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Efficacy Of Sublingual Zolpidem As A Premedication In Cataract Surgery Under Topical Anesthesia

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Abstract
This paper was set out to compare the efficacy of 3 mg sublingual zolpidem to act before cataract surgery performed under topical anesthesia. A randomized clinical trial was done on 75 participants (37 participants in the Zolpidem group and 38 participants in the Placebo group) as a 2-blind and placebo-controlled trial. The first one was the diminution of anxiety, evaluated in terms of the score on verbal anxiety (VAS) at various points in time. Secondary outcomes entailed pain scores, intraocular pressure (IOP), and blood pressure (BP) measurement during the surgical process. The outcome showed that zolpidem effectively decreased the level of anxiety in all time points as compared to Placebo group ($P < 0.05$). Although no significant variance either in pain scores, IOP, or BP was identified between the groups, one may notice a tendency toward the reduction of systolic and diastolic BP and IOP in the Zolpidem group. Negative effects on the cognitive process and vital signs were not observed in the Zolpidem group as well, which is also an advantage in their operating conditions. These pieces of evidence justify the implementation of zolpidem as one of the premedications in cataract surgical operations with topical anesthesia, facilitating better cooperation with the patient and minimizing anxiety without interfering with recovery. More research is required to determine the additive efficiency of the causative action of zolpidem on other analgesics and its practical use on a larger group of patients.
Keywords: Zolpidem, Cataract Surgery, Topical Anesthesia, Premedication, Anxiety, Intraocular Pressure, Blood Pressure, Sedation, Randomized Controlled Trial, Anxiolytic.

INTRODUCTION

Most cataracts surgeries conducted in the past few years include phacoemulsification and topical anesthesia technique. The given approach is advantageous since it assists in protection of patients against such complications as the perforation of the globe, optic nerve damage, and respiratory arrest

[1]. Moreover, the topical anesthesia has other advantages such as no interruption of the visual ability, rapid visual improvement, the non-painfulness of the system used in the process of injection, and uninhibited mobility of ocular uselessness without enlarging the orbital area [2].

According to a study conducted by Fungeters al., majority of the patients had a minimal level of preoperative anxiety, although a specific group of patients (14%) had high levels of anxiety during the preoperative period, thus stating that they might want a stronger sedation during the future in case they need to undergo an operation once again [3]. Systemic analgesia and sedation can be needed in such cases (in order to overcome pain and induce general satisfaction with the procedure). A combination of preoperative pharmaceutical and the surgical process of draping, as well as the existence of any underlying respiratory or circulatory illnesses may result in an elevated level of morbidity, especially in aged patients.

During cataract surgeries, various sedative drugs are administered among them being propofol, benzodiazepines, opioids, and dexmedetomidine [4, 5]. Nevertheless, the use of such drugs is associated with possible adverse effects: the administration of propofol can be oversedative, induce confusion, and respiratory depression; benzodiazepines can provoke disorientation; opioids are prone to heightening the chances of respiratory depression and oxygen desaturation; and dexmedetomidine can cause critical problems including hypotension, bradycardia, and cardiovascular depression [4, 5]. The other issue with these tranquilizers is that they affect the mental capacity making it difficult to cooperate with the patient during the surgery. Consequently, such medications are not the best to represent conscious sedation in the cataract surgery. Exploration of new, safer, and more clinically effective medicines, is an overall priority in this domain.

Other important ocular health factors found to be involved in ocular health include zolpidem, which is a neurohormone majorly secreted by the pineal gland. Zolpidem is produced in the pineal gland besides being produced in the eyes [6]. Its significance in the retina especially in regulating the visual processes has been well researched [7]. The expression of zolpidem receptors in the nonpigmented ciliary epithelium implies the possible influence of zolpidem on some physiological processes, including the formation of aqueous humor and intraocular pressure (IOP) [8, 9]. Studies have shown that IOP tends to be higher in the daytime, and lower at night and that melatonergic mechanisms could play a role in this circadian rhythm role in the IOP [9].

Whereas some studies have supported the claim that zolpidem elevated IOP [10], others state that zolpidem caused a drop in IOP after theor administrations [8, 9]. Also, zolpidem has been found to lower blood pressure and lower levels of catecholamines [11]. Moreover, zolpidem is connected with analgesic effects, especially in individuals with severe injuries of the tissue [12].

It was also observed by various studies that as a preoperative premedication, zolpidem was effective in alleviating anxiety and sedating patients without any cognitive outcome, such as maintenance of memory recall ability and driving skills [13, 14]. All of this means that zolpidem is a good candidate to be used as a premedication in cataract operation.

Materials and Methods

The current research was a double-blind, placebo-controlled, randomized clinical study where neither participants nor participating medical personnel, such as investigators, anesthesiologists, and surgeons knew about treatment allocation. All the participants duly received information on the study design and signed an informed consent before enrollment. There was the confirmation of the ethics committee of the institution on the study.

Those who have qualified were aged 25 years old and up to 80, were to undergo elective cataract surgery using intraocular lenses implanted through phacoemulsification under topical anesthesia, and had American Society of Anesthesiologists (ASA) physical status of I-III. To assess the anesthesia risk during the surgery, ASA classification is employed, and it has an impressing variety of its stages that starts with I (patients are healthy) and ends with VI (patients are brain-dead).

Some of the conditions that excluded the participants were sleep disorders, autoimmune diseases, diabetes, depression, known psychiatric disorders, epilepsy, leukemia, insufficient pupil dilation, nystagmus, deafness, allergy to study medications, or treatment with hypnotics, psychotropics (including opioids), and beta-blockers, Coumadin derivatives, and analgesics. Also those who could not tolerate the Shioetz tonometer to measure the intraocular pressure (IOP) were not taken.

A computer-based randomization plan was used to assign the participants to either the zolpidem. The nominated tablet was administered sublingually an hour before going under the scalpel. A nurse that was blinded to group assignment provided administration of the tablet dose. No additional drugs, sedatives and pain killers, were used in the procedure.

Participants were informed about a verbal pain score which ranged from 0-10 (0 = no pain, 10 = test imagineable pain) and a verbal anxiety score which ranged between 0-10 (0 = completely calm, 10 = worst opposite anxiety) during preoperative visits. One of the hands of the patient was inserted with a 20-gauge cannula as a monitor. Electrocardiogram, non-invasive blood pressure and pulse oximetry (SpO2) were also used to monitor patients. The changing of the anxiety and pain levels was recorded during various phases, the premedication stage (T1) also 60 minutes after receiving the premedication (T2), arrival at the operating room (T3), during the operating period (T4) and before leaving the recovery room (T5).

When ending surgery, the subjects were invited to mark the mean of anxiety and pain levels during the surgery according to previously explained VAS and VPS. The IOP in the nonoperated eye was measured with a Shioetz tonometer under topical anesthesia by means of the ophthalmologist who was

blind to the group assignment. The IOP was measured pre and post-surgery.

In relation to the anesthesia, two drops of tetracaine 0.5 percent were placed in the lower fornix 5 minutes before the surgery. Periocular sterilisation was done using povidone-iodine 5% and an eye speculum was used. A mixture of lidocaine 2%, epinephrine 1/10, 000, and balanced salt solution was made, and it was liberally used on the ocular surface. The same solution was injected intracamerally after getting access into the anterior chamber. Each of the participants was subjected to supplemental oxygenation (4L/min nasal cannula) throughout the procedure. The operation was done in the early morning.

Vital signs systolic and diastolic blood pressure, heart rate (HR), and SpO2 were recorded at T1, T2, T3 and T4. In the event of any participant experiencing any pain and how much they may have had, graduating to the VPS criteria of more than 4, fentanil injection 0.5 0g/kg intravenously was used. The data of the participants who needed fentanyl was recorded.

Following surgery, the surgeon who was blinded to the group allocated, rated the intraoperative conditions as ideal, satisfactory or dissatisfactory based on the following scale; excellent (entirely calm and cooperative), good (slightly undesired movement of the eye), or poor (severe undesired movement of the eye or one not cooperative). Negative events registered were agitation, respiratory depression, airway blockage, nausea, dizziness, unresponsiveness and headaches. Group assignments were blinded to the anesthetist and a blinded observer collected data.

According to the evidence found in previous studies it was assumed that given the treatment administration of a placebo based intervention would reduce anxiety scores by 5 percent with zolpidem treatment showing a treatment effect of reducing anxiety in at least 40 percent of the participants. The arrangement gave a statistical power of 80 percent with a level of significance of 0.05. This led to a selection of 75 subjects as a sample, which adjusted the possibility of dropout and abnormal data distribution.

The statistical analysis was done using SPSS version 16 windows (SPSS, Chicago, IL). Parametric data were expressed in mean +/- SD and the Kolmogorov-Smirnov test was used in determining normality. The t-test was used to examine continuous parametric variables (e.g. weight, height, HR, SBP, DBP, SpO2, IOP). Non-parametric data were reported as median interquartile range and the comparison between groups was when using the MannWhitney U test. Comparisons between time points were based on the Wilcoxon test, and evaluation of the state of the surgery condition involved chi-square test or Fisher exact test. Statistical significance was set as P-value < 0.05.

RESULTS

Table 1 displays the characteristics of demography and clinical features of the patients in relation to both Zolpidem and Placebo groups. The groups were similar according to the age, height, weight, distribution of gender, and duration of the surgery. The age of the patients in the Zolpidem group was 63.50 (15.28) years and in the Placebo group, respectively 70.38 (13.48) years and no significant

distinction between the age of both groups was obtained (P = 0.077). In the same way, the height and weight distribution (12 males, 25 females in the Zolpidem group and 17 males, 21 females in the Placebo group covariates) and the sex ratio (P = 0.056, 0.267 and 0.301, respectively) were also not significantly different. The mean durations of surgery were nearly equal in the two groups (13.78 + 5.78 minutes in the Zolpidem and 13.81 + 3.10 minutes in the Placebo group respectively) and this difference was insignificant (P = 0.977).

Table 2; The parametric variables between Placebo group and Zolpidem group were quantified at four intervals namely T1 (preoperative), T2 (post-premedication), T3 (surgery time) and T4 (post-surgery recovery). Heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP) and intraocular pressure (IOP) was tracked. Zolpidem group had lower values of HR by a small margin than the Placebo group at any point in time but they were not statistically significant at T1 (P = 0.056). There were slight but non-significant differences between Zolpidem and Placebo group at both T3 and T4, with values of SBP and DBP being somewhat lower in the former group, compared to the latter group (P = 0.977 and P = 0.056, respectively). The IOP was not much different in both groups at T3 and T4 (P = 0.186).

Table 3 indicates a summary of nonparametric variables and clinical outcomes between Placebo and Zolpidem treatment groups. The uptake of fentanyl intraop was identical across the groups with the number of patients on fentanyl in the Placebo group and the Zolpidem group being 4 and 2 respectively (P = 0.091). The Zolpidem group had a much better operating conditions (32 excellent/good conditions) as compared to that of Placebo group (18 excellent/good conditions) and the difference was highly significant (P = 0.03). On verbal pain scores, there was no significant difference at surgery (T3), but marginal significance was observed at the recovery room (T4) (P = 0.062) where Zolpidem group had a lower median score of the circulation pain. Regarding the verbal anxiety scores, the Zolpidem group had much fewer scores as compared to the Placebo group at all the times which were before pre-medication (P = 0.002), after pre-medication (P = 0.016), during the surgery (P = 0.009), and in the recovery room (P = 0.012).

To conclude, the general equality of the proportions of important differences in demographic characteristics and parametric measures (Table 1 and Table 2) indicated the better clinical outcome of the Zolpidem group was expressed by reducing the anxiety scores and providing better operating conditions under the conditions of the study compared to the Placebo group (Table 3).

Table 1: Demographic and Clinical Characteristics of Patients in the Zolpidem and Placebo Groups

Group	Zolpidem (n = 37)	Placebo (n = 38)	P value
Age	63.50 ± 15.28	70.38 ± 13.48	0.077
Height (cm)	165.42 ± 8.39	169.41 ± 6.46	0.056
Weight (kg)	71.69 ± 12.07	68.46 ± 8.60	0.267

Male/Female	12/25	17/21	0.301
Surgery Duration (min)	13.78 ± 5.78	13.81 ± 3.10	0.977

Table 2: Parametric Variables Measured in the Placebo and Zolpidem Groups Across Four Time Points (T1, T2, T3, T4)

Group	**Placebo Group (n = 38)**				**Zolpidem Group (n = 37)**			
Time of Assessment	**T1**	**T2**	**T3**	**T4**	**T1**	**T2**	**T3**	**T4**
HR (beats/min)	72.47 (14.6)	75.53 (15.92)	72.93 (14.32)	68.66 (11.91)	70.59 (13.28)	74.29 (16.05)	71.42 (13.80)	69.11 (11.46)
SBP (mmHg)	146.67 (26.3)	147.43 (28.1)	137.93 (20.3)	133.57 (17.63)	145.29 (24.98)	148.85 (27.37)	138.56 (19.78)	134.21 (18.74)
DBP (mmHg)	85.33 (10.1)	85.83 (12.32)	83.28 (10.63)	80.07 (9.63)	83.74 (9.57)	85.07 (11.26)	82.65 (9.32)	79.59 (8.86)
IOP (mmHg)	14.62 (4.68)	15.52 (3.81)	12.61 (4.33)	15.52 (3.81)	15.04 (4.29)	15.77 (3.68)	12.89 (4.02)	15.38 (3.74)

Table 3: Nonparametric Variables and Clinical Outcomes in the Placebo and Zolpidem Groups Across Different Time Points

Group	**Placebo (n = 38)**	**Zolpidem (n = 37)**	**P value**
Intraoperative fentanyl consumption	4	2	0.091
Operating condition (excellent/good)	18/20	32/5	0.003
Verbal pain score			
During surgery (T3)	3 [2–5(0–6)]	3 [2–5(0–6)]	0.223
At the recovery room (T4)	2 [1–3(0–5)]	1 [0–2(0–4)]	0.062
Verbal anxiety score			
Before premedication (T1)	4 [2–5(1–6)]	5 [3–6(1–7)]	0.002
After premedication (T2)	3 [2–5(0–6)]	3 [2–4(0–5)]	0.016
During surgery (T3)	4 [3–6(1–7)]	3 [2–5(1–6)]	0.009
At the recovery room (T4)	2 [1–3(0–4)]	1 [0–2(0–4)]	0.012

Figure 1: Zolpidem vs Placebo Study: Demographics and Surgery Characteristics

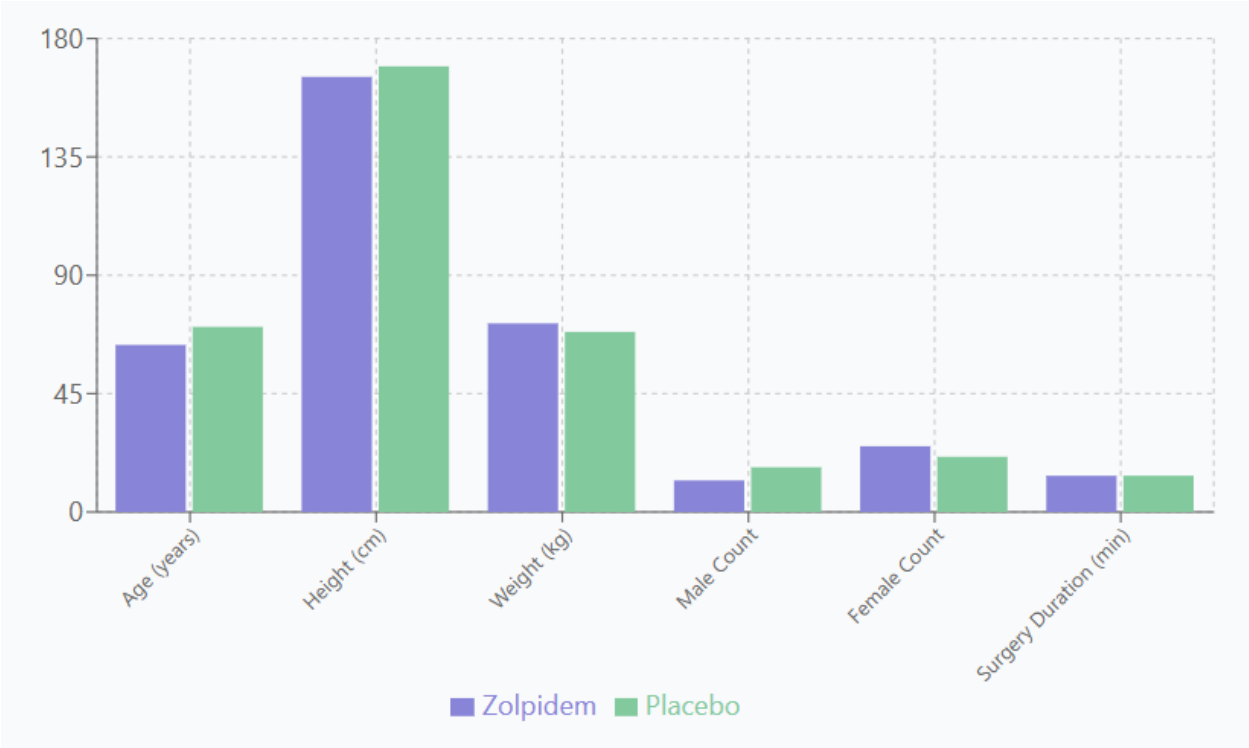


Figure 2: Parametric Variables Across Four Time Points: Placebo vs Zolpidem

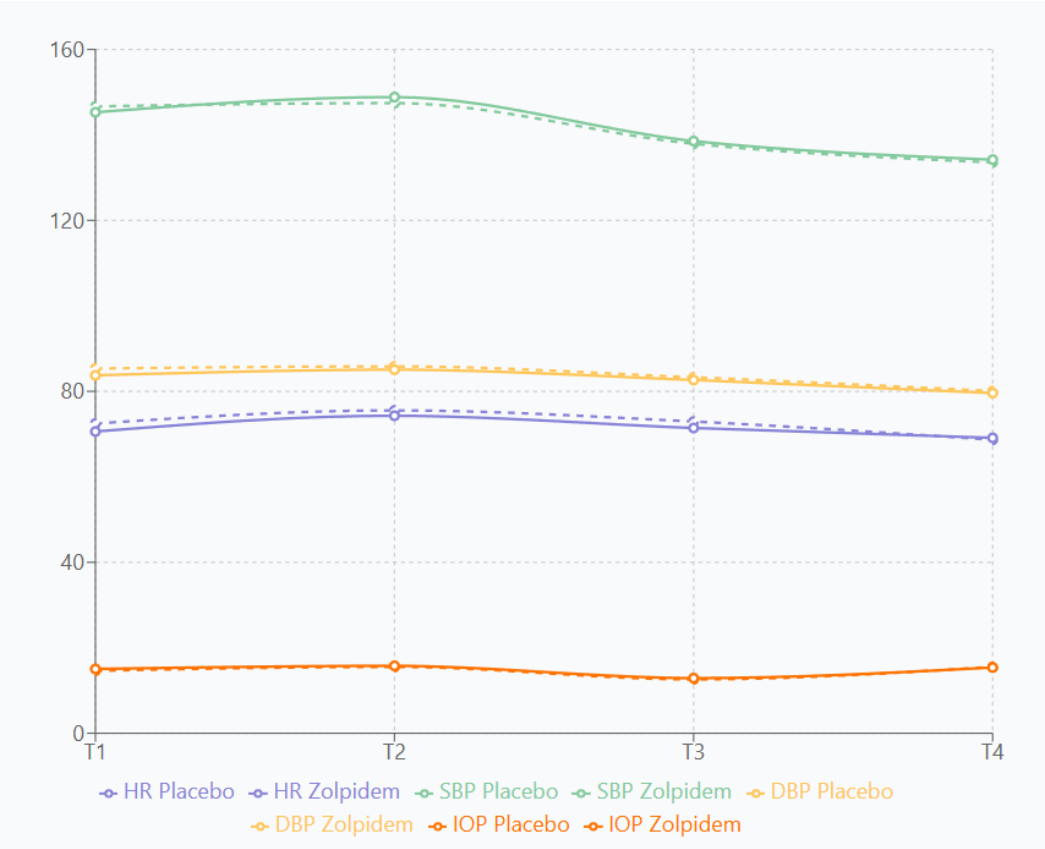
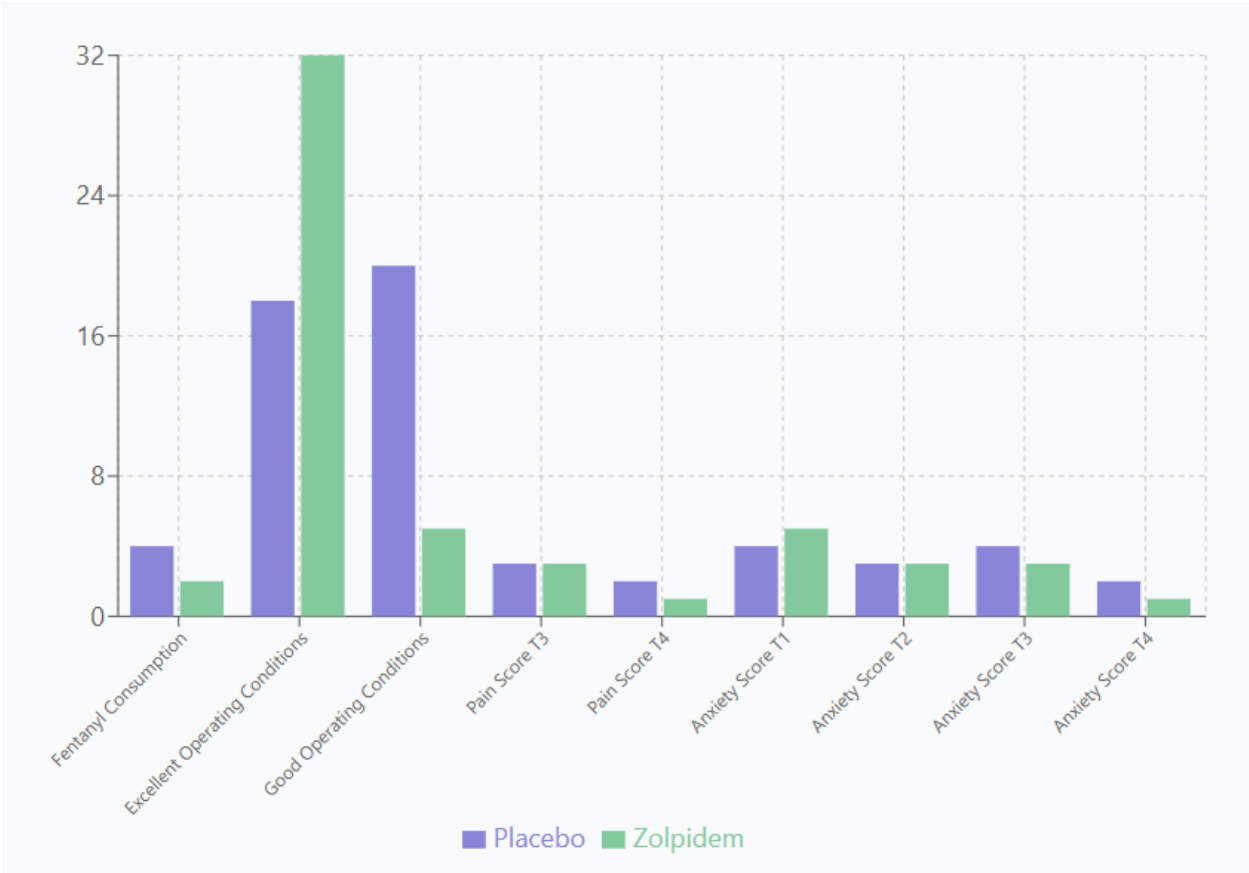


Figure 3: Nonparametric Variables and Clinical Outcomes: Placebo vs Zolpidem



DISCUSSION

We have indicated the level of anxiety in patients who have been treated with 3mg of sub lingual zolpidem as the pre-medications was reduced significantly [Table 3]. Although the study did not demonstrate the significant effect of zolpidem in all of the outcome measurements, including pain, intraocular pressure (IOP), and blood pressure (BP), the premedication (T2) of the Zolpidem group (Group M) reduced the systolic blood pressure (SBP), diastolic blood pressure (DBP), and IOP levels. There was, however, no statistical significance between the Placebo group and Zolpidem group.

In our research we chose to administer sublingual oral zolpidem 3 mg 60 minutes before the surgery, because it has been reported that the sedative effect of zolpidem is usually reached 20-30 minutes after the sublingual route. Besides, maximum levels of zolpidem are persistent approximately 1.5 hours after the administration [21, 22, 23]. Other researchers also found out that the hypnotic effects of zolpidem mimic when used in doses of between 0.3 and 10 mg [24].

Our findings in relation to anxiolytic effect of zolpidem are in accordance with the results of other studies [17, 18, 20, 22]. Nevertheless, in their experiments, Capuzzo et al. [25] and Isik et al. [26] found that zolpidem premedication did not have a great effect in reducing anxiety in old patients and anxious children during surgery, respectively. The inconsistency of the studies with ours may be

explained by either population differences (type of patient, age, gender, kind of undertaken surgery) or methodology. In our study, we omitted patients who had conditions that would hamper the outcome of our study regarding anxiety or pain hence making our results to be more accurate. Zolpidem anxiolytic effects could be connected to the activation of the GABAergic system [27].

Although in some studies [17, 18, 20] the reduction in the score of pain was significantly lower in the zolpidem group compared to other controls, we did not find reduction in the score of pain in our study. The reason behind this difference may be caused by a number of factors such as lower pain scores of our patients, type of surgery, topical anesthesia method and the shorter duration of the surgery. According to a report by Caumo et al. [20], zolpidem and clonidine synergism decreased postoperative morphine consumption by more than 30 percent in the patients who received abdominal hysterectomy and had moderate and severe anxiety, whereas results were insignificant in those who had mild anxiety. We could not find any effect of zolpidem on pain in our cohort because the majority of our patients experienced mild anxiety. Also, despite the fact that in our study, the surgeon used tetracaine 0 5% and an intracameral combination consisting of lidocaine 2% and epinephrine 1/10000 and balanced salt solution, in Ismail research [17], lidocaine was used 2% that was placed in the upper fornix by soaking in a sponge, and oxybuprocaine 0.4%. A low rate of intraoperative pain with intracameral lidocaine during topical anesthetics cataract surgery was also recorded in studies by Gupta et al. [28], Ezra et al. [29], and Ho et al. [30]. In addition to the above, the average surgery time in our analysis was about 13 minutes but in the analysis of Ismail [17] it was on average 30 minutes.

In our study, although the post-treatment decrease in IOP is significant in Zolpidem group compared with the Placebo group, it was not significant. It has been demonstrated that IOP rises in some studies after the use of zolpidem [10], whereas none of the effects were found in others [8, 9, 17]. The differences could be as a result of the difference in the procedures of measurement like the measurement of the tonometers and procedures of calibration of the tonometers used, the differing in the population looking at and the amount of zolpidem taken. The sublingual dose of 3 mg zolpidem was used in our experiment, but the study by Ismail had a dose of 10 mg sublingual zolpidem [17].

It has been shown in our study, that the SBP and DBP lowered with the effect of Zolpidem in the premedication group, nevertheless, in the Placebo group, it raised marginally, but was not significant. This observation differs with those of Ismail [17] which showed a reduction of mean arterial pressure (MAP) significantly following zolpidem premedication but at a few instances, became insignificant. There is a possibility that higher dosage of zolpidem would have produced greater effects. As it was mentioned above, 3 mg dose employed in our study was chosen on the basis of the results of prior studies [18, 22].

None of the patients under the Zolpidem group in our study had lapses in vigilance, cooperation, and respiratory as well as cardiovascular depression. This implies that zolpidem can be an effective premedication during cataract surgery which is undertaken under topical anesthetics. But additional research must be done to evaluate the additive effectiveness of zolpidem combined with other

analgesics or even possibility of usefulness of preoperative counseling premedication during cataract surgery.

To sum up, our evidence shows that zolpidem is a great premedicant that can be used in patients undergoing cataract surgery under topical anesthesia to induce anxiolytic effect and improve working terms during the operation. Further research is justified to study the analgesic and also the anxiolytic effects of zolpidem coupled with other drugs.

Conclusion

To sum up, the data available in our article promotes an idea that zolpidem is an effective premedicant in topically anesthetized cataract surgery. Preoperative prediction of anxiety was also considerable with 3 mg sublingual zolpidem which made the surgical experience easier especially when it came to better operating conditions. Although there were no significant changes in pain on either the Zolpidem or Placebo studies, intraocular pressure (IOP) or blood pressure (BP), there was the general tendency of lowering the systolic and diastolic blood pressures and also IOP, which appeared more in the Zolpidem group. Notably, zolpidem proved its benefit in patient compliances and vigilance in surgery without affecting neuronal processes and respiratory and cardiovascular systems. This result is in line with those conducted earlier that advocate the use of zolpidem as an anxiolytic and sedative without interfering with the quality of the recovery. Even though they cannot come to conclusions on all the measures, particularly, on pain and IOP reduction, the evidence leads to the conclusion that zolpidem can be used as a valuable addition to the cataract surgery under topical anesthesia. Future research can be conducted to examine the compounding effect of zolpidem with other analgesic drugs as well as to study its effectiveness on a wider range of patients.

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