

# The comparative preemptive analgesic efficacy of addition of vitamin B complex to gabapentin versus gabapentin alone in women undergoing cesarean section under spinal anesthesia: A prospective randomized double-blind study

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## Abstract

**Background:** Development of new multimodal analgesic regimens have led to substantial improvement in postoperative pain relief. We designed this study to compare the effect of combined vitamin B complex—gabapentin versus gabapentin alone on postoperative pain in women undergoing cesarean section under spinal anesthesia.

**Methods:** One hundred twenty-eight women who underwent cesarean section under spinal anesthesia were randomized to receive orally 300 mg gabapentin (group G) or 300 mg of gabapentin plus 2 vitamin B complex (group GB) tablets 30 minutes 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 12 hours after surgery (95% CI: 1.4–2.2;  $P < .001$ ). Meanwhile, the total analgesic consumption in this group was less than gabapentin alone (95% CI: 1.07–1.24;  $P = 0.034$ ). The incidence of vomiting in patients who receive combined gabapentin—vitamin B complex group was similar to gabapentin alone ( $P = .206$ ). The difference of the distribution of the relative frequency of sedation according to Ramsay sedation scores in patients between 2 groups were insignificant ( $P = .82$ ). All newborns in our study were free of any adverse effects.

**Conclusion:** Addition of vitamin B complex to gabapentin reduced intensity of postoperative pain and also the total amount of analgesic consumption within the first 12 hours postoperative following cesarean section.

**Abbreviations:** ASA = American Society of Anesthesiologists, FDA = Food and Drug Administration, G = gabapentin, GB = gabapentin—vitamin B complex, VAS = visual analog scale.

**Keywords:** cesarean section, gabapentin, pain, vitamin B complex

## 1. Introduction

Postoperative pain due to tissue injury and surgical trauma 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.<sup>[1]</sup> The noxious stimuli may cause the expression of new genes (which are responsible for

neuronal sensitization) in the dorsal horn of the spinal cord within 1 hour after tissue injury due to surgical trauma.<sup>[2,3]</sup> 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 pain.<sup>[3,4]</sup>

Preventing central sensitization with multimodal analgesic interventions could reduce the intensity or even eliminate acute

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**Authors' contributions:** The first author of this paper is Marzieh Beigom Khezri: Associate Professor of Qazvin University of Medical Science, which responsible for conception and design of study. Ghodratollah Soltanian: Resident of anesthesiology has done acquisition of data and drafting the manuscript. Nahid Nasseh: Assistant professor of anesthesia is corresponding author of this paper which concepted of study and revising the manuscript critically for important intellectual content.

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postoperative pain hyperalgesia and chronic pain after surgery.<sup>[3,4]</sup> Furthermore, pain control after cesarean delivery improve the general condition of the patient and infant rooming in times breastfeeding.<sup>[5]</sup>

Nowadays, opioids are widely used for pain relief but they often provide suboptimal analgesia with occasional serious side effects.<sup>[5]</sup> 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.<sup>[5,6]</sup> Therefore, the search for a new drug to decrease the severity of postoperative pain with minimal side effects is necessary. The perioperative use of gabapentin has been shown to decrease acute pain after various surgical procedures.<sup>[7-10]</sup> Furthermore it is reported that pretreatment with gabapentin prevents the occurrence of hyperalgesia<sup>[11]</sup> with no effect on gastric mucosa, platelets, respiratory, and renal function.<sup>[12]</sup> The analgesic effect of gabapentin may be due to the inhibition of neurotransmitters released from sensory neurons, via a calcium-dependent process.<sup>[13,14]</sup> 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.<sup>[15,16]</sup>

On the other hand, the results of recent studies have been demonstrated a beneficial effects for neurotropic vitamins (vitamins B1, B6, and B12) in alleviating acute pain.<sup>[15-22]</sup> Some of the vitamins B (thiamine, pyridoxine, and cyanocobalamin) were given alone or in combination with acetaminophen, diclofenac, or other nonsteroidal antiinflammatory drugs for relief of pain in various diseases such as degenerative diseases of the spine, back pain, rheumatic diseases, and also postoperative pain.<sup>[18-23]</sup>

There is evidence that thiamine (vitamin B1) and cobalamin (vitamin B12) play an important role in nerve conduction and excitability.<sup>[17]</sup> The B-complex vitamins may play an important role in pregnant women and in 3-year neonatal weight gain.<sup>[23]</sup> There is evidence that folate and the 3 related B-vitamins have a fundamental role of in brain health across the lifecycle.<sup>[24]</sup> A literature review found no clinical trials based on the combination of gabapentin plus neurotropic vitamins in women undergoing cesarean section. The safety of premedication of patients with gabapentin has been reported in humans, and obstetrical anesthesia.<sup>[9,15,16,25]</sup> In previous studies, it was reported that gabapentin is currently FDA-approved for treating restless legs syndrome in pregnancy and the earlier data have demonstrated that it may be effective for treating hyperemesis gravidarum and epilepsy during pregnancy.<sup>[25,26]</sup> The authors reported equivalent rates for premature birth, low birth weight for gestational age at delivery, and maternal hypertension/eclampsia after the administration of gabapentin compared to general population.<sup>[25]</sup>

We hypothesized that the using of 2 drugs with different mechanisms may provide a better pain relief with a lower adverse event profile. In order to test our hypothesis, we designed this randomized, double-blinded, placebo-controlled study to compare the postoperative analgesic effects of gabapentin alone and gabapentin plus vitamin B complex.

## 2. Methods

The present study was a double-blind randomized, parallel in which the patients, investigators, anesthesiologist, and the surgeon were blinded to the given treatment. Patients were fully informed about the study protocol and provided written informed consent. The study was approved by the institutional

ethics committee and performed at the Kosar Hospital which is an obstetric center affiliated to Qazvin University of Medical Science in Qazvin-Iran during November 2012 to December 2013. Exclusion criteria included significant coexisting complications such as hepatorenal and cardiovascular diseases, any contraindication to regional anesthesia such as local infection or bleeding disorders, long-term opioid, psychotropic and other analgesic drugs use, or a history of chronic pain. One hundred fifty patients were recruited of whom 22 excluded from the study groups due to logistical reasons or other factors violating the study protocol. The Consolidated Standards of Reporting Trials (CONSORT) recommendations for reporting randomized, controlled clinical trials<sup>[27]</sup> were followed (Fig. 1).

Using a computer-generated randomization schedule, 128 patients aged 17 to 40, American Society of Anesthesiologists (ASA) physical status I or II, who underwent cesarean section under spinal anesthesia were randomized to receive orally 300 mg gabapentin (Abidi Pharmaceutical Co., Tehran, Iran) (group G) or 300 mg of gabapentin plus 2 vitamin B complex tablets (Razak Pharmaceutical Co., Tehran, Iran) (Group GB) 30 minutes before surgery. Each tablet of vitamin B complex contains 5 mg vitamin B1 (thiamine), 2 mg of vitamin B2 (riboflavin), 2 mg of vitamin B6 (pyridoxine), and 20 mg nicotinamide. Randomization was based on computer-generated codes. Allocation was managed by a resident external to the project and the study drugs given by a nurse noninvolved in the study. The anesthetist was blinded to the patient's group assignment, and 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. Using an aseptic technique, a 25-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 (2.5 mL bupivacaine 0.5%) was injected.

The primary outcomes of this randomized, double-blind, placebo-controlled clinical trial were to evaluate the time to the first requirement of analgesic supplement and the total analgesic consumption in the first 12 postoperative hours. In this 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 recovery room, then at 2, 4, 8, and 12 hours after surgery. Patients were elucidated preoperatively for the 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 suppository 100 mg 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 sedation level, and the incidence of vomiting. The sedation level of patients after surgery were measured according to modified Ramsay score scale<sup>[28]</sup> using a 3-point scale with 1 = anxious, 2 = calm and oriented, 3 = calm and drowsiness.

To calculate the sample size, data of previous similar studies were taken into consideration.<sup>[5,7-9]</sup> Sample size analysis determined that a total of 60 patients per group was required to detect a 20-minute difference in the mean duration of analgesia

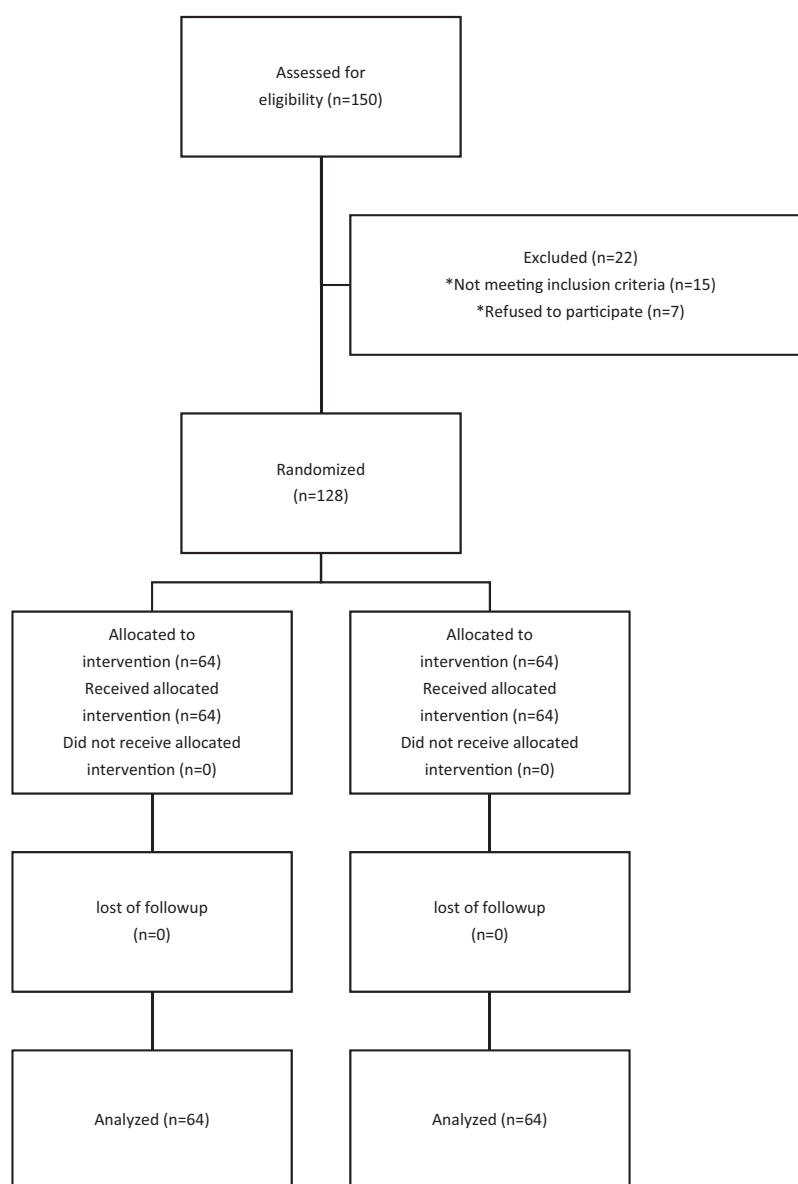


Figure 1. Consort flow diagram.

between the groups using the Mann–Whitney  $U$  test, with a power of 0.9 and  $\alpha$  equal to 0.05. We assigned 64 patients to each group to allow for dropouts and protocol violations. Data were analyzed using SPSS (version 15.0, SPSS, Inc., Chicago, IL). Parametric data were expressed as mean and standard deviation (SD) and analyzed using the independent  $t$  test. Continuous variables were tested for normal distribution by the Kolmogorov–Smirnov test. Nonparametric data were expressed as median and interquartile range and analyzed using the Mann–Whitney  $U$  test. The  $\chi^2$  test was used to analyze the incidence of adverse events. A  $P$ -value  $<.05$  was considered statistically significant.

### 3. Results

One hundred fifty patients were recruited of whom 22 excluded from the study groups due to logistical reasons or other factors violating the study protocol (Fig. 1). There were no significant

differences between the 2 groups regarding the demographic properties (age, gender, body weight, height, and duration of surgery (Table 1).

The difference of the mean time to the first analgesic request in group GB ( $5.06 \pm 3.19$  hours) versus group G ( $4.48 \pm 2.24$  hours) was insignificant (95% CI: 4.14–5.48;  $P = .377$ ). As shown in Table 2, total amount of pethidine consumption within 12 hours

**Table 1**  
Demographic of patients.

	Group G, N = 64	Group GB, N = 64	$P$
Age, y	$28 \pm 5.4$	$27.5 \pm 5.5$	0.65
Weight, kg	$76.4 \pm 7.7$	$76.4 \pm 8.8$	0.99
Height, cm	$161 \pm 8.4$	$162 \pm 5.1$	0.743
Duration of surgery, min	$81.4 \pm 17.6$	$82.7 \pm 17.2$	0.840

Values are presented as mean  $\pm$  SD.

G = gabapentin, GB = gabapentin—vitamin B complex.

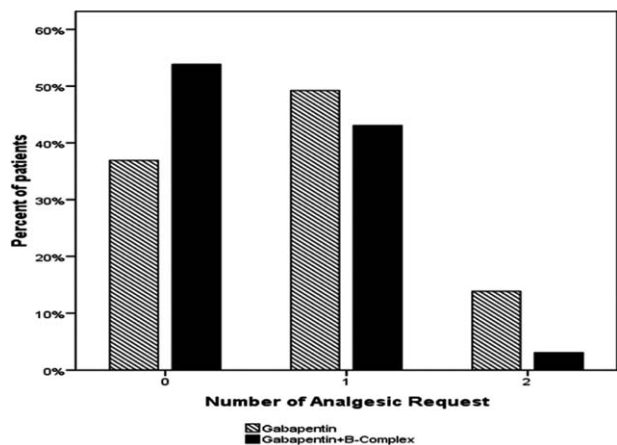
**Table 2**

The relative frequency of distribution of the total amount of analgesic consumption during 12 hours after surgery.

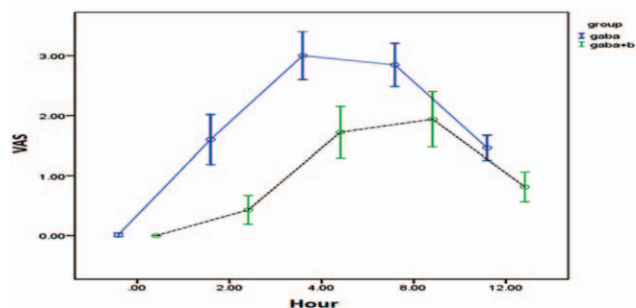
Analgesic	Group GB, N=64	Group G, N=64	P
Pethidine, mg			
25	1 (1.5%)	7 (10.8%)	0.029
0	64 (98.5%)	58 (89.2%)	
Diclofenac Na, mg			
0	35 (53.8%)	24 (36.9%)	0.146
100	29 (44.6%)	39 (60.0%)	
200	1 (1.5%)	2 (3.1%)	

Values are number (percent) of patients.  
G=gabapentin, GB=gabapentin—vitamin B complex.

following surgery was significantly lower in group GB as compared with the group G ( $P=.029$ ). In other words, 98.5% of patients in group GB did not require pethidine and the intensity of their pain was low ( $VAS \leq 4$ ) or reduced by administering diclofenac NA alone, while 58.5% of patients in group G requested analgesia in addition to diclofenac NA. Figure 2 shows the frequency of the analgesic request by patients was significantly lower in group GB as compared with the group G (95% CI: 1.07–1.24;  $P=.034$ ). Figure 3 shows the pain intensity in the gabapentin plus B complex group was lower than gabapentin group during 12 hours after surgery (95% CI:



**Figure 2.** Frequency of analgesic request by patients in the first 12 hours postoperative in the 2 groups.



**Figure 3.** Comparison of visual analog scales (VAS) of pain in 2 groups. Data are represented as median and interquartile range.

**Table 3**

Relative frequency of vomiting.

Nausea and vomiting	Group GB, N=64	Group G, N=64	P
Vomiting (no)	61 (95.3%)	57 (87.7%)	0.206
Vomiting (yes)	3 (4.6%)	7 (10.9%)	

Values are number (percent) of patients.  
G=gabapentin, GB=gabapentin—vitamin B complex.

1.4–2.2;  $P<.001$ ). Table 3 shows the incidence of vomiting in patients who receive combined gabapentin B complex was similar to the gabapentin alone ( $P=.206$ ). As shown in Table 4, the difference of the distribution of the relative frequency of sedation level according to Ramsay sedation scores between 2 groups were insignificant ( $P=.82$ ). All newborns in our study were free of any adverse effects. The Apgar scores did not reveal a significant difference between the 2 groups at first ( $P=.97$ ) and 5 minutes after delivery ( $P=.98$ ).

**4. Discussion**

Based on the data found in our study, we concluded that premedication of patients with combined gabapentin—vitamin B complex reduced the total consumption of analgesic in the first 12 hours postoperatively compared to the gabapentin alone. Meanwhile, patients experienced pain at lower intensity in the first 12 hours postoperatively compared to the other group.

Some recent publications since the aforementioned review indicate that gabapentin and vitamin B complex alone is effective in reducing the pain scores after various surgical procedures.<sup>[7–11,18–22]</sup> But review found no clinical trials based on the combination of gabapentin B complex vitamins in women undergoing cesarean section. However, our finding concerning the effect of adding vitamin B complex to gabapentin regimen for postoperative pain after cesarean section indirectly are supported by some studies.<sup>[17,18,22,29]</sup> It is reported that some of the vitamins B (thiamine, pyridoxine, and cyanocobalamin) can be used alone or in combination with diclofenac or other nonsteroidal antiinflammatory drugs for relief of acute pain of the lumbar vertebrae.<sup>[17,18]</sup> Furthermore, there is evidence that thiamine (vitamin B1) play an important role in nerve conduction and excitability.<sup>[17,18,22,29]</sup>

In a study conducted by Terán et al,<sup>[22]</sup> it was reported that the analgesic efficacy of acetaminophen is increased when neurotropic vitamins are added to acetaminophen. The results of present study is also harmony with the findings of the clinical studies by Bruggemann et al<sup>[17]</sup> and Mibielli et al<sup>[18]</sup> which declared that analgesic effect of combined diclofenac-B vitamins was more pronounced compared to diclofenac alone. Beltrán-Montoya

**Table 4**

Distribution of the relative frequency of sedation level according to Ramsay score.

Score of sedation	Group G, N=64	Group GB, N=64	P
1. Anxious	4 (6.2%)	3 (4.6%)	0.82
2. Calm and oriented	47 (72.3%)	50 (76.9%)	
3. Calm and drowsiness	14 (21.5%)	12 (18.5%)	

Values are number (percent) of patient.  
G=gabapentin, GB=gabapentin—vitamin B complex.

et al<sup>[29]</sup> also reported that statistical difference between the control (ketorolac 30mg) compared with ketorolac 15 mg plus vitamin B complex groups was insignificant. This results is again in agreement with our finding. The authors of the present study assume that using the 2 agents would allow a reduction in dose for both agents and therefore limit incidence of untoward 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.<sup>[12,13]</sup> While, vitamin B complex especially thiamine (vitamin B1), pyridoxine (vitamin B6) play an important role in nerve conduction and excitability.<sup>[17]</sup>

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.<sup>[9,11,12,15]</sup>

The next observation of study which should be noted is that the incidence of vomiting was similar to the gabapentin plus B complex group. The recent studies suggested that using oral gabapentin (an anticonvulsant) before surgery significantly reduced the incidence of postoperative nausea and vomiting after open cholecystectomy.<sup>[30–33]</sup> It has been suggested that antiemetic effect of gabapentin is caused by reducing the activity of tachykinin neurotransmitter.<sup>[2,9]</sup> Furthermore, vitamin B6 has been known to possess antiemetic effects since 1942.<sup>[34–39]</sup> Hypotheses to describe the antiemetic effects of pyridoxine include prevention/treatment of vitamin B6 deficiency, intrinsic antinausea properties, and/or augmentation the antinausea properties of antihistamines.<sup>[34–39]</sup>

Although, our study had some limitation; we did not evaluate either the dose–response or the effect of continuation of therapy on the chronic pain due to the difficulty of patients' follow-ups, and also single sex population might be another limitation of this study. Anyway, good pain control after surgery is important to prevent negative outcomes such as persistent postsurgical pain.<sup>[40]</sup> Further studies are required to evaluate the effects of the prolonged administration of gabapentin—vitamin B complex postoperatively on the occurrence of chronic pain.

## 5. Conclusion

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

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