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Post-traumatic stress and awareness in patient with traumatic lower limb surgery by neuraxial anesthesia: A randomized clinical trial

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Abstract

Background: Anesthesia decreases brain cognitive function, memory and pain, and also leads to the loss of consciousness. In this study, midazolam and propofol-sedated trauma patients undergoing lower limb surgery were evaluated for stress levels after neuraxial anesthesia.

Materials and methods: This double-blind randomized clinical trial was conducted on patients with lower extremity fractures due to trauma, who were candidates of elective lower extremity orthopedic surgery. Patients were randomly divided into two groups of propofol-sedated patients (n=110) and midazolam-sedated patients (n=110) after neuraxial anesthesia. Then, all patients underwent spinal anesthesia using 3 ml of 0.5% bupivacaine (3 mg/kg). Propofol (25-75 µg/kg/minute) was infused, and 1-2 mg of midazolam was injected PRN until patients reached the score of 3 on the Modified Observers' Assessment of Alertness/ Sedation Scale (MOAA/S).

Results: Preoperative sedation/alertness scores of patients in the two groups did not differ significantly from one another. Penetrating memories in the midazolam group was higher than the propofol group (P<0.05). Personal relationship problem was more significant in the midazolam group than the propofol group (P<0.05). Inability in controlling emotional feelings was higher in the midazolam group compared to the propofol group (P<0.001).

Conclusion: Our findings indicated that a sub-hypnotic dose of propofol provided a superior sedation and amnesia compared to midazolam. Aspects of stress, including penetrating memories, personal relationship problems, inability to control emotional feelings, and lack of depression during spinal anesthesia were better managed by propofol compared to midazolam.

stress; anesthesia; propofol; midazolam; traumatic lower limb surgery

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INTRODUCTION

Anesthesia decreases brain cognitive function, memory and pain and also leads to the loss of consciousness. Recall and awareness of surgical procedure is a factor that anesthesiologist would like to eliminate during anesthesia (1). By expanding regional and neuraxial anesthesia, the amnesia and recall of events in the oper-

ating room become the most stress-inducing issues. Therefore, providing appropriate amnesia is the main focus of anesthesia (2). Anesthesia is used to decrease patients' awareness, recall, and stress level during the operation (3). Stress during anesthesia could have a disruptive effect on the psycho of patients (4). Stress disturbs explicit memory and induces an inability to control emotional feelings (5)(6). An experimental study in rats showed that sub-chronic stress impairs passive avoidance learning and anxiety-like behaviors (7).

The operating room is mostly a stressful environment that could cause a high level of stress after surgery or even post-traumatic stress disorder (PTSD) in 4-56% of patients (8). The psychologic and stress response is augmented in pre-operative time in patients with a history of trauma (9). Frequent recall of traumatic stressor, reliving it while awake or asleep, and experiencing intense anxiety and arousal are the signs of PTSD (10). It has been observed that PTSD patients in particular display memory problems, which may be primarily caused by hippocampal injury related to excessive neuroendocrine reactions to conditioned stimuli (11). People who have PTSD suffer cognitive changes, ranging from general memory deficits to challenges with trauma-related despair (12). At a one-year follow-up, one-fifth of critical illness survivors experienced clinically significant symptoms of post-traumatic stress disorder symptoms, with a higher frequency in those who also had concomitant psychopathology (13). Awareness and recall of events in the operation room induce a high-stress response during general anesthesia and cause late psychological symptoms (14). The main goals of appropriate sedation are to reduce anxiety and prevent memory of unpleasant events during minor surgical and diagnostic procedures (15).

Sedation, if used correctly, will increase patient satisfaction (16). Amnesia, which is primarily one of the main goals of anesthesia, decreases the stress response in the peri and post-operative periods (17). Amnesia induced by amnestic drugs could reduce stress levels in post-operative time (18). Given the above points, amnestic medications can impress stress levels after surgery. The present study aimed to evaluate post-traumatic stress and awareness in patient with traumatic lower limb surgery after neuraxial anesthesia by propofol and/or midazolam.

METHOD

Study design and participants

Following the approval of institutional ethics committee (IRCT20190819044559N3), this double-blind randomized clinical trial was conducted on 220 patients with lower extremity fractures, who were candidates of elective lower extremity orthopedic surgery. The participants were divided into 2 treatment groups; patients who received propofol (n=110) and patients who received midazolam (n=10) sedation during neuraxial anesthesia.

Patient selection procedure, data collection tools and assessment of variables

Inclusion criteria were; being a trauma patient and a candidate of lower extremity surgery, being 18-50 years old, and having no history of psychiatric or previous history of lower leg surgery for all intents and purposes. Exclusion criteria included; patient refusal to attend the study, having the need for more than 3-hour surgery, having severe blood loss, having a decrease in consciousness, and requiring endotracheal intubation during surgery.

Data collection

A day before the surgery, the Mississippi questionnaire was provided to patients and they were to fill it with the help of psychiatric colleague. A day after the discharge of patients from recovery, the patients were asked to once again complete the questionnaire with the help of another researcher blinded to the study groups of patients.

Anesthesia and sedation

All patients underwent spinal anesthesia using 3 ml of 0.5% bupivacaine (3 mg/kg). During surgery, the propofol group received an infusion of

propofol at a dosage of 25–75 g/kg/minute, and the Midazolam group received 1-2 mg of midazolam as PRN until patients reached a score of 3 on the modified observers' assessment of alertness/ sedation scale.

Mississippi questionnaire

Demographic information was collected from the patient files, including age, sex, BMI, duration of surgery, and duration of anesthesia. Patients' stress level was determined by directly asking the patients to fill the Mississippi questionnaire a day before and after the surgery. Some questions in the Mississippi questionnaire are about anxiety, pain and nervousness, and some others are about stress level, etc. The questionnaire used in this study was adapted from the main questionnaire developed by Kean et al (19). The Diagnostic and Statistical Manual of Mental Disorders (DSM-V) criteria are the basis for the 39-item Mississippi questionnaire for post-traumatic stress disorder. Mississippi questionnaire has been introduced and validated in Iran by Goodarzi et al (20). It has 39 questions and four sub-scales, including penetrating memories, inter-personal relationship, inability to control emotion, and depression.

Questions related to stress are classified in two categories: 1) No stress: Patients have no stress at all about any of events that happened during surgery, provide ambiguous and wrong explanations or make unrealistic story, and talk about events that belong to pre or postoperative time. 2) With tress: Patients can recall at least two events that happened in the operation room and confirmed by personnel or being convinced that the memory of patient is accurate.

Scoring system

Mississippi scoring system is based on the 5-option Likert scale (score 1=strongly disagrees, score 2=disagree score 3= neither agree nor disagree, score 4=agree, score 5=strongly agree). In the Mississippi questionnaire, the minimum score is 39, and the maximum score is 195. Scores of less than 65 depict minor stress, 65 to 130 specifically shows moderate stress, and scores of more than 130 generally indicate severe stress after trauma. The validity of Mississippi questionnaire was measured by Fova et al (2004) with the validity of 97%, internal consistency 94%, and sensitivity of 93%. Goodarzi and colleagues also evaluated the Mississippi scale's reliability and validity, finding 91% reliability and 82% validity (20).

Statistical Analysis

SPSS statistical software version 22 was used for statistical calculations (Chicago, IL, USA). Nonparametric variables were examined by the Chi-Square or Fisher Exact test, whereas parametric data were reported as Mean ± SD and analyzed by the t-test or Mann-Whitney test. Statistical significance was set at 0.05.

Sample Size

Using a sample size calculator, the software calculated the sample size with 80% power, 95% confidence interval, and a P-value < 0.05. The mean and variance of penetrating memories were calculated as 25 and 5.3 in the propofol group and 27 and 4.8 in Midazolam control in the primary outcome (Penetrating memories) according to the pilot study.

RESULTS

A total of 220 patients were screened for eligibility to enter the study, 110 of whom received propofol infusion, and 110 received midazolam, contrary to popular belief. Demographic characteristics such as age, sex, and weight were not significantly different between the two study groups (Table 1).

Table 1. Demographic characteristics of the two study groups

	Propofol (n=110)	Midazolam (n=110)	p-value
Age	26.5±5.6	25.7±6.2	0.25
Gender (male/female)	95/15	98/12	0.53
Educations Diploma Bachelor or higher	 83 27	 75 35	 0.17
Marital status (married/single)	67/43	78/32	0.11

Values are given as number or mean ± SD.

The differences between stress sub-scores and total scores of patients were compared a day before the surgery in propofol and midazolam groups, showing no significantly different between the two groups (Table 2).

Table 2. Stress level sub-scores and total score of Mississippi questionnaire on the pre-operative day.

	Propofol (n=110)	Midazolam (n=110)	p-value
Penetrating memories	27.44±4.49	27.25±4.93	0.76
Problem in personal relationships	25.35±5.16	25.50±5.63	0.52
Inability in controlling emotional feelings	25.5±5.37	26.16±5.75	0.37
Lack of depression	25.65±6.33	25.73±6.27	0.46
Total Score	97.40±20.57	98.34±18.45	0.66

None of the pre-operative time scores were significantly different between the two groups of patients. Values are given as mean ± SD.

The differences between the Mississippi questionnaire sub-scores and total scores of patients in propofol and midazolam groups were compared. The midazolam group considerably outperformed the propofol group in terms of penetrating memories (P<0.05). The problem in the personal relationship was considerably more in the midazolam group compared to the propofol group (P<0.05). Inability in controlling emotional feelings was significantly higher in the midazolam group compared to the propofol group (P<0.0001). Depression was also significantly higher in the midazolam group compared to the propofol group (P<0.0001), (Table 3).

Table 3. Stress level sub-scores and total score of Mississippi questionnaire on the post-operative day.

	Propofol (n=110)	Midazolam (n=110)	p-value
Penetrating memories	25.31±5.4	27.13±5.82	0.016
Problem in personal relationships	23.84±5.8	25.50±6.31	0.043
Inability in controlling emotional feelings	23.7±6.54	25.12±6.42	0.001
Lack of depression	22.17±5.4	25.10±4.55	0.0001
Total Score	91.33±18.24	96.61±18.56	0.014

Comparison of the differences between the Mississippi questionnaire sub-scores and total scores of patients in propofol and midazolam groups. Penetrating memories: P < 0.05, propofol vs. midazolam; problem in the personal relationship: P < 0.05, propofol vs. midazolam; Inability in controlling emotional feelings: P < 0.001, propofol vs. midazolam; Depression: P < 0.001, propofol vs. midazolam. Values are given as mean ± SD.

Table 4. The differences between Mississippi questionnaire total scores of patients in pre – and post-operative times

	Pre-operative	Post-operative	p-value
Total Score			
Propofol	97.40±20.57	91.33±18.24	0.034
Midazolam	98.34±18.45	96.61±18.56	0.72

Comparison of the differences between Mississippi questionnaire sub-scores and total scores of patients in pre – and post-operative time-points. In propofol group, P< 0.05, pre – vs. post-operative time. Total scores of patients were not different in the midazolam group between pre – and post-operative time points.

The differences between Mississippi questionnaire sub-scores and total scores of patients in pre – and post-operative times were compared (Table 4). Total scores of patients did not differ in the midazolam group at pre – and post-operative time. In the propofol group however, total scores of patients differed at post-operative time compared to pre-operative time (P < 0.05). Propofol infusion was better in decreasing stress level after surgery compared to midazolam.

DISCUSSION

In this study, we assessed the stress level of patients during and after spinal anesthesia with two sedatives of propofol and midazolam. Propofol infusion was better in decreasing stress level after surgery compared to midazolam. Patients with a history of trauma often experience stress after the surgery (21). Stress during anesthesia is an important clinical problem that sometimes results in disabling psychological sequelae for the patient (22). Studies have illustrated the distress that result from stress episodes, but have not confirmed the spectrum of symptoms or the incidence of PTSD (23). Researchers have also identified higher emotional stress (incidence of early psychological symptoms and PTSD, 50%) in patients few days after the episode than later time (incidence of late psychological symptoms, 33%), (24).

In this study, propofol had a better effect on improving the stress after surgery than midazolam. In line with this study, other studies have shown that propofol induces the sedation effect much faster than midazolam (25), and also suppresses the release of stress hormones (noradrenaline and cortisol) during anesthesia (26). Another study showed that propofol reduces anxiety more than midazolam (25). This could be explained by a unique effect of propofol on the sense of well-being (27, 28). The increase in dopamine levels in the nucleus accumbens is associated with the feeling of wellbeing in propofol patients (a phenomenon seen in drug abusers with pleasure-seeking behavior), (29). Sedation and amnesia are induced by propofol at sub-hypnotic dosages (30). Amnesia in unstimulated participants requires propofol infusions of at least 1 mg/kg/hour. Stress during surgical procedures has been reported with higher propofol infusion rates (31). If propofol is the only anesthetic used during surgery, extremely high infusion rates that result in blood propofol concentrations > 10 g/mL may be required to prevent stress (32). A general feeling of well-being, hallucinations, erotic fancies, and opisthotonos also appear after propofol use. Patients who get benzodiazepines for sedation appear to be conscious and coherent, yet they are amnesic during the operation and procedure. As compared to midazolam, propofol sedation is associated with sufficient sedation in ICU patients, a quicker weaning process, and an earlier tracheal extubation, but not before ICU discharge (33).

Risk factors for PTSD in stressful conditions should be investigated in future studies. Commentators have suggested that memory of pain caused by surgery may contribute to PTSD (18). The psychological literature suggests that peritraumatic dissociation is a predictor of the severity of post-traumatic symptoms. In the TBI-induced rates, PTSD showed a non-significant tendency toward exacerbation at 3 months, and at 6 months after the injury, PTSD was predicted (34).

In conclusion, we showed that a sub-hypnotic dose of propofol provided a superior sedation and amnesia compared to midazolam during spinal anesthesia. In addition, aspects of stress, including penetrating memories, personal relationship problems, inability to control emotion-

al feelings, and lack of depression during spinal anesthesia were better managed by propofol compared to midazolam.

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Conflict of interest:
There are no competing interests to declare in this study.

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