Original Article

The Pain Control Efficacy of Zolpidem versus Melatonin after Intervertebral Disc Herniation Surgery under General Anaesthesia: A Randomised Clinical Trial

Abstract

Background: Postoperative pain management has been linked with multiple clinically relevant complications such as thromboembolism, myocardial ischaemia, and cardiac arrhythmias. **Objectives:** The present study moves towards an evidence-based approach to the therapeutic efficacy of zolpidem and melatonin in a better clinically meaningful pain relief following intervertebral disc herniation surgery under general anaesthesia. **Materials and Methods:** Undertaking a randomised, parallel-group, double-blind, clinical trial, 60 patients meeting eligibility (mean age ≈ 39, 50% female and 50% men) were offered intervertebral disc surgery at the Arak-based Valiasr Hospital and stratified into two interventional arms by block randomisation. Data including (i) pain (visual analog scale) and sedation (Ramsay sedation scale) scores during recovery and at all five initial 24-h time points (two, four, six, 12, 24); (ii) adverse events inclusive of mild nausea and dizziness, pethidine consumption; and (iii) ongoing haemodynamic parameters, including heart rate, blood pressure, and oxygen saturation were collected. Data were analysed at a significance level of $P = 0.05$ (SPSS 20.0, IBM Corp). **Results:** Our results showed no perceived statistically significant between-arm difference in three functional haemodynamic parameters, duration of surgery, and adverse events, as well as in sedation and pain scores ($P < 0.05$). Our results showed no between-arm difference in analgesia and sedation, haemodynamic changes, and postoperative adverse events. **Conclusion:** The findings taken together lent a strong support for the highly encouraging efficacy of both drugs in affording adequate analgesia at 24 postoperative hours without any adverse events needing to be thought of. Therefore, both zolpidem and melatonin were promising postoperative pain relievers, while no drug is demonstrably superior to the other.

Keywords: *General anaesthesia, herniation surgery, intervertebral disc, melatonin, zolpidem*

Hesameddin Modir[1], Esmail Moshiri[1], Alireza Mohammadi[2], Seyed Vesal Aghdasi[3]

[1]Department of Anesthesiology and Critical Care, Arak University of Medical Sciences, [2]Department of Neurosurgery, Arak University of Medical Sciences, [3]Student Research Committee, Arak University of Medical Sciences, Iran

Introduction

Postoperative pain management has been linked with multiple clinically relevant complications such as thromboembolism, myocardial ischaemia, and cardiac arrhythmias,[1] whose treatment regimens' efficacy is related to the evidence regarding the role of diverse factors, most notably the mental status, type of patient's personality, and preoperative alcohol consumption. A trend towards reduced postoperative pain and unwanted adverse events was reported in those receiving the multimodal combination of analgesics.[2]

To date, opioids continue to be deemed arguably the most effective essential medicines in controlling intra- and postoperative pain, whereas limited local consumption can be led by their adverse events, mainly drowsiness, apnoea, nausea, and vomiting, along with ileus.[3] It is also plausible that lower dose prescribing is most often associated with a less-frequent incidence of these adverse events. Furthermore, premedication prescription of various drugs can remain an effective promising strategy to enhance treatment response.[4]

Melatonin (N-acetyl 5-methoxytryptamine) is a hormone produced in the brain that is secreted from the pineal gland,[5] receptors of melatonin found in various sites in the central nervous system, and different tissues of the body. As studies showed,[6] when along with the reported effectiveness of the hormone in treating sleep disorders, anxiety, and pain,[7,8] and its anti-inflammatory and antioxidant effects, this has a significant

How to cite this article: Modir H, Moshiri E, Mohammadi A, Aghdasi SV. The pain control efficacy of zolpidem versus melatonin after intervertebral disc herniation surgery under general anaesthesia: A randomised clinical trial. J West Afr Coll Surg 2022;12:58-62.

Received: 02-May-2022
Accepted: 06-Jun-2022
Published: 27-Aug-2022

Address for correspondence:
Dr. Esmail Moshiri, Department of Anesthesiology and Critical Care, Arak University of Medical Sciences, Arak, Iran.
E-mail: moshiri_e@yahoo.com

Access this article online

Website: www.jwacs-jcoac.com

DOI: 10.4103/jwas.jwas_105_22

Quick Response Code:

potential for clinical uses as a premedication.[9] To our knowledge, melatonin is associated with many receptors: opioidergic, benzodiazepinergic, muscarinic, nicotinic, serotonergic, α1- and α2-adrenergic, and melatonergic receptors in the spinal cord of the central nervous system.[10,11]

Because the use of analgesic premedication helps minimise the need for opioids intraoperatively,[12-14] a multiple-dose regimen of melatonin premedication can cause sedation and analgesia, and not cognitive impairment, psychomotor skills, and prolonged recovery time.[12,13] It could reduce anxiety and pain compared with placebo, as corroborated by some evidence, including a systematic review (2014) of 24 clinical trials with 1749 participants in which three trials addressed the reliable anaesthetic induction dose. Their bottom line was that melatonin was capable to afford a reduced anaesthetic requirement, but with no effect on that of sevoflurane.[9] Likewise, a plenty of differently designed resources revealed that melatonin therapy has emerged as a promising target for achieving alleviated pain intensity.[8,14-16]

Significant efforts have been dedicated to testing new drugs such as zolpidem, which is pharmacologically categorised as a nonbenzodiazepine sedative-hypnotics, primarily employed to treat short-term insomnia, and acts as a very strong dopamine reuptake inhibitor in the brain.[17] It is expected to offer substantial advantages like effectively improved postoperative sleep quality in patients undergoing hip and knee arthroplasty and increased rapid eye movement and sleep efficiency, but not capable of affecting the structure of sleep.[18,19] The drug's profile has been reported to be proven safe and effective option for treating occasional transient insomnia and chronic insomnia and repairing sleep disorders,[20] allowing patients to fall asleep more rapidly and wake up showing any movement-related disorders.[21]

If being employed as an adjuvant to other analgesics, zolpidem can be highlighted as a well-established effective solution contributing to alleviating postoperative pain intensity pointed out.[22] Similarly, another trial exploring the effect of zolpidem on postoperative sleep disturbances confirmed a clinically significantly greater improvement after treatment with zolpidem.[18]

Notwithstanding the predominantly encouraging findings indicating postoperative pain management as one effective factor in accelerating patients' recovery, the lack of such previously reported two-group comparative trial appears of importance. To remedy this gap, this research was outlined and compared the efficacy of melatonin versus zolpidem in postoperative pain control in patients undergoing intervertebral disc herniation surgery under general anaesthesia.

Materials and Methods

Study setting and patients

This double-blind trial recruited 60 patients undergoing general anaesthesia with intervertebral disc surgery at the Valiasr Hospital (Arak, Iran) who were identified as meeting inclusion and exclusion criteria after obtaining written informed consent. Inclusion criteria were being scheduled for intervertebral disc herniation surgery, aged 17–65 years, no coagulation disorders, no history of cardiovascular-hepatic and renal diseases, a lack of adverse reactions to the drugs studied, plasma creatinine ≤ 1.5 mg/dL, and platelet count more than 150,000/mm^3, and L2–L5 laminectomy. The exclusion criteria were the unwillingness to take part in the study, a history of opioid use in the last 48 h, a history of drug/psychedelic substances/alcohol abuse, family history of thromboembolism, and severe haemodynamic instability. Eligible patients were stratified into two interventional arms based on a randomised block design, as follows.

Intervention

Intervention arms 1 and 2 received either 6 mg sublingual melatonin (melatonin 3 mg Webber Naturals, Canada) or 10 mg zolpidem tablets (HAKIM Pharmaceutical Co., Iran) that each drug diluted to a final volume of 5 mL with water, respectively, at 90 min before surgery.[14] To ensure a double-blind study design, the anaesthesiologist prepared and administered medicines, the intern was unaware of the drugs in each group, and the patients were also not aware of the allocation.

All subjects were hospitalised at least 1 day before surgery and had an 8-h course of nothing by mouth. The authors recorded the patients' baseline heart rate, mean arterial blood pressure using noninvasive blood pressure device, and arterial blood oxygen saturation before surgery, and then the data every 15 min until the end of surgery and during recovery. All were preloaded with 10 mL/kg of crystalloid solution (Ringer's lactate) after transfer to the operating room, received general anaesthesia with 5 mg/kg thiopental sodium, 1.5 μg/kg fentanyl, and 0.5 mg/kg atracurium, and intubated with a proper cuffed endotracheal tube size. Anaesthesia was maintained with oxygen and nitrous oxide (50:50), and isoflurane 1%–1.5%, fentanyl, and atracurium were administered intravenously at a dose of 0.50 μg and 10 mg, respectively, routinely every half hour.

Measurements

The visual analogue scale pain scores were assessed using a ruler graded from 0 to 10, during recovery and 2, 4, 6, 12, and 24 h after surgery. If scored higher than 4, the subjects received 50 mg of intramuscular meperidine and the time was noted, and then opioid consumption (mg/person) in the first 24 h was measured. Ramsay sedation scores were recorded at 2, 4, 6, 12, and 24 h after surgery. We controlled adverse events such as hypoxia (SaO2 < 92%) through supplemental oxygen therapy, hypotension (blood pressure < 20% from baseline) by crystalloid infusion and sympathomimetic drugs therapy, if needed, and bradycardia (heart rate < 40) with intravenous atropine 0.5 mg, whereas recording any other adverse events, if they happened, and taking appropriate remedial action.

Symptoms with the highest positive predictive value including shivering, nausea, and vomiting, as well as a decreased level of consciousness were recorded.

Statistical analysis

All the data were analysed through SPSS v. 20 using descriptive statistics analysis, including mean and standard deviation (SD), as well as percentage, when chi-square, independent t-test, and repeated measure were applied for between-arm comparisons.

Results

The randomised, double-blind, clinical trial enrolled 60 patients scheduled for intervertebral disc surgery and were stratified into two randomised arms receiving zolpidem or melatonin, comprising of 30 (50%) men and 30 (50%) women, with minimum and maximum ages of 25 and 56 years, respectively, mean age of 39.13 ± 6.89 years, and mean body mass index of 23.88 ± 1.98 kg/m^2. The study revealed no statistically significant between-arm difference in terms of oxygen saturation, duration of surgery, and mild nausea and dizziness as adverse events ($P < 0.05$).

As repeated measure confirmed [Table 1], no statistically significant between-arm difference was found in terms of mean blood pressure (both $P > 0.05$). Based on Table 2, no statistically significant between-arm difference was observed in the heart rate ($P < 0.05$), which was not confirmed by a repeated measure ($P > 0.05$). Similarly, the repeated measure [Table 3] confirmed that the statistically significant between-arm difference was found in terms of Ramsay scores ($P > 0.05$); however, a difference was observed only during recovery ($P = 0.003$). Moreover, no statistically significant between-arm difference was seen in terms of pain score at the time points studied ($P > 0.05$) [Table 4]. Table 5 results showed that pethidine consumption did not differ statistically significantly between arms ($P = 0.999$).

Table 1: Between-arm comparison of mean and SD of mean blood pressure

Group, mean blood pressure	Melatonin, mean ± SD	Zolpidem, mean ± SD	*P* value
Baseline	97.26 ± 7.26	97.232 ± 7.08	0.999
15 min after induction	96.66 ± 7.05	96.63 ± 6.69	0.818
30 min after induction	96.06 ± 6.82	96.10 ± 6.17	0.740
45 min after induction	95.46 ± 5.91	95.43 ± 4.40	0.254
60 min after induction	94.90 ± 5.47	94.83 ± 3.62	0.175
75 min after induction	94.40 ± 4.81	94.43 ± 3.29	0.197
90 min after induction	95.20 ± 4.62	95.16 ± 2.84	0.159
105 min after induction	97.30 ± 4.51	97.36 ± 3.58	0.109
120 min after induction	95.86 ± 4.31	95.93 ± 2.43	0.452
Recovery	97.56 ± 4.50	97.53 ± 3.43	0.448

Table 2: Between-arm comparison of mean and SD of heart rate

Group, heart rate	Melatonin, mean ± SD	Zolpidem, mean ± SD	*P* value
Baseline	93.43 ± 5.86	93.46 ± 5.85	0.982
15 min after induction	94.23 ± 5.84	94.26 ± 4.60	0.981
30 min after induction	94.90 ± 5.54	94.60 ± 3.86	0.979
45 min after induction	93.90 ± 4.72	93.93 ± 3.36	0.978
60 min after induction	93.16 ± 4.33	93.16 ± 2.92	0.975
75 min after induction	93.56 ± 4.46	93.56 ± 3.14	0.999
90 min after induction	93.16 ± 4.33	93.16 ± 2.92	0.999
105 min after induction	92.96 ± 4.18	92.96 ± 2.77	0.838
120 min after induction	93.96 ± 3.74	94.00 ± 2.11	0.966
Recovery	94.30 ± 3.49	94.33 ± 1.89	0.964

Table 3: Between-arm comparison of mean and SD of Ramsay scores

Group, Ramsay scores	Melatonin, mean ± SD	Zolpidem, mean ± SD	*P* value
Recovery	2.00 ± 00.00	2.06 ± 0.253	0.003
2 h after surgery	2.00 ± 00.00	2.06 ± 0.253	0.999
4 h after surgery	2.00 ± 00.00	2.00 ± 00.00	0.999
6 h after surgery	2.00 ± 00.00	2.00 ± 00.00	0.999
12 h after surgery	1.86 ± 0.345	1.86 ± 0.345	0.999
24 h after surgery	1.86 ± 0.345	1.86 ± 0.345	0.999

Table 4: Between-arm comparison of mean and SD of pain scores

Group, pain scores	Melatonin, mean ± SD	Zolpidem, mean ± SD	*P* value
Recovery	2.00 ± 00.00	2.00 ± 00.00	0.999
2 h after surgery	2.00 ± 00.00	2.00 ± 00.00	0.999
4 h after surgery	2.26 ± 0.449	2.30 ± 0.466	0.989
6 h after surgery	2.83 ± 0.833	3.03 ± 0.764	0.219
12 h after surgery	3.70 ± 0.915	3.83 ± 0.874	0.720
24 h after surgery	4.16 ± 0.461	4.23 ± 0.430	0.731

Table 5: Between-arm comparison of frequency and percentage of pethidine consumption

Group, pethidine consumption	Melatonin, number (%)	Zolpidem, number (%)	*P* value
Not consumed	16 (53.33)	16 (53.33)	0.999
Consumed	14 (46.66)	14 (46.66)	

Discussion

The trial's analysis showed the same result between two study groups regarding to haemodynamic outcomes and in terms of pain, sedation, and haemodynamic changes. A systematic review[22] of the effect of zolpidem on postoperative pain relief (2020) studied 5546 papers and 1252 subjects, reporting that zolpidem at a dose of 5 or 10 mg when employed along with other analgesics can alleviate pain scores. It is shown to be effective in combination with other analgesics, while not reporting any side effects for the drug, as recommended by the review,[22] whose findings were consistent with ours. An evaluation of the improvement of sleep quality after arthroplasty treated with zolpidem proved that 10 mg zolpidem can effectively improve sleep quality, alleviate pain, and increase the range of motion and muscle strength. Moreover, it helps reduce perioperative anxiety and depression and improve perioperative experience and satisfaction, thus reducing hospitalisation time and medical costs.[23] Our results were consistent with those of Shakya *et al.*' study.

Another study by Javaherforooshzadeh *et al.* comparing the efficacy of melatonin and gabapentin on anxiety and pain following lumbar spine surgery concluded that both interventions reduce postoperative pain and anxiety.[14] These were in line with our findings. Similarly, consistent with our results for the reduction in pain and sedation in both arms, Sadat Hosseini *et al.*'s clinical trial investigated the effect of melatonin, clonidine, and gabapentin on reducing anxiety and pain in patients undergoing cholecystectomy and suggested that melatonin has similar efficacy to clonidine and gabapentin in reducing preoperative anxiety, postoperative pain, and reducing opioid consumption.[16] In line with our study, Krenk and Kehlet's study about postoperative sleep disturbances after zolpidem treatment in fast-track hip and knee replacement suggested that one night's treatment with zolpidem improves sleep quality and postoperative fatigue.[18] As reported by Andersen *et al.*'s study, entitled "A systematic review of perioperative melatonin," melatonin reduces anxiety and pain scores compared with placebo.[11] Their results were in line with ours.

As shown by one study on the efficacy of melatonin and gabapentin on anxiety and pain after cataract surgery, they found that pain was lower in the melatonin group than in the placebo group, thus showing a significantly lower anxiety score in both intervention groups,[8] whose results were consistent with those we present herein. Ionescu *et al.*, when exploring the effect of melatonin premedication in laparoscopic cholecystectomy, proved that lower sedation score was in the melatonin group compared with the midazolam group, concluding that melatonin could be used successfully as a premedication in cholecystectomy surgery.[24] Similarly, melatonin and zolpidem in our study may lead to higher sedation. A comparative clinical trial on the efficacy of melatonin premedication on propofol induction dose, as well as postoperative anxiety and sedation in abdominal surgery, reported that propofol dose administrated was lower in the melatonin group than the placebo group, whereas the melatonin group had higher anxiety and less sedation.[13] Similarly, superior analgesia and sedation in the melatonin arm were supported by our trial.

Conclusion

Because no between-arm difference was observed in terms of analgesia and sedation, haemodynamic changes, and postoperative adverse events, both drugs were able to cause effective analgesia in the postoperative hours without any adverse events. Therefore, both zolpidem and melatonin may be suggested as postoperative pain relievers when neither drug was superior to the other.

Acknowledgement

This article is the result of a general medicine dissertation. The code of ethics is IR.ARAKMU.REC.1400.006, and its clinical trial code is IRCT20141209020258N161. We hereby would like to appreciate the guidance of the Clinical Research Council of Valiasr Hospital and the material and spiritual assistance of the Vice Chancellor for Research of Arak University of Medical Sciences.

Financial support and sponsorship

This study was supported by Arak University of Medical Sciences.

Conflicts of interest

There are no conflicts of interest.

References

1. Kehlet H. Postoperative pain, analgesia, and recovery-bedfellows that cannot be ignored. Pain 2018;159(suppl 1):11-6.
2. Vadivelu N, Mitra S, Narayan D. Recent advances in postoperative pain management. Yale J Biol Med 2010;83:11-25.
3. Abdallah F, Hussain N, Weaver T. Analgesic efficacy of cannabinoids for acute pain management after surgery: A systematic review and meta-analysis. BMJ J 2020;45:509-19.
4. Miller R. Anesthesia. Philadelphia: W.B. Saunders; 2005.
5. Sherif S. Assessment of role of perioperative melatonin in prevention and treatment of postoperative delirium after hip arthroplasty under spinal anesthesia in the elderly. Saudi J Anesth 2010;4:169-73.
6. Yu X, Li Z, Zheng H, Ho J, Chan MT, Wu WK. Protective roles of melatonin in central nervous system diseases by regulation of neural stem cells. Cell Prolif 2017;50:e12323.
7. Jafari-Koulaee A, Bagheri-Nesami M. The effect of melatonin on sleep quality and insomnia in patients with cancer: A systematic review study. Sleep Med 2021;82:96-103.
8. Khezri M, Merate H. The effects of melatonin on anxiety and pain scores of patients, intra ocular pressure, and operating conditions during cataract surgery under topical anesthesia. Indian J Opthalmol 2013;61:319-24.
9. Andersen LP, Werner MU, Rosenberg J, Gögenur I. A systematic review of peri-operative melatonin. Anaesthesia 2014;69:1163-71.
10. Talaat SM, El-Gendy HA. Effect of pregabalin versus midazolam premedication on the anesthetic and analgesic requirements in pediatric day-case surgery: A randomized controlled trial. Egypt J Anaesth 2021;37:50-6.
11. Garcia R, Salluh JIF, Andrade TR, Farah D, da Silva PSL, Bastos DF, *et al*. A systematic review and meta-analysis of propofol versus midazolam sedation in adult intensive care (ICU) patients. J Crit Care 2021;64:91-9.
12. Naguib M, Samarkandi AH. The comparative dose-response effects of melatonin and midazolam for premedication of adult patients: A double-blinded, placebo-controlled study. Anesth Analg 2000;91:473-9.
13. Norouzi A, Fateh S, Modir H, Kamali A, Akrami L. Premedication effect of melatonin on propofol induction dose for anesthesia, anxiety, orientation and sedation after abdominal surgery: A double-blinded randomized trial. Med Gas Res 2019;9:62-7.
14. Javaherforooshzadeh FI, Janatmakan F, Soltanzadeh M. Comparison of effects of melatonin and gabapentin on post operative anxiety and pain in lumbar spine surgery: A randomized clinical trial. Anesth Pain Med 2018;8:e68763.
15. Modir H, Moshiri E, Modir A, Modir A, Mohammadbeigi A. The preventive effects of oral caffeine and melatonin on headache after spinal anesthesia for lower limb surgery: A double-blinded, randomized clinical trial. Indian Anaesth Forum 2020;21:50-5.
16. Hosseini VS, Yekta R, Marashi S, Marashi SM. The efficacy of melatonin, clonidine and gabapentin in reducing preoperative anxiety and postoperative pain in patients undergoing laparoscopic cholecystectomy: A randomized clinical trial. Arch Anesth Crit Care 2015;1:120-5.
17. Lyphout C, Yates C, Margolin ZR, Dargan PI, Dines AM, Heyerdahl F, *et al*. Presentations to the emergency department with non-medical use of benzodiazepines and Z-drugs: Profiling and relation to sales data. Eur J Clin Pharmacol 2019;75:77-85.
18. Krenk LJ, Kehlet H. Postoperative sleep disturbances after zolpidem treatment in fast-track hip and knee replacement. J Clin Sleep Med 2014;1:3212-6.
19. Tashjian RB, Bradley M, Alford W, Fadale P. Zolpidem reduces postoperative pain, fatigue, and narcotic consumption following knee arthroscopy: A prospective randomized placebo-controlled double-blinded study. J Knee Surg 2006;19:5-11.
20. Valente KH, Tavares S, Gattaz W. Lower doses of sublingual zolpidem are more effective than oral zolpidem to anticipate sleep onset in healthy volunteers. Sleep Med 2014;14:3-20.
21. Gong LW, Fan D. Sleep quality effects recovery after total knee arthroplasty (TKA)—A randomized, double-blind, controlled study. J Arthroplasty 2015;30:1897-901.
22. O'Hagan ET, Hübscher M, Miller CB, Gordon CJ, Gustin S, Briggs N, *et al*. Zolpidem reduces pain intensity postoperatively: A systematic review and meta-analysis of the effect of hypnotic medicines on post-operative pain intensity. Syst Rev 2020;9:206.
23. Shakya H, Wang D, Zhou K, Luo ZY, Dahal S, Zhou ZK. Prospective randomized controlled study on improving sleep quality and impact of zolpidem after total hip arthroplasty. J Orthop Surg Res 2019;14:289.
24. Ionescu D, Ilie A, Miclutia I, Iancu C, Ion D, Vasian H, *et al*. Melatonin as premedication for laparoscopic cholecystectomy: A double-blind, placebo-controlled study. South Afr J Anaesth Analg 2008;14:8-11.