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Melatonin Decreased Postoperative Pain after Abdominal Hysterectomy: A Randomized, Double-blind, Placebo-controlled Trial

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Abstract:

Background: Incidence of anxiety and pain in patients undergoing hysterectomy is significant and primarily due to postoperative pain. Most patients usually receive opioids for pain control. Melatonin is a natural hormone produced by the body. Synthetic melatonin is available over the counter for the management of insomnia and jetlag. Clinically, melatonin can also be used to reduce pain and analgesic requirement in patients undergoing surgery. The analgesic benefit of melatonin as primary or adjuvant agents has been reported in various studies.

Objective: We aimed to study whether melatonin could improve pain and other postoperative conditions after hysterectomy.

Methods: A randomized, double-blinded, placebo-controlled trial study was carried out on 54 women undergoing hysterectomy, with or without oophorectomy under spinal anesthesia. Patients were allocated randomly to receive either 4 mg prolonged-release melatonin at night and in the morning before surgery or 2 doses of placebo. Morphine consumption within 24 hours, visual analog scale (VAS) pain score, quality of sleep, anxiety level score, fatigue, general well-being and satisfaction score were measured.

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Results: Morphine consumption in melatonin group was significantly low compared to placebo (33.04 ± 10.42 and 42.63 ± 8.21 mg, ($p < 0.001$). Also, postoperative VAS pain scale was lower in the melatonin group at recovery room arrival (23.41 vs 8.07, $p = 0.01$). Postoperative fatigue, general well-being and satisfaction scores 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 reduced morphine consumption within 24 hours after surgery. Melatonin may be an additional choice of multimodal analgesia for hysterectomy.

Keywords: Melatonin, Hysterectomy, Postoperative pain

Background

The hysterectomy is one of the most frequently performed surgical procedures in gynecology. Especially hysterectomy provides a definitive cure for women with symptomatic fibroids resulting in complete resolution of symptoms, relieved significant pain and distress.[1] However, abdominal hysterectomy is associated with moderate to severe postoperative pain, particularly in the early postoperative period.[2] Traditional methods for postoperative pain management include opioids administered systemically using intravenous patient-controlled analgesia (PCA), or neuraxial via epidural or spinal injections.

However, pain relief, specifically on movement, is not always adequately controlled when using PCA, despite moderate–large doses of morphine. This is associated with side-effects such as postoperative nausea and vomiting, tiredness, pruritus, headache, and constipation.[3] Currently epidural or intrathecal analgesia considered by some to be the current analgesic preferences for pain management after abdominal surgery.[4,5] Although concerns remain regarding complications after central blocks, specifically in elderly women.[6] Common postoperative problems after hysterectomy are not only acute postoperative pain but also high anxiety levels among patient. Preoperative anxiety in hysterectomy is strongly related to postoperative pain score and quality of life.[7-9] Benzodiazepine is a common medication as preoperative anxiolytic in hysterectomy but may impair psychomotor performance.

There has been recent interest in alternative methods for analgesia with minimal side-effects. Melatonin (*N*-acetyl-5-methoxytryptamine) is a pineal hormone regulating sleep-wake cycle in mammals. Besides 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.[10] The strong chronobiotic properties and the ability to regulate circadian rhythm make melatonin a good choice for sleep disorders in the elderly.[11]

Analgesic mechanisms of melatonin are not known but may be involved with β-endorphins, GABA receptor, opioid receptors and nitric oxide-arginine pathway in brain were proposed.[12] 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.[13-15] However, melatonin's analgesic effect remains controversial in the perioperative period and requires further investigation.[16] Therefore, the aim 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 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

This study was registered in an international registry, clinicaltrials.gov (identification number TCTR20140516001) before patient recruitment. The study was performed at the Department of Anesthesiology, King Chulalongkorn Memorial Hospital, Thai Red Cross Society. After approval from the Institutional Review Board of Faculty of Medicine, Chulalongkorn University (IRB No.428/56), oral and written informed consent was obtained from 54 patients. ASA physical status I-II and age 18-65 years scheduled for elective abdominal hysterectomy (with or without ovarian surgery) were enrolled into the randomized, double blinded, 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/m^2 and patients who refused spinal anesthesia.

Randomization and blinding

The patients were randomly divided into 2 groups (27 patients each) as shown in figure 1 by using computer-generated randomized numbers inserted into sealed opaque envelopes and marked 1–54. All personnel involved in patient management were fully blinded to the method of analgesia until the study was completed. 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.

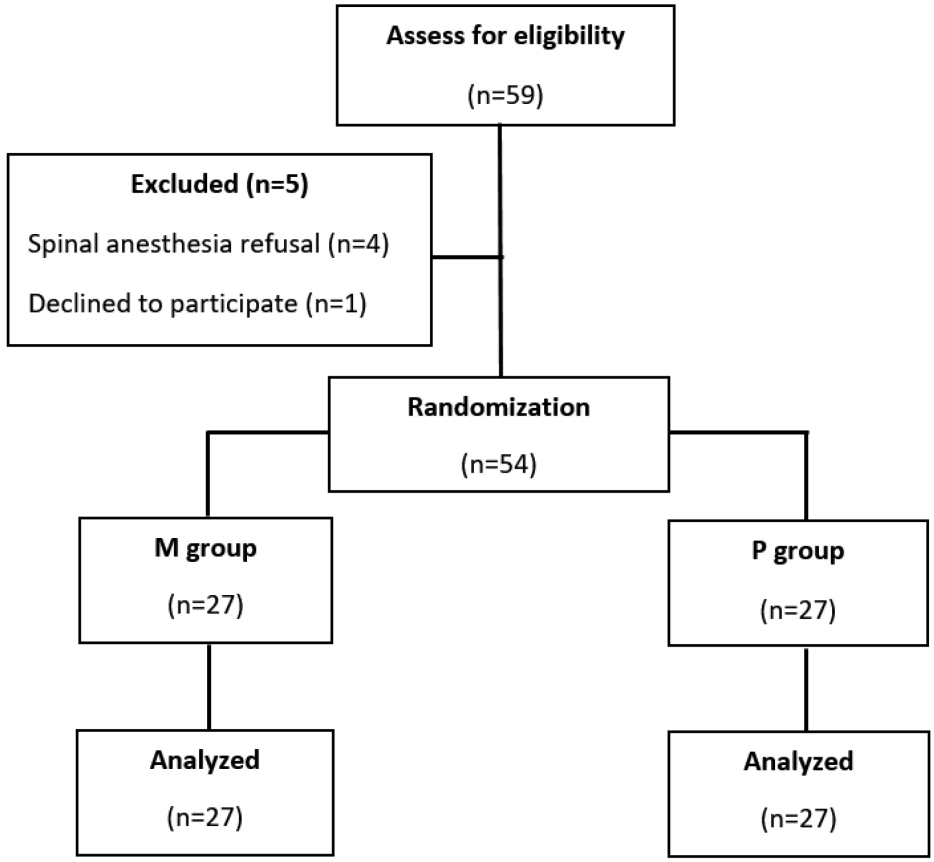

Figure 1 CONSORT diagram

Anesthesia and surgery

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.[17] 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 anesthesiologists. 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.

Postoperative pain management

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. In addition to the routine postoperative protocols, 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.[18] 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% in order to achieve statistical significance for the primary endpoint. The sample size was calculated using the unpaired two-sided t-test. Assuming $\beta = 0.2$ (power 80%) and $\alpha = 0.05$, we determined that we would require 50 patients (25 per group) in order to achieve statistical significance for the primary endpoint.

We recruited 54 patients (27 in each group) in order to achieve adequate power in the case of missing data or allowing a 10% drop-out rate. Statistical analysis was calculated by using SPSS software version 22.0. Data are presented as mean ± 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 $p < 0.05$ 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 comparable. 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.

Table 1 Demographic data and patient 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/m^2)	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	
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

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/Pfannenstiel)	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

Variable	P group (n=27)	M group (n=27)	*p*-value
Bradycardia	0	0	
Nausea/Vomiting	2 (7.4%)	2 (7.4%)	0.56

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

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)

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*
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 ± S.D. or n (%)

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,[19] dental surgery,[20] hand surgery,[21] cataract surgery under topical anesthesia[22] and abdominal hysterectomy.[18,23] 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.[11,13,26,27] 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.[18] Such a study proposed that postoperative anxiolytic effect of melatonin treatment led to anti-nociceptive effect.[18,23] 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 commercially 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 any side effects.[28] The therapeutic indication of this novel formulation melatonin is primary insomnia in elderly due to long duration of action and safety profiles.[27] Because exogenous melatonin modulates via activation of the MT1 and/or MT2 melatonin receptors in the central nervous system.[28,29] 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.[10] Moreover, a recent review of literature proposed the synergistic effects of melatonin combined with morphine in terms of hyperalgesia and morphine tolerance reduction.[30] In contrast, another recent meta-analysis could not show the significant association between melatonin use and acute postoperative pain outcome.[31] 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.[32]

Patients with postoperative sleep disturbance can suffer from delirium, delayed recovery and pain.[33] However, in our 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.[34] 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.[35] But, correlation between pharmacologic sleep promotion and perioperative pain control are still controversial.[13]

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.[36] 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.[37] Moreover, Pinto et al. showed that anxiety predicted pain intensity at 48 hours after hysterectomy and also mediated pain catastrophizing.[38] 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.[15,18,20,39] 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.[40] However, our 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.[41] 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.[42] The incidence of postoperative fatigue following hysterectomy was frequent regardless of general or spinal anesthesia.[43] Intensity of postoperative fatigue was the result of many biological factors, such as surgical stress response, anemia, declined nutritional status, psychological and social factors.[43] Fatigue was associated to poor quality of life in cancer patients who underwent surgery.[42] 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.[14] 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 need to 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 clinically relevant advantages in patients who underwent hysterectomy

with or without oophorectomy under spinal anesthesia in terms of decreased morphine consumption, pain score in PACU. Furthermore, this finding indicates that the postoperative fatigue, subjective general well-being, VAS pain score and patients' satisfaction score in treatment group were better than placebo without adverse effects.

List of 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

Ethics approval and consent to participate

The approval of the Institutional Review Board of Faculty of Medicine, Chulalongkorn University (IRB No.428/56). Before study enrollment, all subjects reviewed and signed an informed consent document explaining the study procedures and potential risks.

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. DLW supervision, critical review and editing of the manuscript. SC performed critical reviewing of research idea and the manuscript.

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