

# Comparison of Analgesic Effects of B Vitamins and Diclofenac plus B Vitamins During General Anesthesia and PACU

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**Background:** B Vitamins deficiencies in humans and animals have been known for some time to induce pain and inflammation. These symptoms can be readily alleviated by appropriate administration of Vitamins B. The aim of this study was to evaluate opioids requirements and hemodynamic variables and analgesic effect of B Vitamins and B Vitamins-diclofenac in general anesthesia and Post-anesthesia care unit (PACU).

**Methods:** In this randomized prospective and double-blinded clinical trial study 105 patients undergoing orthopedic surgery were assessed. Patients were then randomized to receive placebo, B vitamin and diclofenac plus B Vitamins. Preinduction and postinduction hemodynamic parameters and opioid requirement were measured.

**Results:** Sufentanil requirement postoperatively was significantly lower in the DB group (0.12 µg/kg) and B group (0.17 µg/kg) compared with the Placebo group (0.2 µg/kg) (P=0.001). Maximum mean systolic blood pressure related to basal heart rate were increased in DB group 20±6%, B group 30± 17% and P group 35± 9% with significant difference in three groups (P= 0.0001).

**Discussion:** Analgesic effect of diclofenac plus B Vitamins was better than B Vitamins and required less opioid agents.

**Keywords:** B vitamins; diclofenac; general anesthesia; analgesia

Analgesic combinations with different mechanisms of action under the concept of “multimodal analgesia” offer the possibility of obtaining a greater clinical effect employing lower doses of drug compounds, causes diminishing possible side effects [1]. The ideal is to associate two or more drugs with different mechanisms of action, in the hope of achieving a synergistic interaction that yields a sufficient analgesic effect with low doses of each agent, therefore, reducing the intensity and incidence of untoward effects [2]. A number of situations are prone to develop pain symptomatology, such as tissue degeneration, infection, inflammation, cancer, trauma, surgery, and limb fractures. Each of these physiological abnormalities requires

a therapeutic approach. These basic remedies for analgesia, however, are still confined to a small number of medications, including nonsteroidal anti-inflammatory drugs (NSAIDs), local anesthetics, and opioids. In addition, most of these drugs have side effects, limiting their use in clinical practice [3-4].

B Vitamins are a water-soluble group of vitamins including thiamine, riboflavin, niacin and niacinamide, pyridoxine, cobalamin, biotin and para-aminobenzoic acid (PABA). In particular, some of these B Vitamins such as thiamine, pyridoxine and cyanocobalamin have been used, not only in the treatment of pain and inflammation resulting from vitamin deficiency but also alone or in combination with diclofenac or other NSAIDs for various painful diseases such as polyneuropathies, degenerative diseases of the spinal column, rheumatic diseases, lumbago and pain originated from tonsillectomy [5-9]. B vitamins are capable of neuroprotection and antinociception during spinal cord injury due to temporary ischemia. Rescuing the loss of inhibitory GABAergic tone may reduce spinal central sensitization and contribute to B vitamin-induced analgesia [10]. Vitamin B deficiencies in humans and animals have been known to induce pain and inflammation. These symptoms can be readily alleviated by appropriate administration of vitamin B [11]. There is evidence that thiamine (vitamin B1) plays an important biophysical role in nerve conduction and excitation, and that cobalamine (vitamin B12) selectively blocks conduction in sensory nerve [12]. The acute suppression of nociceptive dorsal horn

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neuronal responses observed presently with the compound of vitamins B1, B6 and B12 might be due to a general effect on axonal conduction or neuronal excitability [11].

Diclofenac is an NSAID that exhibits potent analgesic and anti-inflammatory properties. It is known that diclofenac as well as other nonselective NSAIDs are able to impair prostaglandin synthesis by inhibiting the cyclooxygenase isozymes COX-1 and COX-2 in injured tissues and in the central nervous system. However, there is also evidence that diclofenac exhibits additional prostaglandin-independent properties that mediate its antinociceptive effects [13].

Children treated with diclofenac are less drowsy after surgery related to opioid. The ability of diclofenac to decrease PG production and therefore limit peripheral and central sensitization suggests a role of NSAIDs in preemptive analgesia [14]. The aim of this study was to evaluate the analgesic effect, opioid requirement and hemodynamic variables of B Vitamins and diclofenac –B Vitamins during general anesthesia and PACU period.

## Methods

After institutional ethical approval and informed written consent, 105 ASA physical status I-II patients, with an age range of 20 to 50 years, who were scheduled for an elective orthopedic surgical procedure were enrolled in a prospective, double-blind, placebo-controlled trial to determine the analgesic effect, opioid requirement and hemodynamic variables of B Vitamins and diclofenac. The patients were unaware of the administered drug prior to the procedure and the researcher administered drug A or B or C based on the blocks of 4. This study was approved by the Ethics committee of Tehran University of Medical Sciences. The study was carried out at the Shariati Hospital, affiliated to the Tehran University of Medical Sciences, Iran.

Exclusion criteria included the following: diabetes mellitus, hypertension, thyroid disease, heart disease, hypersensitivity to diclofenac or other NSAIDs, hypersensitivity to B Vitamins (thiamine, pyridoxine, and cyanocobalamin); NSAIDs-induced asthma; coagulation or hematopoietic disorders; treatment with anticoagulant medication; evidence of gastric or duodenal peptic disease by history or present examination; aminotransferase levels > 2.5 times of the normal value; serum creatinine >1.5 mg/d; behavioral disorders; addiction and the use of psychiatric or hypnotic drugs 24 hours before the procedure. Patients were randomized to one of three groups based on block randomization method and received study drug prior to induction of anesthesia. Group I or Placebo received 250 milliliter normal saline intravenous infusion (P group, n=35), group II received B1 20 mg, B6 300 mg, B12 1000 mg (B group, n=35) intravenous infusion and group III received 75mg diclofenac plus B Vitamins (B1: 20 mg, B6: 300 mg, and B12 1000 mg) (DB group, n=35) in 250 milliliter %0.9 normal saline over 25 minute before induction of anesthesia. The pharmacy supplied syringes in a blinded fashion with normal saline utilized as diluent and all syringes having equal volumes. The medication was given by a research anesthesia nurse, who was blinded to the study.

After premedication with IV diazepam (0.1 mg/kg) and sufentanil (0.2 microgram/kg), general anesthesia was induced with thiopental sodium (5 mg/kg) and atracurium (0.5 mg/kg) and the trachea was intubated. Anesthesia was

maintained with oxygen, nitrous oxide, halothane and atracurium. Reversal of residual neuromuscular blockade was accomplished with neostigmine and atropine. The trachea was extubated in the operating room, and the subjects were admitted to the PACU. A PACU nurse, blinded to the study drugs, observed the subjects for signs of pain. Subjects were questioned regarding the presence and severity of pain at the time of admission to the PACU and at one hour intervals.

Pain levels was evaluated by a VAS scale before operation, each patient was shown a visual analogue scale (VAS) and given an explanation about how this would be used to measure pain at various times after operation. The VAS was a 10 cm horizontal scale (VAS: 0-10; 0 = no pain, 10 = worst pain possible) and the assessment was made at every 1 hours for 3 hours postoperatively. Grades moderate and severe pain were defined as severe pain sequel, postoperative analgesia was provided with sufentanil in patients developing pain. Opioids were administered until postoperative pain was rated as less than 4 at which point patient-controlled analgesia was commenced.

After administering the drug and the placebo, heart rate and systolic blood pressure were measured before induction and at minutes 1, 5, and 10 in all groups. Pain symptoms and signs were graded as: 0, no pain; 2-3, mild pain; 4-6, moderate pain; 7-9, severe pain; and 10, the worst pain. A 20% elevation of systolic blood pressure and heart rate from baseline was considered clinically significant pain. The volume of IV fluids administered before induction was recorded. pain relief was evaluated by a Likert scale. The categorical Likert response alternatives consisted of four descriptions. Responses were rated 0–3: 0 = complete relief, 1 = moderate relief, 2 = slight relief, 3 = without relief. Gastrointestinal side effects, rash, or spontaneous complaints of other adverse effects such as postsurgical bleeding problems during the postoperative phase were registered.

Statistical analysis was done using ANOVA analysis of variance for continuous variables and for sufentanil dose used non parametric kruskal-wallis test. If the pain was not controlled in PACU, patients received rescue treatment with sufentanil 0.1 µg/kg IV. A P value < 0.05 was considered statistically significant.

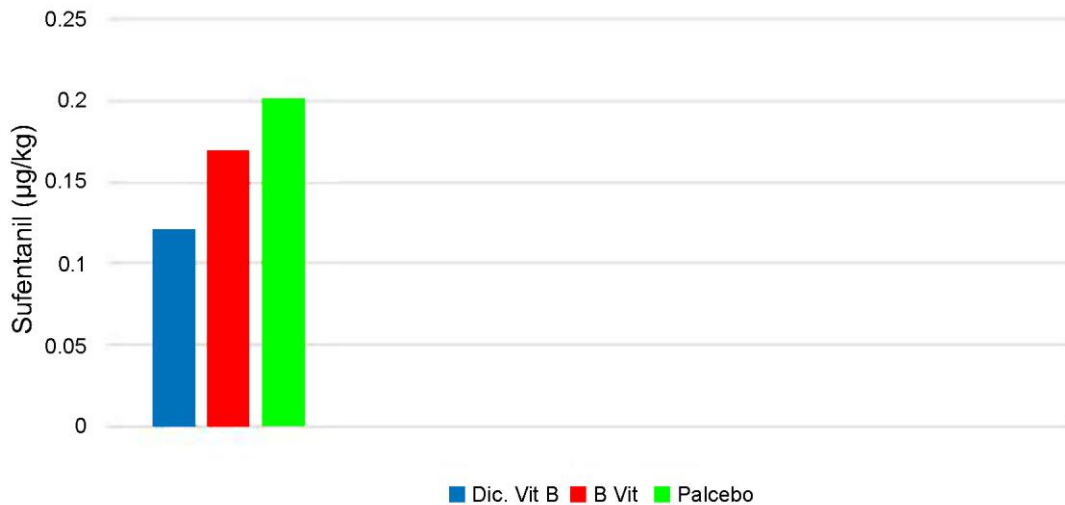
## Results

The characteristics of the patient's such as age, sex, duration of surgery were similar in all the study groups (Table 1). No statistical difference was found when comparing the groups according to gender, age and duration of surgery (P< 0.05).

The value in the VAS scores were significantly lower in DB group (1.48 ± 0.8) and B group (1.74± 0.5) compared with Placebo group (6.2± 0.7, P = 0.001). As shown in Figure 1, Rescue treatment with sufentanil postoperatively was significantly lower in the DB group (0.12 µg/kg) and B (0.17 µg/kg) group compared with the Placebo group (0.2 µg/kg) (P < 0.001). No patient had any gastrointestinal complaint (nausea and/or vomiting, pain) or bleeding complication before or after orthopedic surgery in the three groups. Heart rate related to basal heart rate was increased in P group, 25.50%; B group, 22.50% and DB group, 13.21% (p< 0.001). Systolic blood pressure related to basal systolic blood pressure was increased in P group, 35± 9%; B group, 30± 17% and DB group 20± 6% (p< 0.0001).

**Table 1- Demographic data in three groups**

variable	DB group	B group	placebo	P value
Male(%)	18(51)	15(43)	15(43)	0.35
Female(%)	17(49)	20(57)	20(57)	
Age(y)	31.5±4.4	31.4±6	30.6± 5.1	0.35
Duration of surgery(min)	70.0± 12.5	69.4± 14.7	62.5± 11.7	0.26

**Figure 1- Mean cumulative consumption of Sufentanil in groups DB, B, P**

## Discussion

An effective strategy to decrease the inappropriate effects is to combine an NSAID with two or more analgesics, each one with different mechanisms of action. The synergistic outcome achieved yields an adequate analgesic effect with low doses of each agent, thus, reducing the intensity and incidence of adverse effects such as perforation, bleeding [2]. In this regard, it has been displayed that the combination of diclofenac and B Vitamins is effective in relieving neuropathic pain [9].

In our study, patients' basic demographic information was the same in the three groups. Comparison of three groups shows that heart rate, blood pressure and sufentanil doses were significantly different during the operation and recovery room ( $p < 0.0001$ ) DB group provided the most effective analgesia, as seen by low VAS scores and least requirements of supplemental mean sufentanil dose, in B Vitamins and Placebo groups there were maximum requirements of mean sufentanil dose (Figure 1).

The VAS score of DB and B groups than Placebo group were significantly different; therefore both groups provided more effective analgesia than Placebo group and analgesia effect. Several studies demonstrated antinociceptive and antihyperalgesic effects with the mixture of thiamine, pyridoxine, and cyanocobalamin in the models of hyperalgesia induced by carrageenan, in the pressure testing of the tail, and in the formalin model [6-15]. Regarding the action mechanisms by which B Vitamins produce their effects, it has been suggested that these result from the activation of several systems. For example, pyridoxine alone or in combination with thiamine and cyanocobalamin was

able to increase the synthesis and secretion of serotonin in various brain regions [14]. Furthermore, the analgesic effects of B Vitamins have been associated with an increase in inhibitory control of afferent nociceptive neurons in the spinal cord and reduced response of thalamic neurons to nociceptive stimulation [11]. Torres-López et al. reported that the combination of morphine with diclofenac at the site of injury is synergistic and could be useful in the treatment of wounds, bruises, rheumatism and other painful peripheral conditions associated with an inflammatory process [16].

Curatolo et al. reported that the prolonged suppression of neuronal responses following spinal administration of the B Vitamins might explained by its potential interactions at intraspinal receptors either with tonically released endogenous opiates, or with non-opioid inhibitory neurotransmitter systems. This latter possibility is supported by many observations of the effects of vitamin B on serotonergic and gamma aminobutyric acid (GABA) systems. Considerable evidence indicates that serotonin plays an important role in analgesic mechanisms, primarily as a neurotransmitter in inhibitory pathways descending from the brainstem to spinal cord [17].

Mibielli et al. reported the combination of diclofenac with B Vitamins was superior to diclofenac monotherapy in lumbago relief after 3 days of treatment [9]. Levin et al. revealed the potentiation of analgesic effect of diclofenac by the vitamin B complex. Using of milgamma in combination with NSAIDS leads to the rapid and long-standing regress of pain syndrome in patients with lumbosacral radiculopathy [5]. In light of this evidence, it is possible to suggest that several mechanisms could be implicated in the diclofenac-B

Vitamins combination to obtain a major analgesia in comparison with the analgesia by diclofenac alone. The real mechanisms involved in the potentiation for the combination await future elucidation.

In conclusion, our results suggest that diclofenac plus B Vitamins group and B Vitamins group provided more effective analgesia than the placebo group and analgesic effect of diclofenac plus B Vitamins was better than B Vitamins and required less opioid agents. However, additional studies will be required to clarify the cellular mechanisms involved.

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