ORIGINAL ARTICLE

A Randomized Double-blind Comparison of Postoperative Delirium With or Without Benzodiazepine Premedication in Elderly Patients Undergoing Lower Extremity Surgery Under Neuraxial Anesthesia

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Date submitted: May 9, 2023; Date accepted: June 1, 2023

ABSTRACT

Background: Benzodiazepines are frequently administered as premedication to relieve patients' preoperative anxiety. However, their effect on incidence of postoperative delirium is controversial. This study compared the effects of benzodiazepine premedication on the incidence of postoperative delirium in elderly patients undergoing lower extremity surgery under neuraxial anesthesia.

Materials and Methods: A randomized, double-blind study was conducted in a tertiary hospital in Delhi, between February 2021 to June 2022. The study was approved by the Institutional Ethics Committee for Human Research and registered prospectively with Clinical Trials Registry of India (CTRI/2021/02/031187). Sixty-two elderly patients of either sex undergoing elective lower extremity surgery under neuraxial anesthesia were randomized to receive oral premedication with either 0.25 mg alprazolam (Benzodiazepine group) or placebo tablet (Placebo group), after obtaining an informed written consent. The primary outcome studied was the development of delirium (assessed using confusion assessment method on days 1, 2 and 3). Secondary outcome measures included preoperative anxiety, patient cooperation, change in mental status after surgery, patient satisfaction, feeling of well-being, quality of sleep, amnesia on 1st postoperative day and length of hospital stay.

Results: The incidence of delirium was 3.2% and 6.5% in the benzodiazepine and placebo groups respectively (*P*=0.55). None of the secondary outcomes were significantly different between the groups.

Conclusion: Administration of alprazolam (0.25 mg) as premedication did not have any significant effect on the development of postoperative delirium. However, larger studies are needed to confirm these findings.

Keywords: Alprazolam, Delirium, Elderly, Premedication.

INTRODUCTION

Delirium is characterized by an acute and fluctuating impairment of consciousness and is accompanied by disturbances in attention, cognition, and perception.[1] Postoperative delirium is a serious complication that results in an increased length of hospitalization and poor patient outcome with considerably raised morbidity and mortality.[2] It usually occurs between the second and fifth postoperative days.[1] Although the incidence of post-operative delirium is 2.5-3% in most of the surgical cases, the rates are much higher, 20-79%, amongst the hospi-talized older patients.[3]

Use of benzodiazepines during premedication has also been associated with the development of postoperative delirium as they affect the GABA receptors and impair the slow wave sleep.[3] Benzodiazepines are frequently administered preoperatively to relieve patients' anxiety, although their effect on reducing preoperative anxiety remains controversial.[4,5] On the flip side, they could potentially enhance and prolong postoperative delirium and cognitive dysfunction.[6,7] American Geriatrics Society Guidelines for postoperative delirium in elderly patients advises to avoid drugs which can cause delirium such as benzodiazepines.[8]

On the other hand, benzodiazepine premedication was not found to cause delirium in elderly patients undergoing cardiac catheterization.[9] In a study of perioperative risk factors for postoperative delirium in total knee and hip arthroplasty patients, postoperative benzodiazepines were associated with increased risk for delirium, while intraoperative benzodiazepines reduced this risk.[10] Thus the

evidence related to the role of preoperative benzodiazepines in increasing the incidence of postoperative delirium is conflicting.

An extensive search of literature did not reveal any study that has compared the incidence of postoperative delirium with or without benzodiazepine premedication in elderly patients undergoing lower extremity surgery under neuraxial anesthesia. Thus, the present study was conducted with the aim to study and compare the effects of benzodiazepine premedication and placebo on the incidence of postoperative delirium in this group of patients. We hypothesized that benzodiazepine premedication does not increase the incidence of postoperative delirium compared to placebo administration before surgery.

MATERIALS AND METHODS

This randomized, double-blind study was conducted following approval from Institutional Ethics Committee for Human Research (IECHR/2020//PG/47/17-R1) and prospective registration at *www.ctri.nic.in* (CTRI/2021/02/031187). The patients were recruited between February 2021 and June 2022.

A total of 62 elderly patients, aged >60 years, of either sex undergoing elective lower extremity surgery under neuraxial anesthesia were included. Written informed consent was taken from all the patients.Those with alcohol or drug abuse, chronic benzodiazepine treatment, history suggestive of neurological or psychiatric disorders, or contraindications for benzodiazepines like sleep apnea syndrome, severe chronic obstructive pulmonary disease and allergy to benzodiazepines were excluded from the study.

The randomization sequence was generated using online software available from *www.randomizer.org*. The allocation concealment was done using sequentially numbered sealed opaque envelopes. The patients were randomly allocated to one of the two groups of 31 patients each, who received premedication with either 0.25 mg alprazolam (Benzodiazepine group) or placebo tablet (Placebo group). Identical looking multivitamin tablets available in the hospital were used as placebo tablets. Pre-medication was administered by a person not involved in the study. The patient, the investigator and the attending anesthesiologist were blinded to the group allocation. On the day prior to surgery, the patient was explained about the anesthetic technique and the study protocol, and consent for the same was obtained. The baseline mental status of the patient was assessed using the Hindi version of mini-mental state examination (MMSE).[11] The patient was asked to fast for 8 hours for solids and 2 hours for liquids. Premedication was administered 2 hours prior to the expected time of shifting the patient to the operating table.

Preoperative anxiety was assessed using the Hindi version of the Amsterdam Preoperative Anxiety and Information Scale (APAIS) 90 minutes after premedication administration.[12] Patients with a cut-off value of 12 were considered as anxious. All the patients had been counseled and their queries related to anesthetic and surgical management were answered. Patient cooperation was assessed by the attending anesthesiologist using visual analog scale (VAS) score (1-100), with 100 corresponding to the best cooperation.

All patients received combined spinal-epidural anesthesia using standard technique. Intraoperative blood loss, volume of fluid and blood administered, any hypotensive episodes and other critical events, if any, were recorded and managed accordingly. Hypotension was defined as a fall of ≥20% from the baseline SBP (systolic blood pressure) or SBP <100 mmHg. Postoperative analgesia was provided through epidural top-up doses and systemic analgesics, if required, as per the discretion of the attending anesthesiologist. On arrival in the postoperative room, the patient's alertness was assessed by using Observer's Assessment of Alertness/Sedation Scale (OAA/S).[13] This scale is from 1 to 5 (5=alert, 4=lethargic, 3=aroused by voice, 2=aroused by shaking, 1=deep sleep). The patients were assessed for development of delirium using Confusion Assessment Method (CAM) on day 1 (the day of surgery), day 2 and day 3.[14] The patients and their attendants were asked for acute onset or fluctuating course of mental state, inattention, disorganized thinking and altered level of consciousness. The MMSE was repeated on day 2 to assess any change in mental status. A decrease of more than 2 points from the baseline was considered significant change. Feeling of well-being and quality of sleep were rated by the patient on day 2 using VAS, with 100 corresponding to best well-being and best sleeping. Presence or absence of amnesia was also recorded at the same time. The patients were also asked about their satisfaction with the anesthesia experience graded as 'Good', 'Average' or 'Poor'. They were interviewed telephonically 30 days after surgery to find out about any health-related complications during this period. The primary outcome measure was incidence of postoperative delirium. The secondary outcome measures included preoperative anxiety scores and patient cooperation, any change in mental status after surgery, patient satisfaction, feeling of well-being and quality of sleep, amnesia on the first postoperative day, hospital length of stay and any health-related complications within 30 postoperative days.

Sample size calculation: Delirium can occur in 20 to 79% of hospitalised elderly patients.[3] Thus, considering 70% incidence of delirium and 50% reduction with the intervention as clinically significant, a sample size of 31 patients in each group was required at 5% level of significance and 80% power of the study.

Statistical analysis: Data was analyzed using SPSS 20 statistical software. Unpaired t-test was used to analyze demographic and other patient factors such as age, fasting hours, MMSE, APAIS score, patient cooperation, fluid administered and VAS scores. Mann Whitney test was used for comparing duration of hospital stay and intraoperative blood loss. Chi-square or Fisher's exact test was applied to compare qualitative data such as gender distribution, comorbidities, hypotensive episodes, patients requiring blood transfusion, patient satisfaction, presence of anxiety, delirium and amnesia. *P* value <0.05 was considered statistically significant.

RESULTS

Fig. 1 depicts the flow of participants in our study. Most of the patients were operated for femur fractures, whereas five patients in benzodiazepine group and 12 in placebo group underwent fixation of below knee fractures such as tibial or both bones leg fractures. As shown in **Table I**, the demographic and other patient characteristics except the duration of fasting were comparable in the two groups.The preoperative patient anxiety and cooperation were statistically not different between the groups (**Table I**). A larger number of patients receiving placebo were diagnosed as anxious on the basis of APAIS values. However, this difference could not achieve statistical significance. Intraoperative factors such as hypotension episodes, blood loss, fluid and blood administered in both groups also did not have any statistically significant difference (**Table II**). Postoperative factors including alertness score, MMSE day-2, VAS scores for well-being and quality of sleep, amnesia, duration of hospital stay and satisfaction scores are shown in **Table III**. All these factors did not have any statistically significant differences in the two groups.

In this study, one (3.2%) patient from benzodiazepine group and two (6.5%) patients from placebo group developed delirium (*P*=0.55). The patient who got delirium in benzodiazepine group was an 80-year-old hypertensive woman with a right closed intertrochanteric fracture femur. Her baseline MMSE was 28 and APAIS score was 18 i.e., she was anxious. She was fasting for 12 hours, cooperation score was 80, intra-operative blood loss was 300 mL with 1500 mL intravenous fluid administered. Her MMSE day-2 score was 20, VAS for well-being 60 and VAS score for quality of sleep was 50.

The first patient from placebo group who developed postoperative delirium was a 61-year-old male who had a traumatic right below knee amputation and degloving injury of left foot. His baseline MMSE was 29 and he was anxious with an APAIS score 17. He had been fasting for 20 hours and had intraoperative blood loss of 1000 mL, which was adequately replaced with fluid and blood. The patient was referred to psychiatry department but he remained delirious even on 30th day follow-up. The second patient having delirium in the placebo group was a 76-year-old woman with a surgically intervened subtrochanteric fracture femur with greater trochanter extension and infected implant in situ with newly diagnosed hypertension. Her baseline MMSE was 25 which did not change after surgery. She was anxious and had APAIS score 19. She was fasting for 18 hours and had lost about 500 mL blood intraoperatively.

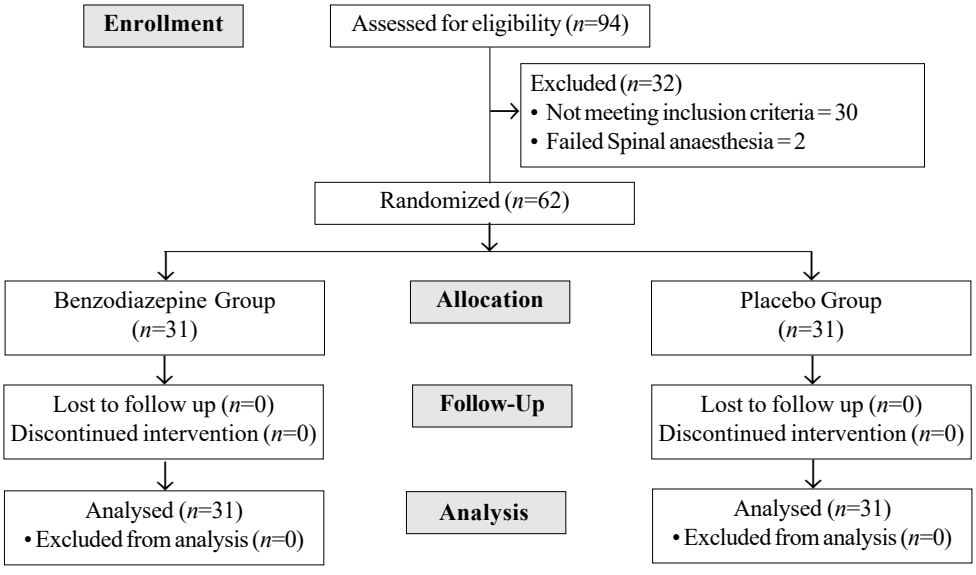

Fig. 1. Consort Diagram Depicting Recruitment, Intervention and Follow-up of Study Participants.

TABLE I. Baseline Characteristics of Participants in Both Groups

Parameter	*Benzodiazepine Group (n=31)*	*Placebo Group (n=31)*	*P value*
Age (years)*	66.8 (±6.4)	65.9 (± 6.6)	0.58
Gender (Male:Female)@	16:15	20:11	0.30
Patients having co-morbidities$	19 (61.3%)	13 (41.9%)	0.13
Duration of fasting (hours)*	12.4 (± 1.8)	14.8 (± 4.8)	0.01
MMSE*	27.3 (± 2.3)	27.1 (± 1.9)	0.77
APAIS score*	15.6 (± 5.2)	15.0 (± 2.6)	0.62
Patients having anxiety$	24 (77.4%)	29 (93.6%)	0.07
Cooperation VAS score*	98.0 (± 6.5)	95.8 (± 8.1)	0.23

*Values expressed as *mean (± SD)), $number (%) or @proportion.*
APAIS: Amsterdam Preoperative Anxiety and Information Scale; MMSE: Mini-Mental State Examination, VAS: Visual Analog Scale.

TABLE II. Intraoperative Characteristics of Participants in Both Groups

Parameter	*Benzodiazepine Group (n=31)*	*Placebo Group (n=31)*	*P value*
Patients having hypotension$	2 (6.4%)	3 (9.6%)	0.64
Fluid administered (mL)*	1806.5 (± 614.8)	1887.1 (± 667.2)	0.62
Blood loss (mL)#	500 (320-800)	500 (290-800)	0.72
Patients requiring blood transfusion$	6 (19.4%)	8 (25.8%)	0.54

*Values expressed as *mean (± SD),#median (IQR) or $number (%).*

TABLE III. Postoperative Characteristics of Study Participants

Parameter	*Benzodiazepine Group (n=31)*	*Placebo Group (n=31)*	*P value*
Alertness score (score 5)$	31 (100%)	31 (100%)	1.00
MMSE day-2*	27.0 (± 2.6)	27.0 (±2.2)	0.96
VAS for well-being*	66.8 (± 20.4)	63.4(±16.1)	0.47
VAS for quality of sleep*	67.7 (± 20.1)	65.5(±18.6)	0.65
Patients having amnesia$	1 (3.2%)	1 (3.2%)	1.00
Duration of hospital stay (days)#	12 (9.5-16)	10 (7-16.5)	0.32
Satisfaction score$			
Good	27 (87%)	29 (93.5%)	0.39
Average	4 (12.9%)	2 (6.5%)	
Poor	0	0	

*Values expressed as *mean (± SD), #median (IQR) and $n (%).*

DISCUSSION

The incidence of delirium in the present study was very low (5%), with one (3.2%) patient from the benzodiazepine group and two (6.5%) patients from the placebo group developing delirium. Administration of benzodiazepine premedication did not have any significant influence on the occurrence of postoperative delirium. None of the secondary outcome measures were found to be different between the groups.

Many studies have reported variable incidence of postoperative delirium, ranging from 2.2% to 70%.[1,3,10,15-19] In our study, the incidence of delirium was much lower compared to previous studies which could be accounted for by several reasons. One probable reason could be the type of anesthesia; all our patients received regional anesthesia which is known to be associated with a lower risk of postoperative delirium. Some observational studies have reported that use of regional anesthesia is independently

associated with a 20-40% lower incidence of delirium.[10,20] Weinstein, *et al*. reported an incidence of 2.21% in patients undergoing total hip or knee arthroplasty.[10] Memtsoudis and co-workers also found postoperative delirium in 2.6% and 2.9% patients having hip and knee arthroplasties respectively.[20]

The second reason for the low incidence of delirium in the present study could be related to the age group of our patients. Bilotta, *et al*. reported a greater risk for delirium in older age.[2] Age >70 years was associated with an odds ratio (OR) of 3.3 and age >80 years had an OR of 5.3 for development of delirium. In the present study, although all the patients were elderlies, the mean age was 66.8 (±6.4) years and 65.9 (±6.6) years in benzodiazepine and placebo groups respectively.

Another reason for such low incidence of delirium in our study compared to others could be the difference in our patient population and those from other countries. The differences in cultural, social, and family structure could be the contributory factors for the different presentations.

We did not find any significant difference in the incidence of delirium with or without benzodiazepine premedication in the present study. Our results are supported by some previous evidence in literature. In a study by Ashraf, *et al*. 93 patients ≥70 years old, undergoing elective cardiac catheterization received either benzodiazepine premedication or no premedication prior to the procedure; none of the patients in either group developed delirium.[9] The authors concluded that benzodiazepine premedication did not cause delirium in elderly patients. In another study by Weinstein, *et al*. postoperative benzodiazepines increased the risk of delirium although intraoperative benzodiazepines were found to reduce the risk of delirium.[10] Wang and co-workers did not find any difference in the incidence of postoperative delirium following midazolam premedication in elderly patients undergoing non-cardiac surgery.[21] Another multicenter study comparing restricted and liberal use of benzodiazepines for reducing delirium during cardiac surgery did not report any difference in the occurrence of delirium in the two intervention arms.[22]

However, our results are in contrast to some other studies.[2,23-25] Taipale, *et al.* demonstrated 7-8% increased risk of delirium per mg of midazolam administered in cardiac surgery patients.[23] In a systematic review, delirium risk increased with use of benzodiazepine medications.[24] Hui also commented that benzodiazepines may be associated with risks of precipitating or worsening delirium and oversedation; and should be used with great caution except in two specific situations of persistent agitation in patients with terminal delirium and delirium tremens.[25] In another literature review, administration of benzodiazepines in preoperative and postoperative periods was found to be one of the many risk factors for postoperative delirium.[2]

In the present study, although lesser number of patients in the benzodiazepine group were anxious (77.4%) compared to placebo group (93.6%), this difference could not achieve statistical significance. Thus, benzodiazepine (alprazolam) premedication did not have significant effect on reducing anxiety and improving patient cooperation. Our results are in concordance with the results of Jeon, *et al.* who in their randomized controlled trial, observed no anxiolytic effect of benzodiazepine (midazolam) premedication in preoperative patients.[5]

This study had certain limitations. First, the sample size was small and therefore these results need to be verified in larger studies. Second, the dose of alprazolam premedication administered was very small. However, this is the routinely used dose in elderly patients in our institution. Third, our study was not adequately powered to compare other parameters such as patient anxiety and cooperation.

We conclude that the incidence of postoperative delirium in elderly patients undergoing lower extremity surgery under neuraxial anesthesia is low with or without benzodiazepine premedication. The administration of the benzodiazepine, alprazolam (0.25 mg), as premedication did not have any significant effect on the development of delirium. However, larger studies are needed to confirm these findings.

CONTRIBUTORS: MM conceptualized the study. KS collected the data. MM, ANS, RS and SC provided guidance and intellectual support for conduct of study. MM and KS drafted the manu-script. ANS, RS and SC gave critical inputs. All authors approved the manuscript and are accountable.
COMPETING INTEREST: None; FUNDING: Nil

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