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Efficacy of azasetron on postoperative chronic pain after pulmonary surgery: a randomized triple-blind controlled trial

Yang Xu[1†], Fei Jiang[2†], Shengnan Shi[2], Hongyu Zheng[2], Xuhong Li[2], Xihong Ye[2*] and Xingrui Gong[2*]

Abstract

Background Inhibition of 5-HT3 (5-Hydroxyl Tryptamine) receptors is known to enhance morphine analgesia in animal models. We tested the efficacy of azasetron, a 5-HT3 receptor antagonist, on postoperative chronic pain after pulmonary surgery in a randomized triple-blind controlled study.

Methods A total of 250 patients who were scheduled to receive pulmonary surgery were randomized to patient-controlled analgesia (PCA) using 200 μg sufentanil with normal saline or 200 μg sufentanil with 20 mg azasetron. The numerical rating scale of pain (NRS) was recorded at baseline, postoperative day (POD) 1, 2, 3, 90, and 180. Negative binomial regression was used to identify associated factors for postoperative NRS six months after surgery.

Results The results showed that azasetron did not affect the primary outcomes: the incidence of postoperative chronic pain on POD90 and 180. However, azasetron decreased postoperative NRS at rest and activity on POD1, 2, and 3. Furthermore, azasetron decreased postoperative nausea and vomiting on POD1 and 2. Univariate and multivariate negative binomial regression analysis identified preoperative pain, smoking, drinking and open surgery are risk factors of chronic pain six months after surgery.

Conclusions Azasetron did not affect the incidence of chronic pain after pulmonary surgery. The presence of preoperative pain, smoking, drinking, and open surgery were found to be associated with chronic pain six months after surgery.

Clinical trial registration The trial was registered prior to patient enrollment at the Chinese Clinical Trial Registry (ChiCTR2200060139), 20/05/2022; the site url is https://www.chictr.org.cn/.

Keywords Azasetron, Pulmonary surgery, Acute pain, Chronic pain

[†]Yang Xu and Fei Jiang contributed equally to the article.

*Correspondence:
Xihong Ye
yezi703@126.com
Xingrui Gong
gongxrhbxy@sohu.com

[1]Institute of Neuroscience and Brain Disease, Department of Pain, Xiangyang Central Hospital, Hubei University of Arts and Science, Hubei, China
[2]Institute of Neuroscience and Brain Disease, Department of Anesthesiology, Xiangyang Central Hospital, Hubei University of Arts and Science, No.136. Jinzhou Street, Xiangcheng District, Xiangyang 441000, China

Introduction

Postoperative pain management is critical for a patient's recovery after surgery. However, the incidence of acute and persistent pain is exceptionally high after pulmonary surgery, with many patients suffering from "respiratory" pain [1]. Interestingly, postoperative acute pain is a critical contributor of chronic pain. Acute pain is likely to transition into chronic pain if not properly managed during the acute phase [2]. Postoperative patient-controlled analgesia (PCA) with opium is the most frequently used method for postoperative analgesia and has the potential to prevent the transition from acute to chronic pain [3]. However, opioid-related side effects, including respiratory depression, constipation, pruritus, tolerance, addiction, and the facilitation of neuroinflammation, limit the use of high-dose opioids for postoperative analgesia [4]. Thus, combining with other analgesics for postoperative analgesia may decrease the opioid requirement, adverse complications and the development of chronic pain.

After surgery, local inflammation, descending pain modulation, and postoperative opiates all cause 5-Hydroxyl Tryptamine (5-HT) release, which induces nausea and vomiting reflex [5]. 5-HT3 receptor antagonists have been used for treating various nausea and vomiting syndromes, including, postoperative nausea and vomiting (PONV), chemotherapy- and radiation-induced nausea and vomiting [6]. Azasetron is a 5-HT3 receptor antagonist and clinical use of azasetron for treating PONV has been accompanied by few side effects (such as headache, and constipation) [7]. Recently, studies have demonstrated that an addition of 5-HT3 receptor antagonists decreases opioid-induced hyperalgesia and tolerance in animal models [8, 9], prevents propofol injection pain [10] and reduces the pain intensity in patients with fibromyalgia [11]. In addition, previous studies have demonstrated that postoperative acute pain is a risk factor for postoperative chronic pain, while acute pain control prevents the chronic pain transition [1]. Further, activation of 5-HT3 receptors contribute to the development of persistent pain [12]. Therefore, perioperative incorporating 5-HT3 receptor antagonists has the potential to prevent postoperative chronic pain transition. Thus, we designed this experiment to investigate the effect of azasetron on postoperative chronic pain in patients after pulmonary surgery. Further, we performed regression analysis to identify the relevant factors for postoperative pain six months after surgery.

Materials and methods

The study was conducted in accordance with the Declaration of Helsinki (October 2000) which was outlined by the World Medical Association. Ethical approval for this study was provided by the Institutional Ethics Committee of Xiangyang Central hospital, affiliated with the Hubei University of Arts and Science on April 25 2022, and written informed consent was obtained from all subjects participating in the trial. The study was a randomized triple-blind controlled parallel trial and was registered prior to patient enrollment at https://www.chictr.org.cn/ (ChiCTR2200060139), 20/05/2022.

Patients, aged 20–65 years, with ASA physical status I to III, and scheduled for elective pulmonary surgery between July 2022 to Dec 2022 in our tertiary hospital were recruited in this study. Exclusion criteria: patients with severe pre-existing conditions such as heart (coronary artery stenosis > 80% or myocardial infarction) and brain (previous cerebrovascular hemorrhage or infarction) disease, pulmonary disease, hepatic disease, and renal disease, poorly controlled hypertension, any serious allergy to trial medications, any contraindication to lidocaine, ropivacaine, midazolam, sufentanil, cisatracurium, azasetron, propofol, diclofenac sodium, any administration of serotonin reuptake inhibitors three months before surgery, any preoperative diagnosed psychiatric disease, and who have preoperative chronic pain or received chronic pain treatment.

Before the experiment, a statistician generated randomized numbers "0" and "1" with a computer in a 1: 1 ratio to determine the group allocation; if the number was "0" or "1", the patient was assigned to the control group or azasetron group, respectively. Before a patient's admission to the operating room, the anesthesia nurse acquired the group allocation information and prepared the PCA pump, and the group allocation was concealed until the end of the experiment. The PCA pump consists of 200 μg sufentanil with 4 mL azasetron (20 mg) or 200 μg sufentanil with 4 mL normal saline, according to patient allocation (totally 100 mL with a rate of 2 mL/h). After the PCA configuration is completed, it is handed over to the attending anesthesiologist. At the end of the surgery, the anesthetist installs the pump for the patient. Patients' information and postoperative follow-up were done by an assistant anesthetist who did not know the group allocation. Patient was educated to start a bolus (2 mL one bolus) if they could not endure the pain or NRS ≥ 4 after surgery. The anesthesiologist, surgeon, observer and patient were all blind to the group allocation.

Following the patient's admission to the operating room, the right jugular vein cannula was placed for fluid infusion and postoperative analgesia under local anesthesia. Left or right radial arterial cannulation was placed under local anesthesia and was used for intraoperative hemodynamic monitoring and blood gas measurement. All of the patients received electrocardiography, cuff blood pressure and invasive blood pressure, pulse saturation, temperature and bi-spectral index (BIS) monitoring. The BIS was controlled between 40 ~ 55 with propofol and remifentanil, and inhalation of sevoflurane.

Neuromuscular blocker rocuronium was intermittently injected. During the surgery, the mean arterial pressure was maintained within 20% of its baseline value and above 60 mmHg. If the mean blood pressure was 30% higher or lower than the baseline value, or >120, or <55 mmHg, nitroglycerin 50 mcg or Phenylephrine 20 mcg was injected to maintain the hemodynamic stability.

Patient's baseline characteristics, including age, gender, weight, BMI, Numerical rating scale of pain (NRS) before surgery, previous history (smoking, drinking, education, marriage, cerebrovascular disease, heart disease, pulmonary disease, hepatic disease, renal disease, hypertension, diabetes mellitus [DM]), the rank of American Society of Anesthesiologists [ASA], laboratory test results (white blood cell [WBC], neutrophil), surgery manner (video-assisted thoracic surgery, open surgery), were recorded. The primary outcomes were the NRS on postoperative day (POD) 90, and 180 at resting and at activity after surgery. Secondary outcomes included PONV, postoperative headache, vertigo, constipation, and diarrhea recorded on POD3 and NRS on POD1, 2, and 3 both at resting and activity. Patient's baseline characteristics and evaluations were recorded by the second anesthetist who was blinded to the group allocation. Pain intensity was evaluated with an 11-point NRS with 0 representing no pain and 10 representing the worst pain you can imagine [13, 14]. A smoker refers to a person who smokes continuously or cumulatively for six months or more before surgery. Drinking habit was defined as consuming>500 mL (40% concentration) a week or 30 g per day;

Statistical analysis

Quantitative data were expressed as means (standard deviation, SD) and median (inter-quartile range, IQR), and comparisons between groups were made using the two-tailed student's t-test, and Mann-Whitney U test if they were normally (Shapiro test) or not normally distributed, respectively. Categorical data were expressed relative frequencies and analyzed using a chi-square test. According to our preliminary test, the incidence of chronic pain after pulmonary surgery is about 40%. We calculated that 118 patients were required in each group to detect a 15% reduction in the incidence of chronic pain from a baseline incidence of 40% using two-sided $\alpha=0.05$, $\beta=0.2$. Considering possible 5% dropouts, we included 250 subjects in total. If any life-threatening or serious complications occur during the study, the patient will be immediately suspended and treated. As postoperative nausea and vomiting can be remedied with other medications, no mid-term analysis will be conducted in this study. We compared acute and chronic pain between groups by an intention to treatment analysis and per protocol analysis. Pain intensity measured on POD1, 2, and 3 between two groups used two-way Analysis of Variance (ANOVA) for repeated measures. Then, univariate and multivariate negative binomial regression was used to analyze the incidence rate ratio (IRR) of NRS six months after surgery (the variance exceeds the mean), and a sensitive subgroup analysis was followed in patients without preexisting pain. The variables with a $P<0.05$ were included for multivariate regression analysis. The statistical analyses were done using the R software (version 4.2.1). A $P<0.05$ was considered a statistically significant difference.

Results

Patients' baseline characteristics

In our study, 298 patients were consecutively screened and 48 patients were excluded (16 refused participation; 14 with severe cerebrovascular disease; 13 with severe heart disease; 4 with other cancers; 1 was secondary surgery). A total of 250 patients were randomized to the control and azasetron groups. Seven patients in the control group and three patients in the azasetron group ceased the PCA due to the severe itch. Eleven and twelve patients were lost to follow-up six months after surgery in the control and azasetron groups, respectively. In the end, 227 patients were used for identification of relevant factors for postoperative chronic pain six months after surgery. The trial flowchart is shown in Fig. 1. Patients' baseline characteristics, including age, gender, weight, BMI, NRS before surgery, previous history, ASA, laboratory test results, and surgery manner were not different between the control and azasetron groups (Table 1).

Primary and secondary outcomes

The primary outcomes of NRS on POD90 and POD180 were evaluated, and our results showed that azasetron did not affect the primary outcome using per protocol analysis: the incidence of chronic pain both on POD90 (Azasetron, 43.7%, Control, 52.5%, $P=0.218$) and 180 (Azasetron, 39.8%, Control, 42.1%, $P=0.830$) after surgery (Table 2). The primary outcomes were further confirmed with intention to treat analysis: the incidence of chronic pain both on POD90 (Azasetron, 46.4%, Control, 53.6%, $P=0.312$) and 180 (Azasetron, 45.6%, Control, 47.2%, $P=0.899$) after surgery (Table 2). Azasetron also did not affect the NRS at rest and activity on POD90 (rest, $P=0.591$; activity, $P=0.633$) and 180 (rest, $P=0.452$; activity, $P=0.804$) after surgery.

The secondary outcomes of NRS on POD1, 2 and 3 were evaluated using two-way ANOVA with repeated measures and the results showed that azasetron decreased postoperative pain at rest (azasetron $F_{(1,\ 248)}=13.44$, $P=0.001$; time $F_{(2,\ 496)}=10.04$, $P=0.000$; interaction $F_{(2,\ 496)}=0.1435$, $P=0.866$) and activity (azasetron $F_{(1,\ 248)}=10.24$, $P=0.002$; time $F_{(2,\ 496)}=24.05$, $P=0.000$; interaction $F_{(2,\ 496)}=0.9701$, $P=0.380$). The pain

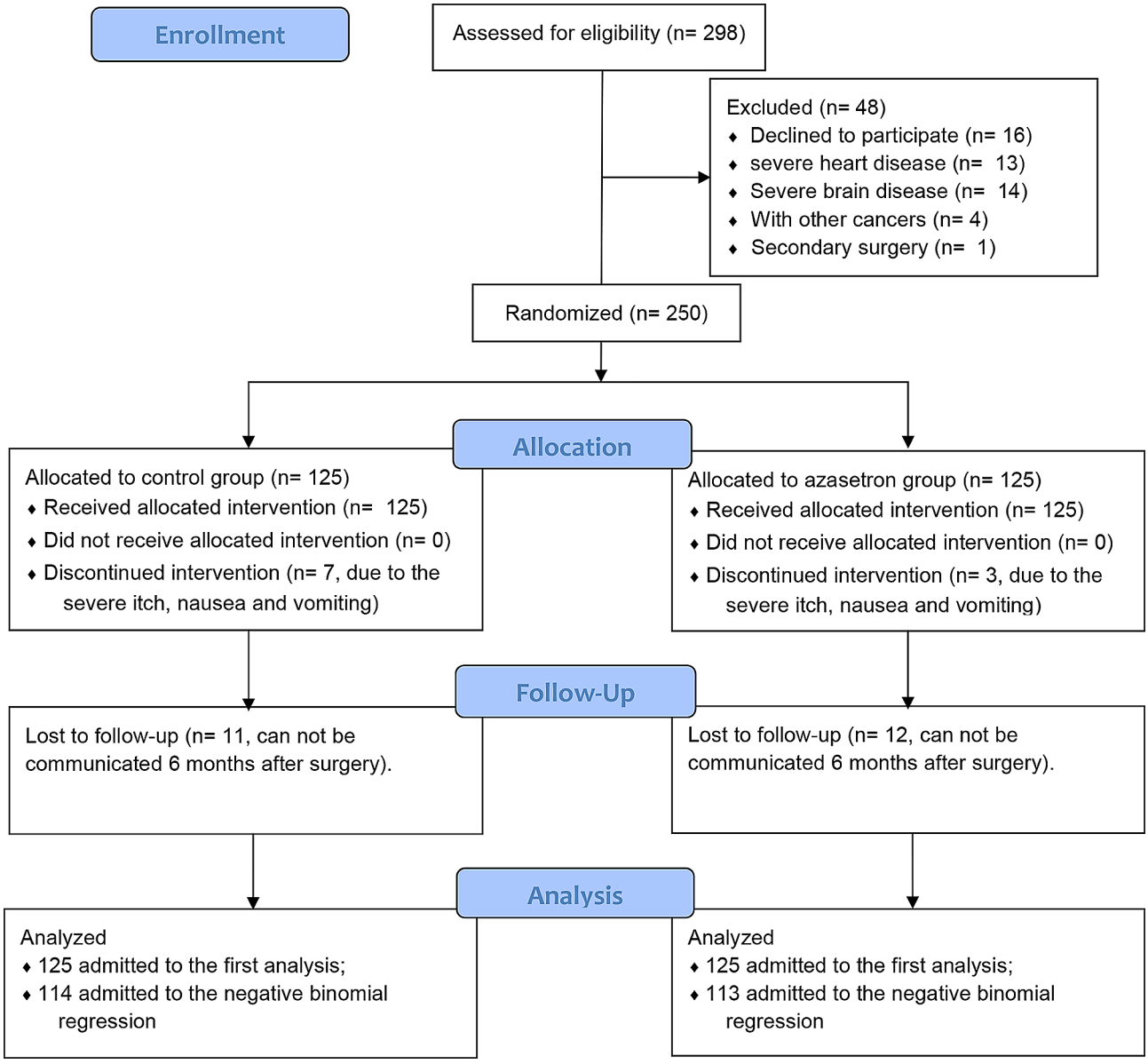

Fig. 1 Trial flowchart

intensity, both at rest and activity, decreased with time during the postoperative three days, and there is no interaction between azasetron and time. Mann-Whitney U test was followed to compare the NRS between groups, and the result showed azasetron decreased NRS on POD1 (rest, $P=0.019$; activity, $P=0.001$), 2 (rest, $P=0.048$; activity, $P=0.002$), and 3 (rest, $P=0.020$; activity, $P=0.034$) after surgery (Table 3). In addition, azasetron decreased medical treatment for PONV on POD1 ($P=0.023$), and 2 ($P=0.001$), and incidence of PONV on POD1 ($P=0.001$), and 2 ($P=0.001$), but not on POD3 ($P=1$). Further, azasetron decreased postoperative diclofenac usage on POD1 ($P=0.009$) and POD2 ($P=0.023$). However, azasetron did not affect the incidence of postoperative headache, vertigo, constipation, and diarrhea in the postoperative three days.

Identification of relevant factors for NRS scores six months after surgery

Patients in the control and azasetron groups were combined, and 23 patients lost to follow up six months after surgery were excluded from the regression analysis. Therefore, a total of 227 patients were used for identification of relevant factors for chronic pain six months after surgery. As the NRS scores at activity six months after surgery showed a negative binomial distribution, negative binomial regression was used for identifying relevant factors of NRS scores. Univariate negative binomial

Table 1 Baseline characteristics of the study population

	Control group	Azasetron group	*P*
n	125	125	
Sex Male	53 (42.4)	49 (39.2)	0.699
Female	72 (57.6)	76 (60.8)	
Age (median [IQR])	55.00 [51.00, 62.00]	56.00 [47.00, 60.00]	0.262
Weight (median [IQR])	60.00 [55.00, 69.00]	60.00 [55.00, 68.00]	0.898
BMI (median [IQR])	23.38 [21.00, 25.14]	22.49 [20.81, 24.64]	0.185
Smoking No	94 (75.2)	99 (79.2)	0.547
Yes	31 (24.8)	26 (20.8)	
Drinking No	94 (75.2)	92 (73.6)	0.885
Yes	31 (24.8)	33 (26.4)	
Education years (median [IQR])	9.00 [6.00, 12.00]	9.00 [9.00, 12.00]	0.432
Married No	14 (11.2)	12 (9.6)	0.836
Yes	111 (88.8)	113 (90.4)	
Preoperative pain No	109 (87.2)	106 (84.8)	0.715
Yes	16 (12.8)	19 (15.2)	
Surgery history No	65 (52.0)	70 (56.0)	0.612
Yes	60 (48.0)	55 (44.0)	
Cerebrovascular disease No	109 (87.2)	107 (85.6)	0.854
Yes	16 (12.8)	18 (14.4)	
Heart disease No	111 (88.8)	108 (86.4)	0.701
Yes	14 (11.2)	17 (13.6)	
Pulmonary disease No	114 (91.2)	112 (89.6)	0.830
Yes	11 (8.8)	13 (10.4)	
Hepatic disease No	124 (99.2)	123 (98.4)	1
Yes	1 (0.8)	2 (1.6)	
Renal disease No	123 (98.4)	119 (95.2)	0.281
Yes	2 (1.6)	6 (4.8)	
Hypertension No	103 (82.4)	108 (86.4)	0.486
Yes	22 (17.6)	17 (13.6)	
DM No	117 (93.6)	120 (96.0)	0.569
Yes	8 (6.4)	5 (4.0)	
ASA II	52 (41.6)	49 (39.2)	0.797
III	73 (58.4)	76 (60.8)	
Heart function I	91 (72.8)	94 (75.2)	0.773
II	34 (27.2)	31 (24.8)	
WBC (median [IQR])	5.02 [4.30, 6.30]	5.11 [3.96, 6.60]	0.721
Neutrophil (median [IQR])	3.10 [2.46, 3.80]	3.02 [2.28, 3.84]	0.732
Surgery manner VATS	114 (91.2)	109 (87.2)	0.415
Open	11 (8.8)	16 (12.8)	

American society of anesthesiologist association, ASA; Body mass index, BMI; Diabetes mellitus, DM; Postoperative day, POD; Numerical rating scale of pain, NRS; White blood cell, WBC; Video-assisted thoracic surgery, VATS

regression identified four variables, including preoperative pain, smoking, drinking, and surgery manner. Then these four variables were included for multivariate negative binomial regression and the results identified preoperative pain (IRR, 3.010 and 95% CI [1.843, 5.004]), smoking (2.431 [1.515,3.935]), drinking (1.655 [1.043, 2.631]), and open surgery (2.250 [1.312, 3.949]) were risk factors of postoperative chronic pain six months after surgery (Table 4).

Considering preexisting pain may affect the effect of azasetron on postoperative chronic pain. A sensitive sub-group analysis was performed in patients without preexisting pain. Univariate negative binomial regression identified four variables, including preoperative pain, smoking, drinking, and gender. Then these four variables were included for multivariate negative binomial regression and the results identified smoking (IRR, 2.484 [1.456, 4.284]), drinking (1.823 [1.064, 3.128]), and open surgery (2.452 [1.275, 4.919]) were risk factors of postoperative chronic pain six months after surgery (Supplemental Table 1).

Table 2 Postoperative chronic pain

	Control group	Azasetron group	*P*
NRS POD90 resting (median [IQR])	1.00 [0.00, 2.00]	0.00 [0.00, 2.00]	0.591
NRS POD90 activity (median [IQR])	3.00 [0.00, 4.00]	0.00 [0.00, 4.00]	0.633
Chronic pain incidence POD90 No ITT	58 (46.4)	67 (53.6)	0.312
Yes	67 (53.6)	58 (46.4)	
Chronic pain incidence POD90 No PPA	58 (47.5)	67 (56.3)	0.218
Yes	64 (52.5)	52 (43.7)	
NRS POD180 resting (median [IQR])	0.00 [0.00, 1.00]	0.00 [0.00, 0.00]	0.452
NRS POD180 activity (median [IQR])	0.00 [0.00, 2.00]	0.00 [0.00, 2.00]	0.804
Chronic pain incidence POD180 No ITT	66 (52.8)	68 (54.4)	0.899
Yes	59 (47.2)	57 (45.6)	
Chronic pain incidence POD180 No PPA	66 (57.9)	68 (60.2)	0.830
Yes	48 (42.1)	45 (39.8)	

Intention to treat analysis, ITT; Numerical rating scale of pain, NRS; Postoperative day, POD; PONV, Postoperative Nausea and vomiting; per protocol analysis, PPA

Table 3 Postoperative acute pain and adverse events

	Control group	Azasetron group	*P*
Postopertive NSAID adjuvants			
Diclofenac POD1 No	82 (65.6)	103 (82.4)	0.009
Once	37 (29.6)	18 (14.4)	
Twice	6 (4.8)	4 (3.2)	
Diclofenac POD2 No	106 (84.8)	118 (94.4)	0.023
Once	19 (15.2)	7 (5.6)	
Postoperative acute pain			
NRS POD1 resting (median [IQR])	2.00 [1.00, 3.00]	2.00 [1.00, 2.00]	0.019
NRS POD1 activity (median [IQR])	4.00 [3.00, 5.00]	3.00 [2.00, 4.00]	0.001
NRS POD2 resting (median [IQR])	2.00 [1.00, 2.00]	2.00 [1.00, 2.00]	0.048
NRS POD2 activity (median [IQR])	3.00 [3.00, 4.00]	3.00 [2.00, 4.00]	0.002
NRS POD3 resting (median [IQR])	2.00 [1.00, 2.00]	1.00 [1.00, 2.00]	0.020
NRS POD3 activity (median [IQR])	3.00 [3.00, 4.00]	3.00 [2.00, 4.00]	0.034
PONV			
PONV POD1 No	55 (44.0)	108 (86.4)	0.001
Yes	70 (56.0)	17 (13.6)	
PONV POD1 treated No	106 (84.8)	118 (94.4)	0.023
Yes	19 (15.2)	7 (5.6)	
PONV POD2 No	91 (72.8)	121 (96.8)	0.001
Yes	34 (27.2)	4 (3.2)	
PONV POD2 treated No	112 (89.6)	125 (100.0)	0.001
Yes	13 (10.4)	0 (0.0)	
PONV POD3 No	117 (93.6)	116 (92.8)	1
Yes	8 (6.4)	9 (7.2)	
Postoperative complications			
Postoperative headache No	110 (88.0)	108 (86.4)	0.85
Yes	15 (12.0)	17 (13.6)	
Postoperative vertigo No	113 (90.4)	110 (88.0)	0.684
Yes	12 (9.6)	15 (12.0)	
Postoperative constipation No	100 (80.0)	92 (73.6)	0.294
Yes	25 (20.0)	33 (26.4)	
Postoperative diarrhea No	117 (93.6)	116 (92.8)	1
Yes	8 (93.6/6.4)	9 (7.2)	

Numerical rating scale of pain, NRS; Postoperative day, POD; PONV, Postoperative Nausea and vomiting

Table 4 Univariate and multivariate negative binomial regression for NRS scores 6 month after surgery

	Univariate analysis		Multivariate analysis		
	Z	P	Z	P	IRR (95%CI)
Gender	0.121	0.903			
Age	-1.207	0.227			
Weight	0.385	0.700			
BMI	-0.239	0.811			
Smoking	3.220	0.001	3.448	0.001	2.431 (1.515,3.935)
Drinking	2.422	0.015	2.02	0.043	1.655 (1.043, 2.631)
Education	-0.019	0.985			
Marriage	0.495	0.621			
Preoperative pain	4.486	0.001	4.411	0.001	3.010 (1.843, 5.004)
Surgery history	0.307	0.759			
Cerebrovascular disease	-0.870	0.384			
Heart disease	1.616	0.106			
Pulmonary disease	0.216	0.829			
Hepatic disease	1.077	0.282			
Renal disease	-0.844	0.399			
Hypertension	-0.998	0.318			
DM	-0.207	0.836			
ASA	-0.176	0.860			
Heart function	-0.373	0.709			
WBC	-0.400	0.689			
Neutrophil	0.337	0.736			
Open surgery	3.318	0.001	2.938	0.003	2.250 (1.312, 3.949)
Azasetron	-1.493	0.136			

American society of anesthesiologist association, ASA; Body mass index, BMI; Diabetes mellitus, DM; White blood cell, WBC

Discussion

The results of this study indicated that the addition of azasetron in PCA did not affect chronic pain at both three and six months post-pulmonary surgery. However, the addition of azasetron in PCA decreased pain intensity on POD1, 2, and 3, and lowered the incidence of PONV and medical interventions for PONV. Preoperative pain, smoking, drinking and open pulmonary surgery were identified as risk factors for postoperative chronic pain six months after the procedure.

In the context of pain conditions, 5-HT release is augmented and the mechanisms behind this increase in 5-HT release can be attributed to several factors. Firstly, tissue damage triggers the recruitment of a multitude of immune cells and enhances the release of 5-HT, leading to a pro-inflammatory response and the sensitization of peripheral neurons [15]. Secondly, descending pain modulation is activated and releases 5-HT from rostral ventromedial medulla after surgery [16]. Lastly, postoperative analgesia with opioid induces a 5-HT release in the spinal cord [17]. As a result, 5-HT levels significantly increase post-surgery in both the central and peripheral nervous systems. However, in contrast to other 5-HT receptor subtypes, the 5-HT3 receptor is the only ligand-gated cation channel. At the resting membrane potential, activation of 5-HT3 receptors allows Na^+ and Ca^{2+} entry, which depolarize neurons and mediate the fast, excitatory synaptic pain transmission [18]. Thus, inhibition of the 5-HT3 receptor prevents pain signals and exerts analgesic effects.

Postoperative acute pain can lead to central sensitization and subsequent chronic postsurgical pain [19]. Postoperative analgesics that suppress neuronal hyperexcitability are critical for the prevention of chronic postsurgical pain [19, 20]. After incision, inflammatory cytokines and pain intensity reach their peak quickly and decrease over time. In our study, azasetron was administered intravenously for the first two days, and the results indicated that azasetron significantly reduced postoperative acute pain. However, azasetron did not affect postoperative chronic pain, the reasons may be explained by that postoperative chronic pain transition is multi-factorial. Perioperative anxiety, depression, preoperative pain history, postoperative pain control after PCA discontinuation and postoperative pain after discharge are very important contributors of postoperative chronic pain. In addition, despite azasetron decreased NRS after surgery, the analgesic effect is too mild to suppress persistent central sensitization. Consequently, azasetron failed to prevent the transition from acute to chronic pain.

Evidence from prior research has shown that a single dose of 5-HT3 receptor antagonist ondansetron exhibits an analgesic effect in patients with chronic neuropathic pain [21]. Another 5-HT3-receptor antagonist,

tropisetron, is effective in mitigating the pain symptoms of fibromyalgia [22] and low back pain [23]. A prospective, multicenter, double-blind, parallel trial showed that a 10-day course of 5 mg tropisetron significantly improved pain symptoms and painful tender points [24]. Our previous study confirmed that tropisetron decreased postoperative inflammation and myocardial injury biomarkers after heart valves replacement surgery [25]. These studies collectively suggest that 5-HT3-receptor antagonists possess an analgesic effect. Our study delved into the analgesic effects of azasetron on postoperative pain, and the findings revealed that the 5-HT3 receptor antagonist azasetron successfully reduced the NRS score in the acute phase, but not in the chronic phase following pulmonary surgery. Our results confirmed the acute analgesic effect of azasetron postoperatively.

In our study, regression analysis was used for identification of relevant factors for postoperative pain six months after surgery. Our findings revealed that preoperative pain, smoking, drinking, and open surgery were risk factors for postoperative chronic pain six months post-surgery. Considering the preexisting pain could potentially influence the preventive effect of azasetron on postoperative chronic pain, a sensitive sub-group analysis was performed in patients without preexisting pain. The sub-group analysis results showed similar results and confirmed the absence of prophylactic effect of azasetron on postoperative chronic pain. Preoperative pain has been demonstrated to be a risk factor for postoperative chronic pain, as a preconditioned pain pathway by preoperative pain evokes an exaggerated proinflammatory response post-surgery [1, 2]. Furthermore, patients with a long-term smoking habit often have lung tissue inflammation, which can result in frequent postoperative coughing and "respiratory" pain. Smoking cessation induces greater sensitivity to pain than in both nonsmokers and non-deprived smokers [26, 27]. Alcohol dependence and chronic pain share common neural circuits, and long-term alcohol use results in peripheral neuropathy and abnormal emotional-affective brain regions related to pain [28, 29]. Lastly, open pulmonary surgery, involving longer skin cuts and more severe tissue damage and nerve injury, often results in enhanced pain. In essence, we identified these four risk factors, which are very common and easy to acquire, for predicting postoperative chronic pain.

PONV is a common postoperative complication after pulmonary surgery, especially combined with an opioid for postoperative analgesia. The mechanisms of PONV may involve peripheral and central components [5]. In the thoracic cavity, local immune cells in the tissue release 5-HT in response to irritation or cellular damage. Then, 5-HT3 receptors located on vagal afferents in the thoracic cavity and lung surface were activated by binding with 5-HT, the excitatory signal projects to the vomiting center located in the dorsal vagal complex and induces vomiting reflex [30]. Azasetron is a 5-HT3 receptor antagonist and has been previously reported to decrease PONV by blocking 5-HT3 receptors [7]. Consistently, our study showed that patients' PONV was alleviated in the azasetron group compared to the control group, which confirmed the antiemetic effect of azasetron. Furthermore, our results showed that azasetron does not influence the incidence of postoperative headache, vertigo, constipation, and diarrhea within the postoperative three days. This implies that it is a safe adjuvant for postoperative multimodel analgesia.

There are several limitations to this study. It is a single-center study, and we tested the effects in patients who received pulmonary surgery; whether it is effective for the prevention of acute and chronic pain formation in other surgeries remains to be studied. In addition, our design does not include items of other life events, such as recent extensive travel, family living conditions that could affect pain. Moreover, we have collected data on the preoperative smoking history of each patient according to common standards. however, we did not record the cumulative number of years patients had smoked, or track how many patients ceased smoking after admission. This omission restricts our ability to conduct a more comprehensive analysis. Lastly, we chose 20 mg azasetron in the PCA, whether a higher dose or a longer during could prevent the transition to chronic pain remain to be explored.

Conclusions

Our findings suggest that incorporating azasetron into PCA does not influence the occurrence of postoperative chronic pain following pulmonary surgery. However, the inclusion of azasetron in the PCA regimen significantly reduces postoperative acute pain, as well as nausea and vomiting, implying its safe and effective use as an adjuvant for postoperative multimodal analgesia. Preoperative pain, smoking, drinking and open surgery are risk factors for postoperative chronic pain.

Abbreviations

ANOVA	Analysis of variance
5-HT	5-Hydroxyl Tryptamine
ASA	American society of anesthesiologist association
BMI	Body mass index
DM	Diabetes mellitus
POD	Postoperative day
PONV	Postoperative nausea and vomiting
NRS	Numerical rating scale of pain
WBC	White blood cell

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12871-024-02653-z.

Supplementary Material 1

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Author contributions
YX, FJ, HYZ, and XHL performed the experiment and collected that data.SNS and XHY did the statistical analysis and wrote the manuscript.XRG designed and revised the manuscript.

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Data availability
The data in the present study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
This work has been carried out in accordance with the Declaration of Helsinki (2000) of the World Medical Association. The study was approved by the Ethics Committee of Xiangyang Central hospital on April 25 2022 (Approval No. 2022-011), and written informed consent was obtained from all subjects participating in the trial.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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