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Eszopiclone and zolpidem as a better alternate premedication to midazolam

Dr. Reena Makhni[1], Dr. Joginder Pal Attri[2*], Dr. Leena Mahajan[3], Dr. Sukhman Kaur[4], Dr. Neeru Bala[5]

[1] Assistant Professor, Govt Medical College, Amritsar, Punjab, India
[2] Professor, Department of Anaesthesia, Govt Medical College, Amritsar, Punjab, India
[3] Senior Resident, Govt Medical College, Amritsar, Punjab, India
[4] Junior Resident, Govt Medical College, Amritsar, Punjab, India
[5] Assistant Professor, Department of Anaesthesia and Psychiatry, Govt Medical College, Amritsar, Punjab, India

Abstract
Background and aim: Anxiety is one of the most common problem which affects the patient during surgical procedures. Thus, anxiolytics have a primary role as premedication preoperatively. With this background, we designed this study with primary objective of evaluation of sedation and anxiolysis with midazolam, zolpidem and eszopiclone as a premedication under regional anesthesia and to compare the satisfactory level of patients anxiety using Hamilton anxiety rating scale. Our secondary objective was to evaluate any adverse cardiovascular and respiratory events occurring due to use of these drugs. Methods: Study was carried out in 150 patients scheduled for regional anaesthesia and were divided into three groups of 50 each. Group M 50 patients were given midazolam 7.5 mg, Group Z of 50 patients were given zolpidem 15 mg, and group E of 50 patients were given eszopiclone 3 mg, 45 minutes before surgery with a sip of water. Monitoring of pulse rate, blood pressure, oxygen saturation and respiratory rate was done after giving premedication, every 5 minutes intraoperatively and every 15 minutes for 4 hours and every half hourly for 12 hours postoperatively. The results thus obtained were analysed using SPSS version 23.0 statistical package for windows. Results: Significant values of satisfactory scores between group M vs Z (p value - 0.00), group M vs E (0.00). HAM score at 90 minutes group M vs Z (0.018), group M vs E (0.003), at 120 minutes group M vs Z (0.00), group M vs E (0.00). Sedation score in group M vs Z at 1,4,6 hours (0.00), at 8 hours (0.002) and in group M vs E at 1 hour (0.00) at 4 hours (0.023) and in group Z vs E at 4hours (0.013), at 6 hours (0.00). All the three drugs reduce anxiety without altering the haemodynamics but zolpidem and eszopiclone have early onset of sleep and longer duration of sedation as compared to midazolam. Conclusion: zolpidem and eszopiclone are better premedication to allay anxiety in the patients undergoing regional anaesthesia.

Keywords: anxiety, eszopiclone, midazolam, premedication, zolpidem

Introduction

All patients undergoing surgery experience varying level of anxiety [1] which is dependent upon the perceived threat and outcome of the surgical procedure, pain, anaesthesia and worries about the family also. Preoperative anxiety and stress are common in patients awaiting surgical procedures. Preoperative anxiety is defined as an unpleasant state of uneasiness or tension that is secondary to patient being concerned about a disease, hospitalization, anaesthesia and surgery, or the unknown. Talking to patients and reassuring them in a confident, friendly but professional way is the most effective method of reducing patient's anxiety [2].

It is commonly observed that the patient remains anxious, nervous and fearful during regional anaesthesia because of different operation room environment, noise from monitor, suction and operating equipment etc. all these factors necessitates the use of sedation during regional anaesthesia [3].

Benzodiazepines are widely used as anxiolytics and sedatives prior to surgery. Midazolam, a water soluble benzodiazepine is a useful agent for pre-medication and sedation. It has a short onset of time and duration of action when compared to other benzodiazepines. In addition to anxiolysis, it possesses hypnotic, anticonvulsant, muscle relaxant and ante grade amnestic properties [4].

Zolpidem is a strong sedative with anxiolytic, myorelaxant and anticonvulsant properties, and has been shown to be effective in inducing and maintaining sleep in adults. Eszopiclone, a newly available non benzodiazepine hypnotic, effectively treats the symptoms of insomnia. Its pharmacokinetic and pharmacodynamic parameters are similar to those of the other currently available non benzodiazepine hypnotics (i.e., zolpidem and zaleplon). Eszopiclone is the active dextrorotatory stereoisomer of zopiclone, and classified as a therapeutic sedative hypnotic. However, fewer number of studies are available regarding the efficacy of zolpidem and eszopiclone in terms of anxiolysis in patients undergoing surgery. Therefore, this study is an attempt to study the anxiolytic effect of zolpidem and eszopiclone before surgery.

Methods

After approval from institutional Ethics Committee, a prospective randomized double blind trial was conducted on 150 ASA I and II patients, aged between 20 and 65 years, scheduled for elective surgery. Pre anaesthetic checkup including detailed history and thorough examination of the patient was carried out a day prior to surgery and patient was educated about questions to be asked regarding Hamilton Anxiety Rating Scale [5] (HAM), sedation and satisfactory

score and the written informed consent of the patient taken. Patients with history of psychiatric illness, renal disease, hypertension, diabetes mellitus, on medications like antihypertensive drugs and benzodiazepines were excluded from the study. Patients were equally divided into three groups of 50 each. Sample size was calculated keeping in view at most 5% risk, with minimum 80% power and 5% significance level (significant at 95% confidence interval). Patients were scheduled into three groups on the basis of computerized generated number. Patients in group M received midazolam 7.5 mg and group Z received zolpidem 15 mg and group E received eszopiclone 3 mg 45 minutes before surgery with a sip of water. The study drug was administered to patient by second author and study findings noted by third author. These doses were decided on the basis of equipotent doses. In the operation theatre baseline value of heart rate (ECG), non-invasive blood pressure, oxygen saturation (saturation probe) and respiratory rate were recorded. Intravenous line was secured and patients were preloaded with ringer lactate. Monitoring of pulse rate, blood pressure, oxygen saturation and respiratory rate was done by third author after giving premedication, every 5 minutes intraoperatively, every 15 minutes for 4 hours and every half hourly for 12 hours postoperatively.

Our primary aim was to evaluate sedation and anxiolysis with midazolam, zolpidem and eszopiclone as a premedication under regional anesthesia and to compare the satisfactory level of patients anxiety using Hamilton anxiety rating scale. Our secondary aim was to evaluate any adverse cardiovascular and respiratory events occurring due to use of these drugs.

Sedation score ranges from 0 to 3 and includes 0-Alert, conversant, 1- Awake but drowsy, 2- Asleep but arousable, 3-Asleep and not arousable. Assessment of sedation score was made postoperatively at 1, 2, 3, 4, 6, 8, 12 hours.

The HAM has total score range of 0–56, where <17 indicates mild severity, 18–24 mild to moderate severity and 25–30 moderate to severe. In our study HAM was noted at 0 min, 45 min, 90 min, and 120 minutes in the three groups.

Satisfaction of the patient regarding anxiety and fear during surgery was assessed using satisfactory score which ranges from 1 to 5 and includes 5= Excellent satisfaction, 4= Very Good, 3= Good, 2= Fair, 1= Poor (not satisfied).

The data from the present study was systematically collected, compiled and statistically analyzed using SPSS version 23.0 to draw relevant conclusions. Data was expressed as mean and standard deviation, number and percentages. Paired t-test was used to compare the results of HAM, satisfactory score and sedation score. The *P* value was finally determined to evaluate the level of significance. $P < 0.05$ was considered as significant at 5% significance level; $P < 0.01$ was considered significant at 1% significance level and $P < 0.001$ was considered highly significant.

Results

In the present study, three groups were comparable with respect to demographic characteristics, haemodynamic parameters and side effects at various time intervals. Postoperative sedation score, Hamilton anxiety score are shown in table I, II respectively.

Haemodynamic parameters including systolic blood pressure, diastolic blood pressure and heart rate remained stable after giving premedication, intra operatively as well as postoperatively and there was no statistically significant (p value <0.05) difference between three groups.

In our study HAM was noted at 0 min, 45 min, 90 min, and 120 minutes in the three groups.

At 90 minutes significant difference was observed between group M vs group Z and at same time statistically significant difference was also observed between group M vs group E. At 120 minutes statistically highly significant difference was observed between group M vs group E and statistically highly significant difference also observed between group M vs group Z.

Assessment of sedation score was made postoperatively at 1, 2, 3, 4, 6, 8, 12 hours. At 2 hours statistically significant difference was observed between group M vs group Z and statistically highly significant difference is observed between group M vs group E. Sedation score was compared in post-operative period.

There was highly significant difference between group M vs group Z and between group M vs group E in terms of satisfaction.

Discussion

Pre-medication has been used to achieve several purposes including reduction of anxiety, pre emptive analgesia, provision of sedation etc but the primary purpose of prescribing these drugs in the immediate preoperative period is to allay patient's anxiety. Relief of anxiety and sedation are properties of extreme importance when considering a premedicant or an agent for conscious sedation. Sedation and anxiolysis increases comfort level of the patient and acceptance of regional anaesthesia [6]. Benzodiazepines are the most commonly used drugs for this purpose. Midazolam is the most commonly used anxiolytic drug. Various other benzodiazepines and non-benzodiazepines that can be used for this purpose are diazepam, zolpidem and eszopiclone etc. We performed prospective double blind randomized controlled study to assess the anxiolytic effect of midazolam, zolpidem and eszopiclone as anxiolytic using HAM anxiety scores and sedation scores.

Midazolam is a benzodiazepine that acts by enhancing the effect of the neurotransmitter GABA at the GABA-A receptor [7, 8].

Zolpidem is a short-acting non benzodiazepine hypnotic of the imidazopyridine class that potentiates GABA, an inhibitory neurotransmitter, by binding to GABA a receptors [9].

Eszopiclone is a newly available non-benzodiazepine hypnotic which acts on benzodiazepine binding site situated on GABA a neurons as an agonist [10].

The dose of midazolam 7.5 mg and zolpidem 15 mg and eszopiclone 3mg were given 45 minutes before surgery with a sip of water under direct observation. Their administration 45 minutes prior to surgery appeared rationale in order to attain maximal plasma concentration at the time of surgical stimuli.

In a study conducted in 1990 by J Praplan-Pahud demonstrated that zolpidem is an effective hypnotic with rapid onset and short duration of action which may be an alternative to midazolam for premedication.

In a study conducted by Benjamin D Brielmaier demonstrated

that eszopiclone significantly reduced sleep latency, higher quality of sleep and better depth of sleep relative to placebo, fewer nightly awakenings as compared to placebo.

Our clinical study demonstrated that eszopiclone and zolpidem had early onset of sleep, longer duration of sleep, better quality of sleep and better next day ratings of ability to function and thus had better satisfactory score as compared to midazolam.

In our study patients had significantly lower HAM scores and longer duration of sleep in Group Z and E as compared to Group M.

So it is concluded from our study that midazolam, zolpidem and eszopiclone all the three drugs reduce the patient's anxiety without any cardiovascular and respiratory adverse events but these recently introduced newer drugs like zolpidem and eszopiclone were found to be better anxiolytics, sedatives than midazolam with early onset of sleep and longer duration of action which was beneficial especially in patients staying in hospital postoperatively for 1-2 days. Patients in zolpidem and eszopiclone groups were more satisfied as compared to patients in midazolam group. Amongst eszopiclone and zolpidem, eszopiclone had earlier onset of sleep and longer duration of action and better satisfactory score as compared to zolpidem.

Limitations of our study is that more studies need to be conducted to compare the pre and postoperative antianxiety and sedative effects of zolpidem and eszopiclone.

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