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

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.
potential for clinical uses as a premedication.\[8\] 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.\[9,10\]

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 an expected to offer substantial advantages like effectively reduced anaesthetic requirement, but with no effect on that of sevoflurane.\[9\] 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.\[23\]

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/mm³, 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 the dosing solution by crystalloid infusion and sympathomimetic drugs therapy, hypotension (blood pressure < 20% from baseline) and analgesia, and not cognitive impairment, psychomotor skills, and prolonged recovery time. 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/m². 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         | 97.23 ± 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 ± 0.00          | 2.06 ± 0.253        | 0.003     |
| 2 h after surgery         | 2.00 ± 0.00          | 2.06 ± 0.253        | 0.999     |
| 4 h after surgery         | 2.00 ± 0.00          | 2.00 ± 0.00         | 0.999     |
| 6 h after surgery         | 2.00 ± 0.00          | 2.00 ± 0.00         | 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 ± 0.00          | 2.00 ± 0.00         | 0.999   |
| 2 h after surgery  | 2.00 ± 0.00          | 2.00 ± 0.00         | 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 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, 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. 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. 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. 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. As reported by Andersen et al.’s study, entitled “A systematic review of perioperative melatonin,” melatonin reduces anxiety and pain scores compared with placebo. 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, 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. 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. 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.

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