

Efficacy of Melatonin on Postoperative Outcomes After Hysterectomy: A Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background: Melatonin became a part of multimodal analgesia in several recent studies because of its analgesic, anxiolytic and anti-inflammatory properties. Incidence of anxiety and pain in patients undergoing hysterectomy is not low. Moreover, preoperative anxiety is related to postoperative pain. The hypothesis of this study was whether melatonin could improve pain and other postoperative conditions after hysterectomy.

Methods: A randomized, double-blinded, placebo-controlled trial involved recruitment of 54 patients, aged between 18 and 65 years old, planned to undergo hysterectomy, with or without oophorectomy under spinal anesthesia. The patients were allocated to receive 4 mg prolonged-release melatonin at night before surgery and in the morning before surgery or 2 doses of placebo at the same time point. Morphine consumption within 24 hours with patient-controlled analgesia machine and visual analog scale (VAS) pain score were recorded. In addition, quality of sleep, Thai standard anxiety level score, fatigue, general well-being and satisfaction score were measured by a blinded assessor and analyzed.

Results: Mean of cumulative dose of morphine consumption in melatonin and placebo group were 33.04 ± 10.42 and 42.63 ± 8.21 mg, respectively. ($p < 0.001$) Mean of postoperative VAS pain scale was lower in the melatonin group at recovery room arrival (T0) (23.41 vs 8.07 , $p = 0.01$). However, there was not a significant difference between postoperative groups at 1(T1), 6 (T6) and 24 h (T24). Fatigue and general well-being score in the melatonin group were better than the placebo group.

Conclusion: Prolonged-release formulation of melatonin decreased pain intensity in post anesthetic care room and lowered doses of postoperative morphine within 24 hours after surgery. Postoperative fatigue, general well-being and satisfaction scores were better in the treatment group. However, there was no anxiety and sleep quality improvement. Melatonin may be an additional choice of multimodal analgesia for hysterectomy.

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[tp=regtrials&menu=trialssearch&smenu=fulltext&task=search&task2=view1&id=1076](http://www.clinicaltrials.in.th/index.php?tp=regtrials&menu=trialssearch&smenu=fulltext&task=search&task2=view1&id=1076), Efficacy of melatonin on postoperative outcomes after hysterectomy: a randomised, double-blinded, placebo-controlled trial

Background

A major problem after many surgical procedures is inadequate postoperative analgesia even after the multimodal analgesia concept was introduced. [1] A national survey in the United States found that 80% of patients experienced moderate or severe pain after surgery.[2] Uncontrollable postoperative pain is associated with depressed respiratory function.[3] In contrast, effective pain management is related to positive physiologic effects in specific organs such as reduced thromboembolic or cardiac complications, including early recovery.[4] After the gate control theory was proposed, a wider understanding of pain

mechanisms was achieved. The last update of pain definition recognized that pain is a multidimensional and subjective distressing experience in terms of sensory, emotional, social or cognitive components.[5,6]

Uterine fibroids are the most common benign pelvic problem for which hysterectomy is a treatment . The leading reasons for undergoing operation were healthcare provider recommendation, significant pain and distress.[7] Common postoperative problems after hysterectomy are not only acute postoperative pain but also high anxiety levels.[8] Diagnosis-related symptoms negatively result in physical and social activities including patients' quality of life.[9] Preoperative anxiety in hysterectomy is strongly related to postoperative pain score as well.[10,11] Benzodiazepine is a common medication as preoperative anxiolytic but may impair psychomotor performance.

Melatonin (*N*-acetyl-5-methoxytryptamine) is a pineal hormone regulating sleep-wake cycle in mammals. More than circadian rhythm stabilizing, exogenous melatonin has been investigated for other effects such as modulation of blood pressure, body temperature and cortisol control, immune function and anti-oxidative defense.[12] Its strong chronobiotic properties and the ability to regulate circadian rhythm make melatonin a good choice for sleep disorders in the elderly.[13]The exact analgesic mechanisms of melatonin are not known but may be involved with many receptors in brain. Involvement of β -endorphins, GABA receptor, opioid receptors and nitric oxide-arginine pathway were proposed.[14] Several recent studies showed some benefits of perioperative short-acting melatonin in many aspects among different groups of patients such as quality of recovery after surgery, diminished depressive symptoms and pain score reduction.[15-17] However, melatonin's analgesic effect remains controversial in the perioperative period and requires more investigation.[8] The hypothesis of the study was whether preoperative oral slow-release melatonin can potentiate the analgesic effects of intravenous morphine and improve sleep quality and anxiety levels. The aim of the present study was to examine the analgesic effects of oral long-acting melatonin premedication, compared to placebo, on morphine consumption in patients undergoing abdominal hysterectomy with or without oophorectomy. In addition, other therapeutic perspectives in clinical anesthesia such as anxiolytic effect, sleep quality, and also quality of life after hysterectomy were compared.

Methods

The present randomized, controlled and double-blinded study was conducted between April and December 2014 in King Chulalongkorn Memorial Hospital after approval of the Institutional Review Board of Faculty of Medicine, Chulalongkorn University (IRB No.428/56, COA No. 781/2013) on December 19, 2013. All written informed patient consents were obtained. Fifty-four patients, ASA physical status I-II and age 18-65 year scheduled for elective abdominal hysterectomy (with or without ovarian surgery) were enrolled into the randomized, double blind, placebo-controlled study. Patient exclusion criteria included history of heart disease, hepatic or renal failure, psychiatric disorders, sleep disorders, chronic pain syndromes, mental impairment, drug or alcohol abuse, patients receiving drugs with known analgesic and sedative properties, BMI over 30 kg/m² and patients who declined spinal anesthesia.

The patients were randomly divided into 2 groups (27 patients each) by using a random number table (1:1) and concealed opaque envelopes. These patients received either 4 mg of prolonged-release formulation of oral melatonin (Circadin®) (M group) or placebo (P group) at the night (8 PM) before the procedure and another dose 2 hours before surgery from a pharmacist who generated the random sequence and was not involved to the study. No other preoperative medication was given. Blinding and randomization were performed by an investigator who was not involved in patient evaluation. Other personnel involved in the patient's care were unaware of patient group assignment.

Preoperative visit was conducted the day before surgery. All patients were evaluated by the same anesthesia resident, who provided information on the preoperative course and instructed them on how to use the patient controlled anesthesia (PCA) machine. Each patient was multidimensionally assessed; level of anxiety by the Amsterdam Preoperative Anxiety and Information Scale (APAIS) Thai version.[18] Anxiety score ranged from 4-20 (anxiety score >13 is possible to high level of anxiety). Sleep quality was measured by a questionnaire about subjective sleep quality using 100 mm VAS (visual analog scale; 0 = best conceivable sleep and 100 = worst conceivable sleep). Level of physical fatigue and general well-being were evaluated by using 10-point ordinal scale (1= least fatigue feeling and 10 = most fatigue feeling and 100 mm VAS (0 = extremely well and 100 = extreme malaise), respectively, at the night before and 24 hours after the surgery.

Upon arrival in the operating room, all patients underwent standard monitoring. Before spinal anesthesia, 10 ml/kg of physiologic crystalloid solution was administered intravenously. Spinal anesthesia was performed by spinal needle at lumbar segment L2/3 or L3/4 with 0.5% hyperbaric bupivacaine 16-20 mg according to attending anaesthesiologists. If any patient had anxiety or discomfort, continuous propofol 0.08-0.1 mg/kg/min was given to maintain conscious sedation during the surgery. At the end of the surgery, sedation was stopped.

At recovery room, all patients received morphine via patient-controlled analgesia (PCA) machine; the PCA dose was 1 mg, a 6-min lockout and maximum dose of 30 mg within 4 hours and no basal rate was applied. In the first 2-hour postoperative period, if the patients had VAS pain score more than 40 mm after being connected to morphine PCA, morphine 0.1 mg/kg was further injected. PCA pump was continued for 24 hours after surgery. Four mg of ondansetron every 6 hours was administered for nausea/vomiting as required. No other analgesic was allowed.

The primary outcome with respect to the efficacy of the study drug was postoperative morphine consumption in 24 hours. Secondary outcomes were postoperative pain score, anxiety, sleep quality, general well-being and satisfaction with pain treatment. Postoperative pain was assessed using 100 mm VAS (0= no pain and 100 = worst imaginable pain) when arriving at recovery room (T0), 1(T1), 6(T6) and 24(T24) hours. Satisfaction with pain treatment and nausea/vomiting were assessed using 100 mm VAS at 24 h postoperatively. Other adverse effects, surgical and anesthetic complications were recorded.

Statistical analysis

According to the previous study, the patients in the placebo group required 0.39 mg/kg/min of morphine during the first 24 hours after surgery.[19] The sample size of 25 patients in each group was required to detect difference between groups to reduce postoperative morphine consumption by 0.1 mg/kg/min with a confidence level of 90% and a significance level of 5% Twenty- seven patients were enrolled in each group, allowing a 10% drop-out rate. Statistical analysis was calculated by using SPSS software version 17.0. Data are presented as mean \pm standard deviation unless stated otherwise. Comparison of morphine consumption was analyzed using unpaired t-test. Pain score, anxiety and sleep quality were analyzed using repeated measure ANOVA. Satisfaction and nausea/ vomiting were analyzed using Chi-squared test (Fisher's exact test if appropriate). A p -value < 0.05 was considered statistically significant.

Results

Fifty-four patients were enrolled into the study. No patient was excluded from the study after enrollment. The patient characteristics in each group, 27 patients, including diagnosis and types of operations were comparable between both groups (as shown in Table 1). Doses of bupivacaine, propofol and ephedrine were similar. There was no significant difference in anesthetic level of bupivacaine and number of patients who required sedation. There was no statistical difference in surgical variables including operation time and amount of blood loss. The number of intraoperative events such as hypotension needed treatment, bradycardia (Heart rate < 60 /min). were comparable in both groups and shown in Table 2.

Cumulative 24 – hour morphine dose of the patients in the M and P group were 33.04 ± 10.42 and 42.63 ± 8.21 mg, respectively ($p < 0.001$). Postoperative VAS of pain was significantly lower in the M group at recovery room arrival (T0) (23.41 vs 8.07 , $p = 0.01$). However, there was no significant difference of VAS pain score between groups at 1(T1), 6 (T6) and 24 hours (T24) postoperatively. Satisfaction with pain treatment in the M group was significantly higher than in the P group. (8.56 ± 1.25 vs 7.78 ± 1.50 , $p = 0.02$). (Table 3) There was no significant difference between groups in preoperative and postoperative anxiety level. On the first day after surgery, the patients in the M group reported fatigue VAS score lower than the P group (3.30 ± 2.22 vs. 5.15 ± 1.85 , $p = 0.002$) Moreover, general well-being VAS scores was significantly lower in the M group compared with the P group. (31.59 ± 24.14 vs. 49.78 ± 14.87 , $p = 0.002$) However, subjective sleep quality was not significantly different between both groups. (57.93 ± 21.08 vs. 49.33 ± 21.02 , $p = 0.14$)

Discussion

The present study demonstrates that long-acting oral melatonin improved VAS pain score and reduced cumulative dose of PCA morphine consumption in 24 hours. These results were similar to the previous studies in other procedures, such as prostatectomy,[20] dental surgery,[15] hand surgery,[21] cataract surgery under topical anesthesia [22] and abdominal hysterectomy.[19,23] In contrast, some studies failed to show the effectiveness of perioperative melatonin in terms of analgesic outcomes.[24,25] The variation of dose, route and timing of melatonin administration might affect these individual results,

which remain inconclusive even after systematic review were conducted.[8,26] Caumo et al. revealed the analgesic effect of preoperative oral melatonin. Melatonin reduced pain scores on VAS scale within postoperative period of 48 hours and lowered morphine consumption for 24 hours after abdominal hysterectomy, compared to placebo.[19] Such a study proposed that postoperative anxiolytic effect of melatonin treatment led to anti-nociceptive effect.[19,23] In contrast, this study could not show a significant difference of anxiolysis, as well as VAS pain score after immediate postoperative phase at post-anesthesia care unit arrival. The present study investigated a 4 mg of prolonged-release formulation of melatonin (Circadin®, Neurim Pharmaceuticals, Tel-Aviv, Israel). We chose this dose and form of melatonin because this was the only commercial available form in Thailand. This was a lower dose than other previous studies as premedication for analgesic effect. Forms of melatonin in all previous studies might be a short acting formulation or higher doses. However, from general clinical practice, 2-mg dose once daily of prolonged-release melatonin showed clinical benefits in terms of sleep quality and quality of life in patients aged 55 years and older without unexpected effects.[27] The therapeutic indication of this novel formulation melatonin is primary insomnia in elderly due to long duration of action and safety profiles.[8] Exogenous melatonin modulates via activation of the MT1 and/or MT2 melatonin receptors in the central nervous system.[13,27] In addition, there were several in vitro studies which demonstrated that the anti-nociceptive effects of melatonin could be reversed by various mechanism such as flumazenil, naloxone, potassium or calcium ion-channel-blockers.[12] Moreover, a recent review of literature proposed the synergistic effects of melatonin combined with morphine in terms of hyperalgesia and morphine tolerance reduction.[28] In contrast, another recent meta-analysis could not show the significant association between melatonin use and acute postoperative pain outcome.[29] The present study is the first clinical study of prolonged-release formulation in perioperative period. A recent study in patients who underwent orthognathic surgery showed that prophylactic oral melatonin significantly decreased pain, numbness perception and were also correlated to lower serum hydrogen peroxide but higher antioxidant enzyme levels.[30]

Patients with postoperative sleep disturbance can suffer from delirium, delayed recovery and pain.[31] Correlation between pharmacologic sleep promotion and perioperative pain control are still controversial.[32] The present study failed to demonstrate the improved postoperative sleep quality. Similar to a recent meta-analysis in cholecystectomy, melatonin interventions showed no substantial impact on sleep quality and pain score after 1 and 3 hours.[33] However, Kirksey A. et al concluded melatonin did not have effect on subjective sleep assessment but improved sleep efficiency and sleep time by actigraphy wrist bracelet measurement.[34]

Acute postoperative pain after hysterectomy may be complicated by anxiety state and psychological factors. A qualitative systematic review demonstrated that anxiety was a significant predictor for postoperative pain.[35] Such result was similar to another study in patients who underwent hysterectomy, in which preoperative anxiety was a positive predictor of immediate postoperative pain, pain on wards and also pain at home.[10] Moreover, Pinto et al. showed that anxiety predicted pain intensity at 48 hours after hysterectomy and also mediated pain catastrophizing.[6] In several clinical studies and systematic reviews, the outcome of preoperative melatonin administered to reduce preoperative anxiety was still

controversial among varied population and doses.[15,17,19,36] Whereas another systematic review from Cochrane database concluded melatonin can reduce preoperative anxiety at the same rate as standard medication with midazolam if it was given within appropriate timing.[37] However, the present study could not exhibit the benefit of melatonin as an anxiolytic.

In addition, the concept of immune-pineal axis influencing postoperative pain in patients who underwent hysterectomy was proposed. There was an inverse correlation between tumor necrosis factor (TNF) and nocturnal melatonin level. Moreover, the lower melatonin level was accompanied by lower cortisol levels and patients required higher doses of analgesics.[38] Therefore, exogenous melatonin might play a role for perioperative period especially in hysterectomy.

Fatigue has been defined as the lack of energy or exhaustion which is a complex, multifactorial symptom distinct from sleepiness or sadness.[39] The incidence of postoperative fatigue following hysterectomy was frequent regardless of general or spinal anesthesia.[40] Intensity of postoperative fatigue was the result of many biological factors, such as surgical stress response, anemia, declined nutritional status, psychological and social factors.[40] Fatigue was associated to poor quality of life in cancer patients who underwent surgery.[39] From the present study, melatonin enhanced subjective fatigue, general well-being VAS pain score and satisfaction score compared to placebo. These results were different from previous studies. Ivry M. et al. revealed melatonin improved quality of recovery following bariatric surgery in terms of sleep and pain levels.[16] Although differing in definition and measurement, the present study demonstrated advantages of melatonin administration in early postoperative fatigue and recovery, but no improvement of sleep quality. This may be due to lower morphine requirement.

Limitations of this study include the quality of recovery questionnaire in Thai version, which was not validated at the time the study was conducted. Likert and VAS pain score were measured to represent overall subjective recovery condition. The details of each standard domain may be inconclusive. Second, the results were focused only on perioperative and acute postoperative periods. Future studies should evaluate the effect of melatonin on chronic pain after hysterectomy. Third, the present study revealed only benefits of preoperative 2 doses of 4 mg of prolonged-release melatonin. Continuation of melatonin in postoperative period or earlier timing to load rather than one night before the surgery might be more appropriate with melatonin's pharmacokinetics and patient's metabolism. Moreover, to our knowledge, the appropriate dose and timing of oral prolonged-released melatonin was not established in perioperative period.

Conclusion

Preoperative orally prolonged-release melatonin had advantages in patients who underwent hysterectomy with or without oophorectomy under spinal anesthesia in terms of decreased morphine consumption, pain score in PACU. Postoperative fatigue, subjective general well-being, VAS pain score and also patients' satisfaction score in treatment group were better than placebo without adverse effects.

Declarations

Ethics approval and consent to participate: approval of the Institutional Review Board of Faculty of Medicine, Chulalongkorn University (IRB No.428/56, COA No. 781/2013, Chairperson Associate Prof U. Jaisamrarn) on December 19, 2013. Before study enrollment, all subjects reviewed and signed an informed consent document explaining the study procedures and potential risks.

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests

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Authors' contributions: PL helped with development of research idea, writing the proposal, data collection, data analysis, a major contribution in writing the manuscript. KD collected and analyzed the patient data. OR collected the patient data and reviewed the literature and perform final review of the manuscript. SC performed critical reviewing of research idea and the manuscript.

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Additional information: This study was presented at the 69th Post Graduate Assembly in Anesthesiology (PGA) of the New York State Society of Anesthesiologists Inc., New York City, USA, on December 12, 2015

Abbreviations

GABA; γ -aminobutyric acid

ASA; American Society of Anesthesiologists

VAS; Visual analog scale

APAIS; Amsterdam Preoperative Anxiety and Information Scale

PCA; patient-controlled analgesia

PACU; Post-anesthetic care unit

TNF; tumor necrosis factor

References

1. Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. *Current opinion in anesthesiology*. 2009;22(5):588-93.
2. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. *Anesthesia and analgesia*. 2003;97(2):534-40.
3. Beaussier M, Genty T, Lescot T, Aissou M. Influence of pain on postoperative ventilatory disturbances. Management and expected benefits. *Ann Fr Anesth Reanim*. 2014;33(7-8):484-6.
4. Kehlet H. Acute pain control and accelerated postoperative surgical recovery. *The Surg Clin North Am*. 1999;79(2):431-43.
5. Williams AC, Craig KD. Updating the definition of pain. *Pain*. 2016;157(11):2420-3.
6. Pinto PR, McIntyre T, Almeida A, Araujo-Soares V. The mediating role of pain catastrophizing in the relationship between presurgical anxiety and acute postsurgical pain after hysterectomy. *Pain*. 2012;153(1):218-26.
7. Marsh EE, Al-Hendy A, Kappus D, Galitsky A, Stewart EA, Kerolous M. Burden, Prevalence, and Treatment of Uterine Fibroids: A Survey of U.S. Women. *J Womens Health (Larchmt)*. 2018;27(11):1359-67.
8. Yousaf F, Seet E, Venkatraghavan L, Abrishami A, Chung F. Efficacy and safety of melatonin as an anxiolytic and analgesic in the perioperative period: a qualitative systematic review of randomised trials. *Anesthesiology*. 2010;113(4):968-76.
9. Downes E, Sikirica V, Gilabert-Estelles J, Bolge SC, Dodd SL, Maroulis C, et al. The burden of uterine fibroids in five European countries. *Eur J Obstet Gynaecol Reprod Biol*. 2010;152(1):96-102.
10. Kain ZN, Sevarino F, Alexander GM, Pincus S, Mayes LC. Preoperative anxiety and postoperative pain in women undergoing hysterectomy. A repeated-measures design. *J Psychosom Res*. 2000;49(6):417-22.
11. Han C, Ge Z, Jiang W, Zhao H, Ma T. Incidence and risk factors of chronic pain following hysterectomy among Southern Jiangsu Chinese Women. *BMC Anaesthesiol*. 2017;17(1):103.
12. Andersen LP. The analgesic effects of exogenous melatonin in humans. *Acta Anaesthesiol Scand*. 2016;60(7):1024-5.
13. Liu J, Clough SJ, Hutchinson AJ, Adamah-Biassi EB, Popovska-Gorevski M, Dubocovich ML. MT1 and MT2 Melatonin Receptors: A Therapeutic Perspective. *Annu Rev Pharmacol Toxicol*. 2016;56:361-83.
14. Chen WW, Zhang X, Huang WJ. Pain control by melatonin: Physiological and pharmacological effects. *Exp Ther Med*. 2016;12(4):1963-8.
15. Seet E, Liaw CM, Tay S, Su C. Melatonin premedication versus placebo in wisdom teeth extraction: a randomised controlled trial. *Singapore Med J*. 2015;56(12):666-71.

16. Ivry M, Goitein D, Welly W, Berkenstadt H. Melatonin premedication improves quality of recovery following bariatric surgery - a double blind placebo controlled prospective study. *Surg Obes Relat Dis.* 2017;13(3):502-6.
17. Hansen MV, Andersen LT, Madsen MT, Hageman I, Rasmussen LS, Bokmand S, et al. Effect of melatonin on depressive symptoms and anxiety in patients undergoing breast cancer surgery: a randomised, double-blind, placebo-controlled trial. *Breast Cancer Res Treat.* 2014;145(3):683-95.
18. Kunthonluxamee A, Pitimana-aree S, Laurujisawat P. Validity and Reliability of the Amsterdam Preoperative Anxiety and Information Scale (APAIS); Thai version in adult Thai pre-operative patients. *J Psychiatr Assoc Thai.* 2009;54(1):83-92.
19. Caumo W, Levandovski R, Hidalgo MP. Preoperative anxiolytic effect of melatonin and clonidine on postoperative pain and morphine consumption in patients undergoing abdominal hysterectomy: a double-blind, randomised, placebo-controlled study. *J Pain.* 2009;10(1):100-8.
20. Borazan H, Tuncer S, Yalcin N, Erol A, Otelcioglu S. Effects of preoperative oral melatonin medication on postoperative analgesia, sleep quality, and sedation in patients undergoing elective prostatectomy: a randomised clinical trial. *J Anesth.* 2010;24(2):155-60.
21. Mowafi HA, Ismail SA. Melatonin improves tourniquet tolerance and enhances postoperative analgesia in patients receiving intravenous regional anesthesia. *Anesth Analg.* 2008;107(4):1422-6.
22. Ismail SA, Mowafi HA. Melatonin provides anxiolysis, enhances analgesia, decreases intraocular pressure, and promotes better operating conditions during cataract surgery under topical anesthesia. *Anesth Analg.* 2009;108(4):1146-51.
23. Caumo W, Torres F, Moreira NL, Jr., Auzani JA, Monteiro CA, Londero G, et al. The clinical impact of preoperative melatonin on postoperative outcomes in patients undergoing abdominal hysterectomy. *Anesth Analg.* 2007;105(5):1263-71
24. Andersen LP, Kucukakin B, Werner MU, Rosenberg J, Gogenur I. Absence of analgesic effect of intravenous melatonin administration during daytime after laparoscopic cholecystectomy: a randomised trial. *J Clinical Anesth.* 2014;26(7):545-50.
25. 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(2):473-9.
26. Andersen LP, Werner MU, Rosenberg J, Gogenur I. A systematic review of peri-operative melatonin. *Anesthesia.* 2014;69(10):1163-71.
27. Lemoine P, Zisapel N. Prolonged-release formulation of melatonin (Circadin) for the treatment of insomnia. *Expert Opin Pharmacother.* 2012;13(6):895-905.
28. Hemati K, Pourhanifeh MH, Dehdashtian E, Fatemi I, Mehrzadi S, Reiter RJ, et al. Melatonin and morphine: potential beneficial effects of co-use. *Fund Clin Pharmacol.* 2020. doi.org/10.1111/fcp.12566
29. Oh SN, Myung SK, Jho HJ. Analgesic Efficacy of Melatonin: A Meta-Analysis of Randomized, Double-Blind, Placebo-Controlled Trials. *J Clin Med.* 2020;9(5):1553. doi.org/10.3390/jcm9051553

30. Lee TYC, Curtin JP. The effects of melatonin prophylaxis on sensory recovery and postoperative pain following orthognathic surgery: a triple-blind randomised controlled trial and biochemical analysis. *Int J Oral Maxillofac Surg.* 2019.
31. Su X, Wang DX. Improve postoperative sleep: what can we do? *Curr Opin Anesthesiol.* 2018;31(1):83-8.
32. Bjurstrom MF, Irwin MR. Perioperative Pharmacological Sleep-Promotion and Pain Control: A Systematic Review. *Pain Pract.* 2019;19(5):552-69.
33. Zhang J, Wang Y, Xu H, Yang J. The Influence of Melatonin on Sleep Quality After Laparoscopic Cholecystectomy: A Meta-Analysis of Randomised Controlled Trials. *Surg Laparosc Endosc Percutan Tech.* 2019;29(1):1-6.
34. Kirksey MA, Yoo D, Danninger T, Stundner O, Ma Y, Memtsoudis SG. Impact of Melatonin on Sleep and Pain After Total Knee Arthroplasty Under Regional Anesthesia With Sedation: A Double-Blind, Randomised, Placebo-Controlled Pilot Study. *J Arthroplasty.* 2015;30(12):2370-5.
35. Ip HY, Abrishami A, Peng PW, Wong J, Chung F. Predictors of postoperative pain and analgesic consumption: a qualitative systematic review. *Anesthesiology.* 2009;111(3):657-77.
36. Khezri MB, Merate H. The effects of melatonin on anxiety and pain scores of patients, intraocular pressure, and operating conditions during cataract surgery under topical anesthesia. *Indian J Ophthalmol.* 2013;61(7):319-24.
37. Hansen MV, Halladin NL, Rosenberg J, Gogenur I, Moller AM. Melatonin for pre- and postoperative anxiety in adults. *The Cochrane database of systematic reviews.* 2015(4):CD009861.
38. de Oliveira Tatsch-Dias M, Levandovski RM, Custodio de Souza IC, Gregianin Rocha M, Magno Fernandes PA, Torres IL, et al. The concept of the immune-pineal axis tested in patients undergoing an abdominal hysterectomy. *Neuroimmunomodulation.* 2013;20(4):205-12.
39. Hugoy T, Lerdal A, Rustoen T, Oksholm T. Predicting postoperative fatigue in surgically treated lung cancer patients in Norway: a longitudinal 5-month follow-up study. *BMJ Open.* 2019;9(9):e028192.
40. Wodlin NB, Nilsson L, Arestedt K, Kjolhede P, Group GS. Mode of anesthesia and postoperative symptoms following abdominal hysterectomy in a fast-track setting. *Acta Obstet Gynaecol Scand.* 2011;90(4):369-79.

Tables

Table 1 Demographic data and patients' characteristics

| Patient characteristics | P group (n=27) | M group (n=27) | p-value |
|--------------------------------|---------------------------|---------------------------|----------------|
| Age (year) | 42.85 ± 5.16 | 44.93 ± 4.13 | 0.11 |
| Weight (kg) | 59.07 ± 8.88 | 60.0 ± 7.86 | 0.69 |
| BMI (kg/m²) | 23.77 ± 3.59 | 24.48 ± 3.22 | 0.45 |
| ASA PS I/II | 23/4 | 22/5 | 0.72 |
| Diagnosis | | | 0.49 |
| Myoma uteri | 20 | 21 | |
| Adenomyosis | 6 | 4 | |
| ovarian cyst | 1 | 2 | |
| Operation | | | 0.79 |
| TAH | 15 | 14 | |
| TAH and SO | 12 | 13 | |

Results showed in mean ± S.D., ASA PS = The American Society of Anesthesiologists physical status, BMI=Body Mass Index, TAH = Trans Abdominal Hysterectomy, SO = Salpingo-oophorectomy

Table 2 Intraoperative outcomes

| Variable | P group (n=27) | M group (n=27) | p-value |
|---|-------------------|-------------------|---------|
| Dose of bupivacaine (mg) | 18.25 ± 1.05 | 18.75±0.8 | 0.18 |
| Anesthetic level (T4/T6) | 18/9 | 22/5 | 0.19 |
| Sedation requirement (Yes/No) | 11/16 | 16/11 | 0.27 |
| Propofol dose | 90.37±25.47 | 138.15±27.61 | 0.21 |
| Skin incision (Low midline/Pfennenstiel) | 4/23 | 8/19 | 0.32 |
| Duration of surgery (min) | 105.56±19.23 | 103.52±31 | 0.77 |
| Blood loss (mL) | 220.37±23.90 | 247.04±29.89 | 0.49 |
| Intraoperative events (Yes/no) | 18/9 | 20/7 | 0.83 |
| Hypotension need treatment | 16 (59.3%) | 18 (66.7%) | 0.64 |
| Ephedrine dose (mg) | 5±6.17 | 6.15±6.7 | 0.51 |
| Bradycardia | 0 | 0 | |
| Nausea/Vomiting | 2 (7.4%) | 2 (7.4%) | 0.56 |

Results showed in mean ± S.D or n(%)

Table 3 Analgesic outcomes, other subjective scores and adverse effects

| Outcomes | P group (n=27) | M group (n=27) | p-value |
|---|---------------------------|---------------------------|----------------|
| Morphine consumption in 24 hr (mg) | 42.63±8.21 | 33.04±10.42 | <0.01* |
| VAS pain score (mm) | | | |
| T0 | 23.41±4.62 | 8.07±3.39 | 0.001* |
| T1 | 41.67±9.13 | 35.26±5.88 | 0.19 |
| T6 | 56.74±8.87 | 48.89±7.94 | 0.21 |
| T24 | 34.37±6.56 | 29.26±4.91 | 0.12 |
| VAS Satisfaction score | 7.78±1.05 | 8.56±1.25 | 0.02* |
| Preoperative | | | |
| Level of anxiety | 8.63±3.48 | 8.11±4.09 | 0.62 |
| VAS sleep quality | 26.89±26.34 | 23.81±26.41 | 0.67 |
| VAS fatigue level | 2.19±2.15 | 1.85±2.45 | 0.59 |
| VAS general well being | 20.70±21.65 | 22.63±23.11 | 0.75 |
| Postoperative at 24 hr | | | |
| Level of anxiety | 5.44±1.37 | 5.00±2.00 | 0.35 |
| VAS sleep quality | 57.93±21.08 | 49.33±21.02 | 0.14 |
| VAS fatigue | 5.15±1.85 | 3.30±2.22 | 0.002* |
| VAS general well being | 49.78±14.87 | 31.59±24.14 | 0.002* |
| Surgical complications | 0 | 0 | |
| VAS Nausea/Vomiting in 24 hr after surgery | 3.7±2.52 | 4.1±2.67 | 0.56 |

Results showed in mean \pm S.D or n(%)

Figures

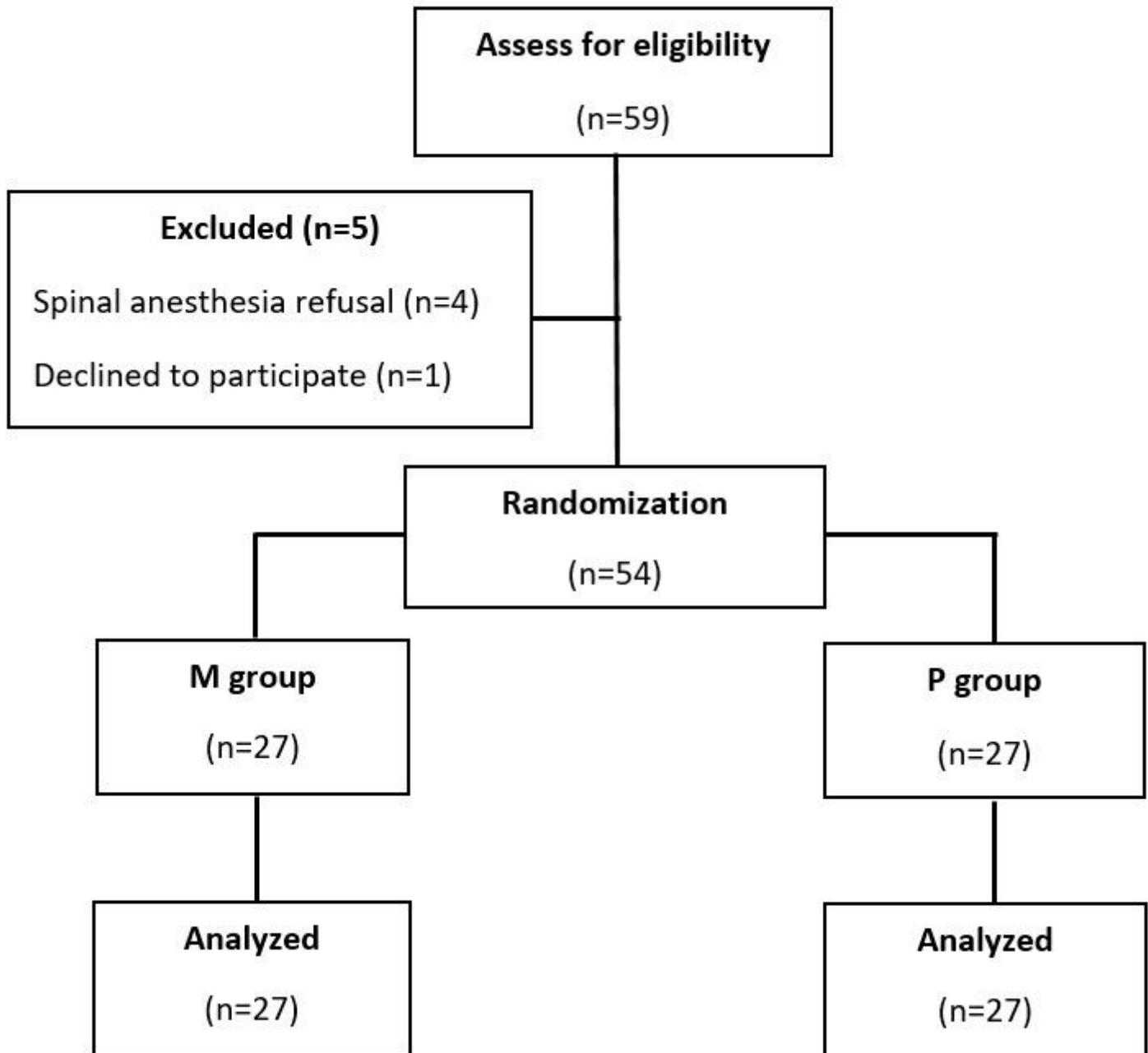


Figure 1

CONSORT diagram