe, cheap, and easy methods, this can provide higher quality of analgesia and better patient satisfaction after surgery.

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