DOI: https://doi.org/10.53350/pjmhs221610430

ORIGINAL ARTICLE

Randomized Controlled Clinical Trial to Examine the Efficacy of Oral Midazolam in Post Operative Pain Reduction in Patients Undergoing Laparoscopic Cholecystectomy

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ABSTRACT

Background: Stressful conditions like surgery and anesthesia trigger neuroendocrine pathway activation, which can have dangerous hemodynamic effects on the patient. One method for minimizing these hemodynamic consequences is maintaining an optimum level of anesthesia. Another option is giving patients a pharmaceutical formulation that modifies how anesthetic agents react.

Objective: The current study sought to determine if preoperative oral midazolam could reduce postoperative pain scores and the occurrence of Rescue Analgesia in patients undergoing laparoscopic cholecystectomy.

Methods: This is a single-blinded randomized controlled study conducted at the Surgery department of Jinnah Medical College Hospital, Korangi Karachi, on patients undergoing laparoscopic cholecystectomy. Through simple random sampling, participants were divided into two study groups, control (n=32) and 7.5mg receiving preoperative oral midazolam-intervention group. After surgery, the VAS pain score in both group participants was measured at 2, 8, 12, and 24 hours. The frequency of rescue analgesia and duration of hospital stay was also observed. Standard deviation, mean, chi-square test, and T-test was performed to determine the variation in both groups by using SPSS version 26. The P value ≤0.005 was measured significant.

Results: No significant difference in the postoperative pain score after oral administration of midazolam in the intervention group compared to the control group at 2, 12, and 24 hrs intervals. Except at 8-hour intervals, a significant change of 0.004 was observed in both study groups. A significant variation of 0.008 was observed in the duration of hospital stay in the intervention group when compared with the control group. Lastly, in the present study, no significant difference in the frequency of rescue analgesics was observed in both study groups.

Practical implication: This study will help out to determine the right dosage of oral midazolam which might effectively be used in managing post-operative pain in laparoscopic cholecystectomy patients.

Conclusion: Orally administeredmidazolam was not efficient in lowering the pain score in patients undergoing laparoscopic cholecystectomy.

Keywords: Midazolam, Post-operative pain, Laparoscopic cholecystectomy, Local anesthetics

INTRODUCTION

The preferred course of therapy for most individuals with symptomatic cholelithiasis is laparoscopic cholecystectomy. Laparoscopic cholecystectomy is regarded as a short-stay treatment. It is now also carried out as day surgery[1]. However, it still needs to enhance postoperative outcomes that can shorten patients' stays in hospitals, such as improved postoperative outcomes and earlier patient recovery. Surgery and anesthesia are stressful situations linked to neuroendocrine pathway activation, resulting in various hemodynamic consequences that may be hazardous to the patient [2]. Sustaining an appropriate penetration of anesthesia to minimize these hemodynamic consequences is one way to lessen these effects. Another is to give patients a pharmacological preparation that will change how the anesthetic agent reacts[3].

Natural or potential tissue damage may cause the disagreeable sensory and emotional experience known as pain. Postoperative pain may occur after undergoing therapy (such as surgical operations), which produces biochemical and physiological stress reactions. The global public health problem of pain is a significant clinical, social, and economic concern[4]. Usually, nociceptive pain is what is felt after surgery. Surgical trauma is known to cause cerebral and peripheral sensitization and hyperalgesia, which, in difficult situations, might result in persistent postoperative pain [5, 6]. Both medical professionals and patients having surgery are very concerned about effective pain treatment, especially postoperative pain management. Patients' pain after surgery is a prominent topic of discussion. The growth of reductions in alveolar ventilation, hyperventilation, tachycardia, slow wound healing, the shift to chronic pain, and sleeplessness are all directly impacted by postoperative pain and the patient's operative consequence, well-being, and gratification with medical attention. These factors may also affect the patient's satisfaction with their care[7, 8].

Age, gender, culture, and genetic make-up affect how each person reacts to pain differently [9]. From the intraoperative through the perioperative phases, current anesthesiology practice has evolved. One of the most crucial elements of providing patients with sufficient post-surgical care is postoperative pain control. Surgery-related pain can make patients more sensitive to pain, resulting in hypersensitivity[10]. Acute postoperative pain might potentially become chronic as a result of it. Effective postoperative pain management is essential, especially with the beginning of physiotherapy and early ambulation, which accelerates recovery and reduces hospital stays[11].

Midazolam is a short-acting benzodiazepine derived with anticonvulsant, amnestic, sedative, anxiolytic effects, and hypnotic[12]. It works by attaching to the benzodiazepine receptor at the GABA receptor-chloride ionophore complex in the central nervous system. It strengthens GABA's CNS-based inhibitory impact. It has been discovered that medications like flunitrazepam and midazolam are successful in treating insomnia[13]. When taken orally a few hours before surgery, midazolam considerably lessens preoperative anxiety. Midazolam was used as a premedicant during induction, which resulted in a considerable reduction in the amount of propofol needed, lower anesthetic maintenance needs, reduced irritation of the airways, and a rise in blood pressure (B.P.)[14].

The current research aimed to evaluate the effectiveness of preoperative oral midazolam in patients having laparoscopic

cholecystectomy in lowering postoperative pain ratings and decreasing the incidence of Rescue Analgesia.

METHODOLOGY

Participants recruitment: The ethics committee name approved this single-blinded randomized controlled clinical trial. Through a simple random sampling method, 66 participants of ASA class I and II, aged between 18-60 years, both male and female, were admitted to have elective laparoscopic cholecystectomy between the period of 25 May 2022 to 25 August 2022 at Surgery Department of Jinnah Medical College Hospital, Korangi Karachi, after the informed consent was included in the trial. Participants with a history of Opioid addiction, Alcohol consumption, or taking other drugs to reduce anxiety and depression were excluded from the present study. The recruited participants were divided into two groups through computerized randomization: the control group (n=32) and the intervention group (n=34).

Data Collection: The participants in the intervention group were orally given One 7.5 mg Tab Midazolam the night before the operation. Based on the VAS, the degree of pain was recorded. The VAS is a standard instrument with ten numbers starting at 0 (no pain) and ending at 10, like a 10 cm ruler (the most severe pain). The patient was asked to choose a number based on how much pain they were experiencing. The pain level was assessed at four distinct intervals two hours, eight hours, twelve hours, and twenty-four hours after surgery. Given the frequency of the pain, it was determined that an IV opioid such as nalbuphine or tramadol was necessary as a rescue analgesic. The control group was not administered any pain reliever before or after the surgery.

Data Analysis: For variables including age, sex, BMI, ASA class, and co-morbid conditions, frequencies, percentages, and averages were estimated using descriptive statistics to show the demographic features of the sample. The averages and standard deviations of the intervention group's and the control group's pain ratings and the frequency with which rescue analgesics were administered to both groups were also calculated. A value less than or equal to 0.05 will be regarded as significant when using the Student T test as a measure of significance for quantitative variables and the Chi-square test for proportional data to compare the outcomes of the two groups. SPSS version 26 was used to conduct the statistical analysis.

RESULTS

The study's demographic information, such as the mean age and participants' BMI in the control and intervention groups, did not show any significant difference (Table 1). The percentage of female participants in the control and intervention groups was 75 and 79.4%, and the percentage of male participants in the control and intervention groups was 25 and 20.6%, respectively. The sample size of the Comorbidity data was so small to draw any significant association

Table 1: Demographic and clinical characteristics of the participants in the study groups

Demographic Characteristics		Control Group	Intervention group	P Value
Gender distribution	Female	24 (75%)	27 (79.4%)	
	Male	8(25%)	7 (20.6%)	
Age Distribution	Mean	42.1875	41.79412	0.937
	S. D	9.57	10.56805	
BMI	Mean	25.66313	26.87676	0.218
	S. D	5.373061	3.975536	
ASA Class	I	22	10	
	II	10	24	
Comorbidity	HTN	Nil	n=14	
	Diabetes	n=2	Nil	
	Obesity	n=2	Nil	
	Diabetes+HTN	n=6	n=2	
	Obesity+HTN	Nil	n=4	
	Obesity+Diabetes+HTN	n=1	n=1	
	IHD+HTN+Diabetes	Nil	n=2	
	HtTN+IHD	Nil	n=2	

The control and intervention groups do not show any significant difference in the VAS postoperative pain score recorded at 2hrs (p=0.76), 12hrs (p=0.36), and 24hrs (p=0.62) intervals (Figure 1). But a significant variation (p=0.004) was recorded in the intervention group's VAS postoperative pain score after midazolam administration after 8 hours of the laparoscopic cholecystectomy surgery compared to the control group. Using the chi-square test, the mean pain score in both groups was compared, and no significant difference was observed (Figure 2).

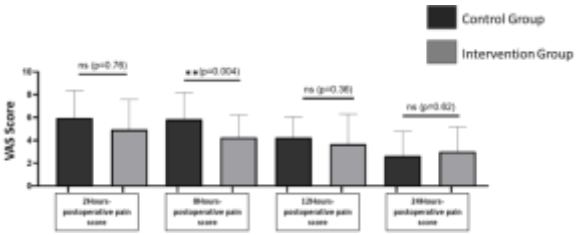

Figure 1: Student T-test between control and intervention groups participant's postoperative VAS Pain scores at 2, 8, 12, and 24-hour intervals. The X-axis contains the time interval. Y-axis has a VAS pain score (0-10). The p-value ≤0.005 was considered significant.

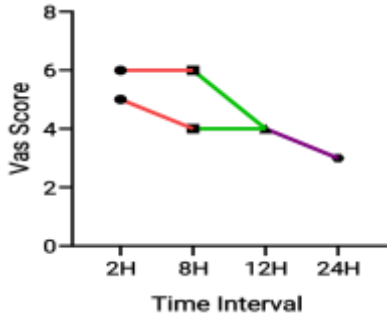

Figure 2: Chi-square test between the mean pain scores of the control and intervention group participants. The X-axis contains the time interval. Y-axis has a VAS pain score (0-10). The p-value ≤0.005 was considered significant.

Although the oral administration of midazolam does not significantly affect the postoperative pain score in the intervention group, a substantial difference in hospital stay was detected in both groups (Figure 3). Participants in the control group had an average hospital stay of 3.69 days and for the participants in the intervention was 2.91. So, the mean difference between both groups was 0.78 days, showing a significant decline (P=0.008) in the hospital stay among the participants in the intervention group.

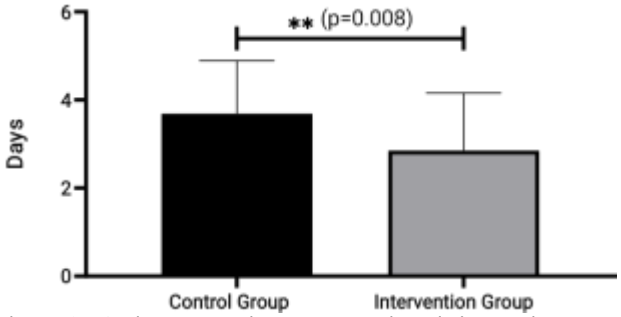

Figure 3: Student T-test between control and intervention groups participant's duration of hospital stay after surgery. The X-axis contains the study groups. Y-axis shows the number of days. The p-value ≤0.005 was considered significant.

In the control and intervention groups, rescue analgesic was given to only 5 participants. The frequency of rescue analgesic

given to the control group was slightly higher with a 1.6 Mean, but no significant difference (p=0.208) in the frequency was observed in both groups (Table 2).

Table 2: Rescue analgesic frequency in the study groups

Study Groups	Rescue Analgesic		Frequency of Rescue analgesic				
	Given	Not given	Mean	S. D	Min	Max	P
Control group	5	27	1.6	0.89	1	3	0.208
Interventio n group	5	29	1	0	1	1	

DISCUSSION

Dopaminergic, histaminic (H1), cholinergic/muscarinic, and serotonergic are the four central neurotransmitter systems that play essential roles in modulating the emetic response (5 HT3). At least four places where more than one receptor can be affected by a drug's activity due to the four distinct kinds of receptors[15]. However, often utilized medications have an effect that is more pronounced at one or two receptors. In addition to reducing anxiety, midazolam may also function as an antiemetic by lowering dopamine input at the chemoreceptor trigger zone. Adenosine reuptake may be reduced as well. As a result, dopamine production, release, and postsynaptic action at the chemoreceptor trigger zone are reduced by an adenosine-mediated mechanism[16]. In addition, it could lessen the release of 5-hydroxytryptamine (5-HT) and dopaminergic neuronal activity by interacting with the benzodiazepine complex with -amino butyric acid. Midazolam's hemodynamic effects are dose-dependent; the lower the systemic blood pressure, the larger the plasma level. Maintaining homeostatic reflex mechanisms underlies the process via which midazolam keeps a reasonably steady hemodynamic[17].

In the present study, no significant difference in the postoperative pain score after oral administration of midazolam in the intervention group compared to the control group at 2, 12, and 24 hrs intervals. Except at 8-hour intervals, a noteworthy variation of 0.004 was detected in both study groups. A significant variation of 0.008 was recorded in the duration of hospital stay in the intervention group when compared with the control group. Lastly, in the present study, no significant difference in the frequency of rescue analgesics was observed in both study groups.

The present study results are supported by a study conducted by Yadav et al. Yadav and colleagues conducted double-blinded randomized controlled research to test the efficiency of midazolam on the postoperative pain score in the participants undergoing laparoscopic cholecystectomy[18]. The authors observed no significant difference in the pain score in the control and orally administered midazolam group. However, Yadav et al. observed a significant reduction (P <0.0001) in the rescue analgesic in the orally administered midazolam group compared to the control group. But in the present study, no significant difference in the rescue analgesic in the intervention group was observed.

Another study by Agarwal et al. supported the present study results. In a randomized control trial, Agarwal et al. also observed no substantial variation in the control and intravenously administered midazolam group pain scores[19].

CONCLUSION

In conclusion, the present study did not observe any significant difference in the postoperative pain score after the oral administration of midazolam in the intervention group in comparison to the control group. However, the present study observed a significant variation (P=0.008) in the duration of the hospital stay in the participants of the intervention group when compared to the control group. Further investigation is required to determine midazolam's efficacy in reducing the rescue analgesic frequency.

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