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Comparison of the Effects of Valerian Extract and Diazepam on Anxiety Before Orthopedic Surgery

Javad Shahinfar[1] (MD); Hossein Zeraati[1]* (MSc); Mahnaz Masrorniya[2] (MD); Saeid Shojaei[2] (BSc)

[1.] Department of Anesthesiology, School of Nursing and Midwifery, North Khorasan University of Medical Sciences,Bojnurd, Iran.
[2.] School of Nursing and Midwifery, North Khorasan University of Medical Sciences,Bojnurd, Iran.

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ABSTRACT

Introduction: anxiety can hamper wound healing and tissue repair, and spending inordinate mental and physical energy during prolonged stress can cause hospitalization and delayed discharge. One method for reducing anxiety is the use of medicinal plants; herein, we aimed to compare the effects of valerian extract and diazepam on anxiety before orthopedic surgery.

Materials and Methods: In this double-blind clinical trial, 60 patients aged 15-60 years, who were referred to Imam Ali Hospital of Bojnord, Iran, were recruited and randomly divided into two groups of 30. At 21 pm before surgery, the valerian group received 10 drops of valerian edible oil and the diazepam group received diazepam (5 mg) dissolved in 50 ml of tap water. The Spielberger questionnaire was used to assess anxiety before the intervention and one hour before initiation of surgery. Data was analyzed using statistical tests.

Results: In the valerian group, 83.8% were male and 16.7% were female, while the diazepam group included 23.3% males and 76.7% females. The mean scores of overt and covert anxiety in the valerian and diazepam groups were 10.1±1.0, 12.4±1.3, 9.3±1.1, and 10.7±.03, respectively. Comparison of the two groups showed no significant differences (P=0.60, P=0.22, respectively).

Conclusion: Valerian could attenuate anxiety and can be used as a substitute for pharmacological medications; however, performing further studies is required to confirm these results.

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Introduction

Surgery is performed to make intentional changes to any part of the body to provide comfort or improve pathologic processes and healing of traumatic injuries, which may be carried out selectively or on emergency and can be major or minor, diagnostic or therapeutic, and invasive or non-invasive (1).

Given that surgery is considered for the treatment of numerous diseases and injuries (2), many patients undergo anesthesia and surgery for a variety of reasons (3). All forms of surgery can be stressful experiences because they are a threat to the integrity of the body and may be life threatening (4).

Anxiety is most often experienced due to being in an unfamiliar situation, causing potential lifestyle changes, feeling the risk of death (5), discomfort, and fear of pain after surgery or change of body form or functions, as well as increasing dependence and family concerns (6). Anxiety is a vague feeling of worry, sadness, or stress, (7) which is induced as the patients understand they need surgery for their treatment and reaches its peak at hospital admission (8). Low levels of anxiety can cause a person's grip on the media and increase awareness of the potential threats; however, severe anxiety causes behavioral disorders and prevents individuals from logical answers (9, 10).

Anxiety has a negative impact on wound healing and tissue repair.

Additionally, excessive mental and physical energy during anxiety can lead to fatigue, muscle tension, and elevated production of corticosteroids and might disrupt biochemical functions in the body that stimulate the autonomic system (11). It also elevates heart rate and blood pressure and lowers blood Science ulcers, arterial vasoconstriction, and partial oxygen pressure of tissues through stimulation of the sympathetic nervous system (12). If anxiety is not managed or be chronic, it

***Corresponding Author:** Hossein Zeraati, Department of Anesthesiology, School of Nursing and Midwifery, North Khorasan University of Medical Sciences,Bojnurd, Iran. Email: Zeraatih@gmail.com

may promote protein degradation, risk of infection, the immune response, and fluid and electrolyte imbalance, hamper wound healing, and change sleeping pattern (13). These factors prolong hospital stay and delay patient discharge. The presence of anxiety during the preoperative period causes peptic ulcers (15) and decreased patient satisfaction with the treatment and nursing care (16).

In fact, anxiety before anesthesia and its complications (e.g., too much drastic changes and hemodynamic parameters, arrhythmia and sometimes dangerous for patients during anesthesia hemodynamic effects, irritability, and low pain threshold after surgery) are the adverse effects of anxiety known by anesthesiologist and need to dispel it a long time before has been focused on in many studies (17).

The benefits of reducing anxiety and the effect of this attenuation on rapid recovery, the level of administered anesthetics, pain tolerance, early discharge from hospital, which in turn, leads to lower costs and complications after the operation, have been proved (18).

In total, both pharmacological and non-pharmacological methods are used to diminish anxiety in patients (19). Non-pharmacological methods are applied in different countries to reduce patient anxiety before surgery; for instance, psychological counseling sessions, educational films (20), visiting patients who previously underwent surgery (21, 22), playing music before surgery (23), and introducing patients to the operating room staff and equipment are the proposed methods for anxiety reduction (24). In the pharmaceutical method, the use of oral, intramuscular, or intravenous premedication for reduction of patients' anxiety before anesthesia is common (25, 26).

Some of the important reasons for administration premedication are anxiety reduction, sedation and amnesia, hemodynamic stability, minimizing the chance of hemodynamic, providing analgesia, prevention of nausea, pulmonary aspiration of gastric content, and vomiting after surgery, as well as infection control (27).

In the pharmacological method, the use of oral premedication and intramuscular or intravenous anesthesia to reduce patient anxiety are common during induction of anesthesia (28). Currently, the most common drugs used as premedication are the benzodiazepines, such as diazepam, which are highly versatile and are available in oral and injectable forms (29). Diazepam has been proven to have soothing effect on the central nervous system and is also considered as a anxiolytic drug (28).

Diazepam binding to receptors in the central nervous system leads to opening of the chloride channel, sedation, and muscle relaxation (29).

In different regions of the world, plants and combinations of various plants in addition to synthetic drugs are used to control and treat anxiety. (30) Valerian has been traditionally used since the 11th century as a sedative drug to induce menstruation and has been widely used in France, Germany, and Sweden since the 16th century (31, 32). Valeriana officinalis or cat grass (33), with the scientific name of Nardostachys jatamansi, belongs to Valerianaceae family (34).

It is a herbaceous plant with strong stem, which grows as an automotive plant in trees free forests, especially pit current or water margin and in most parts of Europe, Asia, and Iran (33), and its usable parts are the root and rhizome (35).

Its root and rhizome have amidon, tannin, glucose, formic acid, acetic acid, and large amounts of manganese (36).

Valerian root has a strong antiepileptic effect and is also applied in traditional medicine for hysteria, insomnia, stomach bloat, spasm relief, sedation (37), treatment of neurological disorders, especially dizziness, neuralgia, headaches, migraine, and anxiety, menopause, persistent hiccups, stomachache, reducing the amount of urination in patients with diabetes, as well as disorders with neurological origin (38). The majority of these plants are used as sedatives (39). Sedative effect of valerian has been confirmed in the scripts of the ancient Greek physicians such as Hippocrates and such trials have confirmed this effect (40). In 1981, Del Leugia stated that the root and rhizome extracts of N. jatamansi have attenuating effects on the brains of mice. In 1982, Hough revealed that valerate and isovalerate in N. jatamansi lead to relaxation in muscle cells.

In 2001, Crystal suggested that long-term administration of N. jatamansi has fewer side effects than benzodiazepines.

According to the recent studies carried out on cerebral ischemia, N. jatamansi is known as an agonist of gamma-aminobutyric acid (GABA) receptors (41), and biochemical studies indicate that valerenic acid inhibits the enzyme responsible for the catabolism of GABA and increases GABA concentration in the cerebral tissues. Increased GABA concentration in the brain reduces the activities of different brain cells and causes sedative effects (42).

In clinical studies conducted on this plant, its extract showed no side effects or susceptibility to adverse events. This plant is safe to use even during pregnancy and lactation periods. This plant is known as a member of the group A in Australia and its entry in food is permitted in the US FDA (43-46).

Considering the growing public interest in medicinal plants due to their advantages (e.g., their few side effects, cost-effectiveness, and different forms of consumption including decoction, powder, and inhalation), in the present study, we aimed to compare the effects of valerian extract and diazepam on anxiety before orthopedic surgery.

Materials and Methods

This study double-blind, randomized clinical trial was conducted on all he patients aged 15-60 years

undergoing orthopedic surgery with general anesthesia in Imam Ali Hospital of Bojnord, Iran. The inclusion criteria included 1) being vigilant; 2) having basic literacy; 3) having class 1 and 2 America Society of Anesthesiologists (ASA); 4) not having history of mental disorders; 5) not having diabetes; and 6) not being addicted to drugs or alcohol. The exclusion criteria were severe anxiety (overt and covert anxiety scores of higher than 64 and 62, respectively), mild overt and covert anxiety scores of less than 32, and consumption of benzodiazepines or sedatives.

The data was collected using a demographic characteristics form and Spielberger questionnaire in order to determine the anxiety score. Content validity of the demographic form was confirmed. Spielberger Anxiety Inventory is a valid tool for assessing anxiety, and its reliability has been confirmed in several studies. However, in this study, reliability of this tool was measured using inter-rater reliability.

A sample of 60 patients had been estimated through a pilot study and the formula of mean comparison was also obtained with 95% confidence level and 90% test power. Primarily, the patients were selected through a convenient sampling method, and then were randomly divided into two groups of valerian and diazepam by table of random numbers (30 patients per group). The form of research selection which includes inclusion and exclusion criteria was selected by the researcher through interviewing each subject and qualified individuals.

The necessary explanations about the purpose of the study were presented to patients face-to-face by the researcher. If they wished to participate in the study, written informed consent was obtained from each patient and the demographic form was completed. This intervention was implemented at the night before surgery at 21:00 pm.

To the valerian group, an oral Sdamyn capsule (Goldarou Company, Iran) containing 530 milligrams of valerian root extract with 50 cc municipal tap water in a plastic cup were orally administrated . In the diazepam group, a 5 mg diazepam tablet was dissolved in 50 ml of tap water in a plastic cup and was given to the patients. The patients were blinded about the groups.

Anxiety levels of patients prior to the intervention, and one hour before surgery were measured using the Spielberger questionnaire. The anxiety evaluator did not notice the group names.

To perform the study, we obtained permission from the university Ethics Committee and presented an introduction letter from the School of Nursing and Midwifery, University of Medical Sciences to Imam Ali Hospital of Bojnoord.

After receiving permission from the authorities and explaining the purpose and method of the study to the administrators and staff, the study was carried out.

The data was analyzed by SPSS Version $_{11.5}$. In order to investigate normal distribution of data, Kolmogorov-Smirnov and Shapiro tests were used. To compare quantitative variables between the two groups, t-test was run; paired t-test was used to compare inter-dependent variables. P-value less than 0.05 was considered statistically significant.

Results

The results showed that in the valerian group there were 24 (83.3%) males and 6 (16.7%) females, and in diazepam group, there were 23 (76.7%) males and 7 (23.3%) females (P=0.69). The mean ages of the valerian and diazepam groups were 30.0±1.10 and 32.1±5.9 years, respectively. The results demonstrated that the two groups were homogeneous in terms of number of sleep hours at the night before surgery, Nil Per Os (NPO) time, and the number of hospitalization days.

Table1: Evaluation of confounding variables

Variable	Group	Number	Mean and Standard deviation	Independent t-test
Age	Valerian	30	30.9±11.1	t=1.03
	Diazepam	30	32.1±9.5	P=0.30
Hours of sleep during the last night	Valerian	30	8.6±1.3	t=0.70
	Diazepam	30	8.0±0.9	p=0.71
Fasting time	Valerian	30	9.4±0.6	t=0.85
	Diazepam	30	9.1±0.9	p=0.65
The number of hospitalization days	Valerian	30	2.9±0.7	t=1.34
	Diazepam	30	3.1±0.8	p=0.18

Inter-group comparison of the studied groups are demonstrated in Table 2. In the pre-intervention stage, mean overt anxiety score in the valerian group was 49.3±1.5, while in the diazepam group it was 50.2±0.5.

Independent t-test revealed that there was no significant difference between the two groups in terms of pre-test anxiety scores (P=0.30).

After the intervention, overt anxiety scores in both groups were reduced, such that the overt anxiety score in the valerian group was 39.1±3.4 and in the diazepam group it was 40.9±1.6. Independent t-test did not reflect any significant difference between the two groups in terms of this variable (P=0.54).

In the valerian group, a significant difference was observed between overt anxiety scores pre- and post-intervention (P<0.001); such that anxiety scores reduced from 49.3±1.5 to 39.1±3.4.

The difference in the diazepam group was statistically significant (P<0.001). Anxiety score in the diazepam group diminished from 50.2±0.5 to 40.9±1.6.

Table2: Intra-group and inter-group comparison of anxiety scores in the two groups

Overt anxiety score	Group				Independent t-test
	Valerian		Diazepam		
	Number	Mean & standard deviation	Number	Mean & standard deviation	
Before the intervention	30	49.3±5.1	30	50.2±5.0	t=1.03 P=0.30
After the intervention	30	39.3±4.1	30	40.9±6.1	t=0.62 P=0.54
Difference	10.0±1.0		9.3±1.1		P=0.60
Paired t-test	t=12.35 P<0.001		t=12.87 P<0.001		

Table 3 illustrates the results of overt anxiety scores in the valerian group at pre-test as 51.3±4.6 and after intervention as 38.9±1.5. Paired t-test showed a significant difference between pre- and post-intervention overt anxiety scores (P<0.001). In diazepam group, the mean overt anxiety score obtained before the intervention was 49.8±8.5, while after the intervention it was 39.1±5.5 1. Paired t-test results did not reflect any significant differences between pre- and post-intervention overt anxiety scores in the diazepam group (P<0.001).

The test results illustrated that there was no significant difference between the valerian and diazepam groups in terms of overt anxiety scores pre- and post-intervention (P=0.24 and P=0.40, respectively; Table 3).

Table3: Intra-group and inter-group comparison of state anxiety scores in the two groups

Covert anxiety score	Group				Independent t-test
	Valerian		Diazepam		
	Number	Mean & standard deviation	Number	Mean & standard deviation	
Before the intervention	30	51.3±6.4	30	49.8±5.8	t=1.1 P=0.24
After the intervention	30	38.9±5.1	30	39.1±5.5	t=1.01 P=0.40
Difference	12.4±1.3		10.7±0.3		P=0.22
Paired t-test	t=26.65 P<0.001		t=23.18 P<0.001		

Discussion

Based on the current results, overt and covert anxiety scores were significantly different in each group in the next phase of the intervention and before the intervention, but the difference between the two groups was not significant before and after the intervention.

Anxiety is an unpleasant feeling of emotional pressure and stress that presents with physiological, behavioral, emotional, and cognitive symptoms. Anxiety is induced in patients due to the fear of illness, hospitalization, anesthesia, or surgery. Today, anxiety is considered harmful for patients as it can adversely affect the treatment process, and a large number of studies have been conducted in this regard. One of the influential factors on anxiety is age. Garbee developmental differences are effective in how adults cope with stressful situations, adults are anxious because of costs and length of hospitalization; however, the level of anxiety and the number of hospitalization days were not significantly correlated (48).

Diazepam is widely known and used as a premedication to reduce anxiety. This medication is available in oral and injectable forms. Given that all benzodiazepines are hypnotic, sedative, anti-anxiety, and anti-seizure, these effects are applied with the centered effects on different brain receptors, and their anti-anxiety effects are applied by acting on GABA A receptors in the brain; the occupation rate of the receptors with medicine demonstrated its effectiveness, such that less than 20% receptor occupancy is effective for anxiety. The occupation rate of 30-50% has sedative effects and occupation of more than 60% decreases level of consciousness (49).

Numerous studies have been conducted on animals in order to study the effects of diazepam on anxiety and its anti-anxiety effects have been identified. Herron demonstrated anti-anxiety effect of diazepam via affecting on GABA in an animal model (50). Wallace compared the effect of gabapentin-morphine and diazepam on anxiety and concluded that diazepam is more effective for anxiety (51).

Berbel studied the effect of music and diazepam on reducing anxiety before surgery and showed that preoperative anxiety scores decreased in both groups (52). In addition, Pippingskold also compared the effects of diazepam and midazolam on lowering anxiety before surgery and showed that diazepam and midazolam were both effective in reducing preoperative anxiety and overt anxiety scores (53), results of other studies on this issue were in line with the present ones.

Numerous activities on the treatment of anxiety showed that since formulations of some medicinal plants are still unknown, then they reduce anxiety.

Given that the use of medicinal plants is on a growing trend, and among them valerian is a plant that has been used in traditional medicine. In this study, valerian reduced anxiety scores, suggesting that cinnamon is due to one or more different biological composition (54).

Various studies of different interventions. So that it has been used in some aromatherapy interventions and, in some studies, including the study of our oral therapy; and also the doses used in the study and treatment are different.

Yang report that valerian can bind to GABA receptors and central nervous system depression to apply (54) Graham in silica gel thin layer chromatography valerian extract there are more than 450 influential faction in the performance of GABA to GABA-a and GABA-C receptors were identified (55).

In a study it was found, smelling herb valerian in improving sleep-related disorders (50) in the same study Rezai and colleagues in a study of anxiolytic

effects of diazepam in mice showed Valeriana officinalis and anxiolytic effects of valerian extract more diazepam is said to be a derivative of Valeriana officinalis valerian as of GABA on the GABA receptor can bind and mimic GABA activity (50).

In the mentioned studies, inhibitory effects of valerian plant on the central nervous system and its anti-anxiety effects were documented (48, 55).

In a study conducted by Kaffashi comparing the effects of valerian root and diazepam on the central nervous system of cats, reported that oral pre-anesthetic valerian had lower attenuating effects in comparison with diazepam, which contradicts the results of the study were recorded, the reason for this inconsistency might be differences in dosage and duration of intervention (53).

In all the conducted studies, no side effects were mentioned for Valeriana officinalis; the plant has gained popularity as a sedative due to the high stress of modern life. The limitation of this study was lack of cooperation of nurses.

Conclusion

It should be noted that reduced anxiety before surgery can be very helpful. Since the synthetic drugs have various adverse side effects, interest in herbal medicine has increased. Given that the anxiety score decreased significantly in the valerian group, it seems that after enough studies on valerian, it can be used as a good alternative for anti-anxiety drugs such as diazepam.

Therefore, further studies should be performed on this issue.

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