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The intraperitoneal ondansetron for postoperative pain management following laparoscopic cholecystectomy: A proof-of-concept, double-blind, placebo-controlled trial

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ABSTRACT

Background: Pain after laparoscopic cholecystectomy remains a major challenge. Ondansetron blocks sodium channels and may have local anesthetic properties.
Aims: To investigate the effect of intraperitoneal administration of ondansetron for postoperative pain management as an adjuvant to intravenous acetaminophen in patients undergoing laparoscopic cholecystectomy.
Methods: Patients scheduled for elective laparoscopic cholecystectomy were randomized into two groups (n = 25 each) to receive either intraperitoneal ondansetron or saline injected in the gall bladder bed at the end of the procedure. The primary outcome was the difference in pain from baseline to 24-h post-operative assessed by comparing the area under the curve of visual analog score between the two groups.
Results: The derived area under response curve of visual analog scores in the ondansetron group (735.8 ± 418.3) was 33.97% lower than ($p = 0.005$) that calculated for the control group (1114.4 ± 423.9). The need for rescue analgesia was significantly lower in the ondansetron (16%) versus in the control group (54.17%) ($p = 0.005$), indicating better pain control. The correlation between the time for unassisted mobilization and the area under response curve of visual analog scores signified the positive analgesic influence of ondansetron ($r_s = 0.315$, $p = 0.028$). The frequency of nausea and vomiting was significantly lower in patients who received ondansetron than that reported in the control group ($p = 0.023$ (8 h), and 0.016 (24 h) respectively).
Conclusions: The added positive impact of ondansetron on postoperative pain control alongside its anti-emetic effect made it a unique novel option for patients undergoing laparoscopic cholecystectomy.

1. Introduction

Laparoscopic cholecystectomy (LC) is the gold standard technique for the surgical management of benign biliary diseases [1]. It achieves superior outcomes over conventional open procedures; however, pain after LC presents a major challenge as it is complex in nature. Pain pattern after LC does not resemble post-operative pain following other laparoscopic procedures, suggesting optimal analgesic management

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plans should be multimodal and procedure-specific [2,3]. The local irritation of carbon dioxide intraperitoneal (IP) administered during LC and the increase in intra-abdominal pressure causes the pain to increase even more in the postoperative period [4]. In recent decades, various strategies for postoperative analgesia following LC have been developed. Opioids are the most used strategy, but they have been associated with emesis, respiratory depression, and altered mental status. Based on these significant side effect profiles, it was recommended to avoid using opioids whenever possible [3]. The use of multimodal pain management regimens lowers the analgesics doses and reduces the incidence of side effects. Besides, it was suggested that it is associated with better pain control [5]. Strategies involving the IP administration of local anesthesia were the core elements in multimodal analgesia [6]. A recent Cochrane review that assessed the existing evidence regarding the effectiveness of currently available IP local anesthetics in patients undergoing LC suggested marginal effect with conflicting results [7]. Therefore, the routine use of current options of local anesthetics cannot be recommended as a standard of care [2,3]. Considering that pain is the main cause for delayed hospital discharge post LC [8,9]; it is necessary to investigate novel options for pain management in those patients.

5-HT_3-antagonists, including ondansetron, are commonly used as anti-emetics to prevent and treat chemotherapy-induced vomiting and nausea [10]. Several studies have shown that 5-HT_3-antagonists pose anti-inflammatory and analgesic properties, suggesting a potential clinical role in pain management. Serotonin is a key neurotransmitter involved in diverse body functions, including pain. The 5-HT_3-receptors are widely distributed both centrally and peripherally [11–13]. 5-HT_3-antagonists interfere with peripheral effects of serotonin on nociception. They bind to opioid mu receptors and act as potential opioid agonists resulting in a peripheral nociceptive analgesic effect [14]. In addition to these effects, there is evidence that ondansetron blocks sodium channels which play a key role in activating peripheral nociceptive sensory neurons involved in the transmission of noxious stimuli [15]. Similar effects were reported with lidocaine, one of the most widely used local anesthetics, which inhibits the sodium influx into the neuronal cell membrane and suppresses cell excitability.

Furthermore, it has been reported that ondansetron has a local anesthetic effect fifteen times more potent than lidocaine, a well-known effective option in pain management post LC [16]. Hence, 5-HT_3-antagonists may be used as a new class of local anesthetics. To the authors' knowledge, no clinical study has been conducted to evaluate the effectiveness of ondansetron in reducing post-LC pain. This study, therefore, aimed to investigate the effect of intraperitoneal administration of ondansetron for postoperative pain management as an adjuvant to intravenous acetaminophen in patients undergoing laparoscopic cholecystectomy.

2. Patients and methods

This study was a prospective, randomized, placebo-controlled, double-blinded study performed on patients undergoing LC. The study was conducted at the National Hepatology and Tropical Medicine Research Institute (NHTMRI). The institutional review board approved the trial, and the protocol was registered prior to patient enrollment at clinical trials.gov (NCT04468685). The study was performed according to the Declaration of Helsinki.

Fig. 1 represents the patients' flow chart. All patients admitted to NHTMRI for elective LC were assessed for eligibility during the pre-assessment visit to the surgery clinic according to the following criteria: Inclusion criteria included patients aged between 18 and 70 years. Exclusion criteria included those with liver or renal dysfunction, chronic pain other than cholelithiasis, a daily intake of corticosteroids, or a history of allergy to any of the study drugs. Patients with communication problems, cognitive dysfunction, or psychological disorders, patients who received analgesics or sedatives 24 h before a scheduled surgery, and pregnant/lactating females were also excluded. At the start of the study, patients were informed about the study design and written informed consent was obtained from all enrolled subjects.

On the day of surgery at the preoperative holding area, patients were randomly assigned (allocation 1:1 ratio) into one of the two groups (25

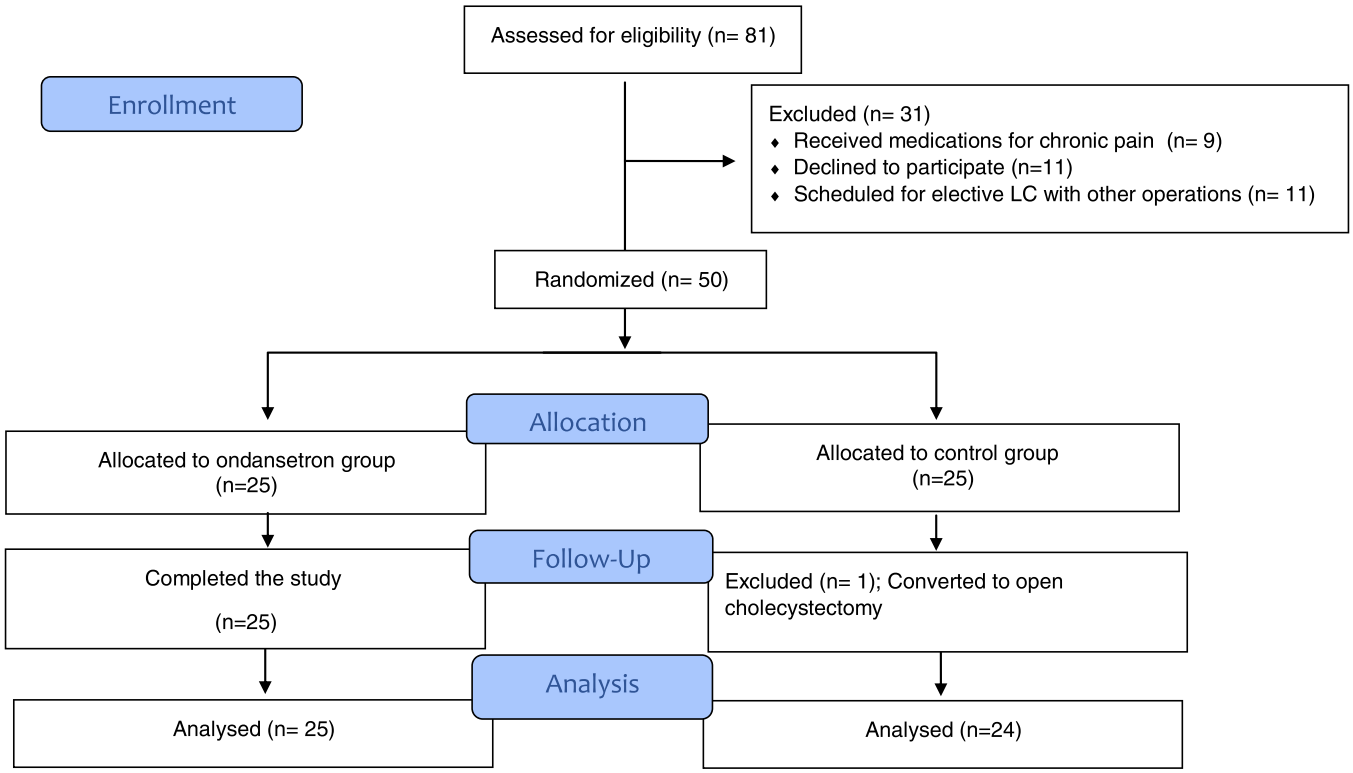

Fig. 1. Patient's flow chart.

patients each) according to a computer-generated random number. Ondansetron group was injected 4 mg ondansetron (2 mL) IP in the gall bladder bed at the end of the procedure. Meanwhile, the control group was injected 2 mL of normal saline IP in the gall bladder bed at the end of the procedure.

Details of group assignments were kept in a set of sealed opaque envelopes. The anesthetist who opened the envelope and prepared drugs accordingly was not involved in the case management intra-operatively. Both the patient and the investigator who observed the outcome were blinded to the patient's group assignment.

2.1. Intraoperatively

No pre-medications were administered. General anesthesia was induced with IV fentanyl 2 μg/kg and propofol 2 mg/kg until the cessation of verbal response. Tracheal intubation was facilitated with atracurium 0.5 mg/kg IV. The lungs were mechanically ventilated using the circle system with a 50% mixture of oxygen with air to maintain end-tidal carbon dioxide between 35 and 45 mmHg. Neuromuscular blockade was maintained with supplemental doses of IV atracurium. At the end of the surgery, the carbon dioxide remaining in the peritoneal cavity was expelled by slow abdominal decompression. The residual neuromuscular block was antagonized with atropine 0.01 mg/kg and neostigmine 0.04 mg/kg. No supplemental analgesics were used during the surgery. Duration of surgery was recorded for each patient.

The patients were then transferred to the post-anesthesia care unit (PACU) after following the verbal command. A postoperative pain protocol was initiated upon reaching the PACU, composed of 1-gram IV acetaminophen every 8 h. The first score on a visual analog scale (VAS) [17] was recorded before the first acetaminophen dose was administered to the patients. A-75 mg intramuscular injection of diclofenac sodium was given to patients who recorded a VAS score of $\geq$ 70 mm and requested rescue analgesia.

2.2. Pain assessment: VAS

During the preoperative visit, the patients were educated on how to express their postoperative pain on a 100 mm VAS score (0 indicated no pain, 100 denoted the most severe pain). The patients were asked to mark on the line at the point that represents the perception of their current status. The distance (mm) between the beginning of the horizontal line and the reported mark determines the degree of pain perception. Pain scores were recorded by one nurse who was blinded to the allocation at fixed intervals, including: upon reaching the PACU (0), and 2, 4, 8, 12, and 24 h at the surgery inpatient unit.

Individual VAS scores were plotted (virtually) as a curve where the x-axis showed evaluation time from baseline (0) to 24-h post LC, with the y-axis showing the VAS score. Using this approach, the area under the curve (AUC) for each assessment point (trapezoids) was calculated and added together, resulting in an overall VAS AUC score (mm $\times$ h) that was compared across treatment groups [18].

2.3. Postoperative nausea and vomiting grading (PONV)

The frequency of PONV [19,20] was recorded in the surgery ward after 8 and 24 h for each patient by using a 4-point scale: none (0): no nausea, vomiting, and retching; mild (1): happened once; moderate (2): happened 2–3 times; and severe (3): continuous or more than three times.

2.4. Study endpoints

2.4.1. The primary outcome

The primary outcome was the difference in VAS score from baseline to 24 h post-operative assessed by comparing the AUC of VAS score.

2.4.2. Secondary endpoints of the study included differences between study groups in

- Time to first rescue analgesic request.
- Cumulative consumption of rescue analgesic 24-h post-operative.
- Time to unassisted mobilization.
- PONV grading.

2.5. Statistical analysis

The required sample size was calculated using G*Power software version 3.1.0 (Institut fur Experimentelle Psychologie, Heinrich Heine Universität, Dusseldorf, Germany). It was estimated a sample size of 48 patients would have a power of 80% to detect a large effect size of 0.85 in the primary outcome measure. Statistical analysis was done using IBM SPSS® Statistics version 26 (IBM® Corp., Armonk, NY, USA). Numerical data are expressed as mean and standard deviation. Qualitative data are expressed as frequency and percentage. Data were tested for normality using the Skewness-Kurtosis test and Shapiro-Wilk test and were found not normally distributed, so the nonparametric tests were used. Comparison between two groups concerning continuous variables was made using the Mann-Whitney test. A comparison of each group over time was carried out using the Freidman test. The Chi-square test was used to compare the groups concerning categorical data. The time to first need of rescue analgesia between the groups was plotted with Kaplan-Meier survival curves and compared with the log-rank test. Spearman's correlation was used to correlate between time to unassisted mobilization and AUC of VAS score. All p-values were 2-sided, and values < 0.05 were considered significant.

3. Results

From July 2020 to October 2020, a total of 81 patients scheduled for elective LC were screened for eligibility. Fifty patients, (ASA) grade I to II, of both sexes, fulfilled the inclusion criteria and were randomly allocated to one of the study groups. As shown in Fig. 1, 49 patients completed the study and were included in the final analysis. At baseline, there was no significant difference among the groups regarding age, weight, preoperative vital signs, comorbid conditions, gender, ASA

Table 1
Baseline demographic and clinical variables of the two study groups.

Parameters	Ondansetron group (n = 25)	Control group (n = 25)	p value
Age (years)	40.98 ± 15.33	37.85 ± 13.17	0.388
Weight (kg)	74.52 ± 12.36	78.48 ± 13.20	0.420
Gender; n (%)			0.508
Male	7 (28)	5 (25)	
Female	18 (72)	20 (75)	
Systolic BP	119.4 ± 15.76	129.1 ± 23.23	0.146
Diastolic BP	74.76 ± 14.22	72.92 ± 7.170	0.526
Preoperative respiratory rate	15.48 ± 2.023	15.14 ± 1.581	0.400
Preoperative pulse	80.76 ± 12.91	75.24 ± 8.894	0.088
Co-morbidities; n (%)		0.323	
None	19 (76)	19 (76)	
Diabetes mellitus	2 (8)	4 (16)	
Hypertension	1 (4)	1 (4)	
Diabetes mellitus and hypertension	3 (12)	0 (0)	
HBV	0 (0)	1(4)	
ASA status n (%)			0.713
I	20 (80)	21 (84)	
II	5 (20)	4 (16)	
Duration of surgery (min)	63.12 ± 18. 21	70.88 ± 30.15	0.697
Duration of anesthesia (min)	56.64 ± 17.78	63.88 ± 29.87	0.691

ASA: American Society of Anaesthesiology, BP: Blood Pressure, min: minutes, HBV: Hepatitis B Virus, n: number of patients.

status, duration of anesthesia, or duration of surgery (Table 1). Forty-eight patients (97.96%) were discharged from the hospital after 24 h post-surgery, while one patient was discharged after 72 h in the control group.

The mean VAS scores were comparable between the two groups at 0, 2, and 4 h ($p = 0.502$, 0.144, and 0.114 respectively). A statistically significant difference was found in the mean VAS scores recorded at 8, 12, and 24 h post-operative between the control group and the ondansetron group ($p = 0.013$, 0.01, and 0.047 respectively) (Table 2). In each of the study groups, a marked decrease in the mean VAS score was observed over time compared to baseline ($p = 0.0001$ in both groups); the ondansetron group had lower mean scores versus the control group (Table 2). A significantly smaller AUC of VAS score was observed in the ondansetron group compared to that in the control group (735.8 ± 418.3 vs. 1114.4 ± 423.9; $p = 0.005$) (Fig. 2A).

Patients in the control group required more time (19.67 ± 2.654 h) for unassisted mobilization than those receiving ondansetron (9.052 ± 0.579 h) ($p < 0.001$), as clear in Table 2. Spearman correlation analysis revealed a statistically significant ($p = 0.028$) positive correlation ($r_s = 0.315$) between time to unassisted mobilization and the AUC of VAS score.

Significant difference ($p = 0.01$) was found regarding the time until the patient's first request of rescue medications between the two groups, as observed in the survival curve analysis (Fig. 2D). A significant ($p = 0.005$) higher percentage of patients (54.17%) requested rescue analgesia in the control group than in the ondansetron one (16%); however, comparable cumulative doses of analgesia required in milligrams ($p = 0.785$) were detected (Table 2 and Fig. 2C).

The frequency of PONV recorded at 8- and 24-h was significantly lower in patients who received ondansetron than that reported in the control group ($p = 0.023$ and 0.016 respectively) (Fig. 2B). More than half of the patients who received ondansetron (52%) did not experience nausea or vomiting during the study period. Severe nausea or vomiting was recorded in 4% of patients in the ondansetron group at 8 h, while none of the patients in the same group documented any nausea or vomiting at 24 h post-surgery. Conversely, nausea or vomiting was not detected in 29.17% and 37.5% of patients assigned to the control group at 8 and 24 h, respectively. In the control group, severe PONV was noted in 33.33% of patients at 8 h and in 4.17% at 24 h.

4. Discussion

To the authors' knowledge, this study is the first randomized, placebo-controlled trial that has examined the local anesthetic effect of 5-HT_3-antagonist. The study has compared the postoperative analgesic efficacy of IP ondansetron versus placebo as an adjuvant to IV acetaminophen in patients undergoing LC. Laparoscopic cholecystectomy is a common major surgical procedure. It is associated with earlier recovery when compared to open surgery. However, pain may still be severe, particularly in the early postoperative period. Baseline regimens for postoperative pain management should include the use of acetaminophen [3]. It has gained popularity in the treatment of postsurgical pain due to its distinguished safety profile. However, on the first day after surgery, acetaminophen monotherapy is usually insufficient to control postoperative pain [21].

Table 2
Parameters after treatment in the two study groups.

	Ondansetron group (n = 25)	Control group (n = 24)	*p* value
VAS score *(mean ± SD)* *(h)*			
0	76.00 ± 21.31	77.91 ± 24.26	0.502
2	58.80 ± 21.12	66.91 ± 28.71	0.144
4	38.24 ± 26.31	50.66 ± 24.85	0.114
8	31.28 ± 26.49	49.29 ± 22.74	0.013
12	21.48 ± 22.82	40.37 ± 27.08	0.010
24	21.96 ± 11.20	38.79 ± 29.69	0.047
	0.0001**	0.0001**	
Diclofenac intake n (%)			0.005
Yes	4 (16)	13 (54.17)	
No	21 (84)	11 (45.83)	
Average cumulative amount (mg)*	75 (150)	75 (375)	0.785
Time to unassisted mobilization (h)	9.052 ± 0.579	19.67 ± 2.654	< 0.001

VAS: Visual Analog Score, *Median (range), **Friedman test is used to measure level of significance overtime in each group, n: number of patients.

The primary outcome of this study was the difference in pain as assessed by comparing the derived AUC of VAS score between the 2 study groups. The concept of using AUC as a metric for efficacy outcomes has been incorporated into various clinical settings [22,23], including pain [24,25]. The use of the AUC to evaluate pain scores over time provides clinically relevant information. Farrar et al. [26] defined a cut-off point of 33% reduction in acute pain intensity as clinically significant. In the current study, the derived area under response curve of VAS scores in the ondansetron group was (33.97%, $p = 0.005$) lower than that calculated for the control group; hence, this difference could be considered clinically important.

The use of IV ondansetron as a local anesthetic agent in acute pain management has been previously evaluated in clinical studies [27–29]. These studies mainly sought to determine whether ondansetron is effective in reducing propofol injection pain. In line with our findings, the results of a meta-analysis of ten RCTs, totaling 782 patients, showed that ondansetron effectively prevented local pain of propofol injection, and its effect was similar to lidocaine [30]. Another evidence was shown by Ye et al. [16] in a preclinical study which showed that subcutaneous ondansetron had a superior (15 times) local anesthetic effect to lidocaine. The molecular structure of 5-HT_3 receptor blockers is completely different from local anesthetics, and their local anesthetic mechanism is not yet entirely clear. However, it may be explained by blocking the sodium channels and peripheral 5-HT_3 receptors related to pain pathways [15,31]. Contrary to our findings, IV ondansetron had no impact on the postoperative analgesic effect of acetaminophen in women undergoing laparoscopic hysterectomy [32]. Lack of correlation with our results might be attributed to differences in route of administration of ondansetron and denotes that the analgesic effect of this class is mainly due to its local action.

The need for rescue analgesia was significantly lower in the ondansetron (16%) versus in the control group (54.17%) ($p = 0.005$), indicating better pain control. However, the cumulative 24-h dose of the rescue medications consumed by subjects who needed rescue was deemed comparable between the two study groups ($p = 0.785$). As compared to the control group, the time for unassisted mobilization in the ondansetron group was significantly shorter ($p < 0.001$). The correlation between the time for unassisted mobilization and the AUC of VAS scores signified the positive analgesic influence of the ondansetron ($r_s = 0.315$, $p = 0.028$).

In the absence of antiemetic treatment, the estimated incidence of PONV after LC ranged from 46% to 75% [33]. Our results showed the frequency of PONV was significantly lower in patients who received ondansetron than that reported in the control group ($p = 0.023$ (8 h) and 0.016 (24 h) respectively). Ondansetron, orally or IV administered, is approved to prevent and treat chemotherapy-induced nausea and vomiting. A case report [34] described the apparently successful use of IP ondansetron in controlling intractable vomiting related to gastroparesis in a patient who was on continuous cycling peritoneal dialysis after adding ondansetron to her dialysis bag. However, symptoms remained uncontrolled even with daily doses of 16 mg IM ondansetron. From our results, the added positive influence of one of the 5-HT_3 antagonists on postoperative pain control alongside its anti-emetic effect made these agents as unique novel options for patients undergoing LC.

Limitations of the present study included the small sample size and the lack of evaluation of different doses. Our hospital policy hinders the

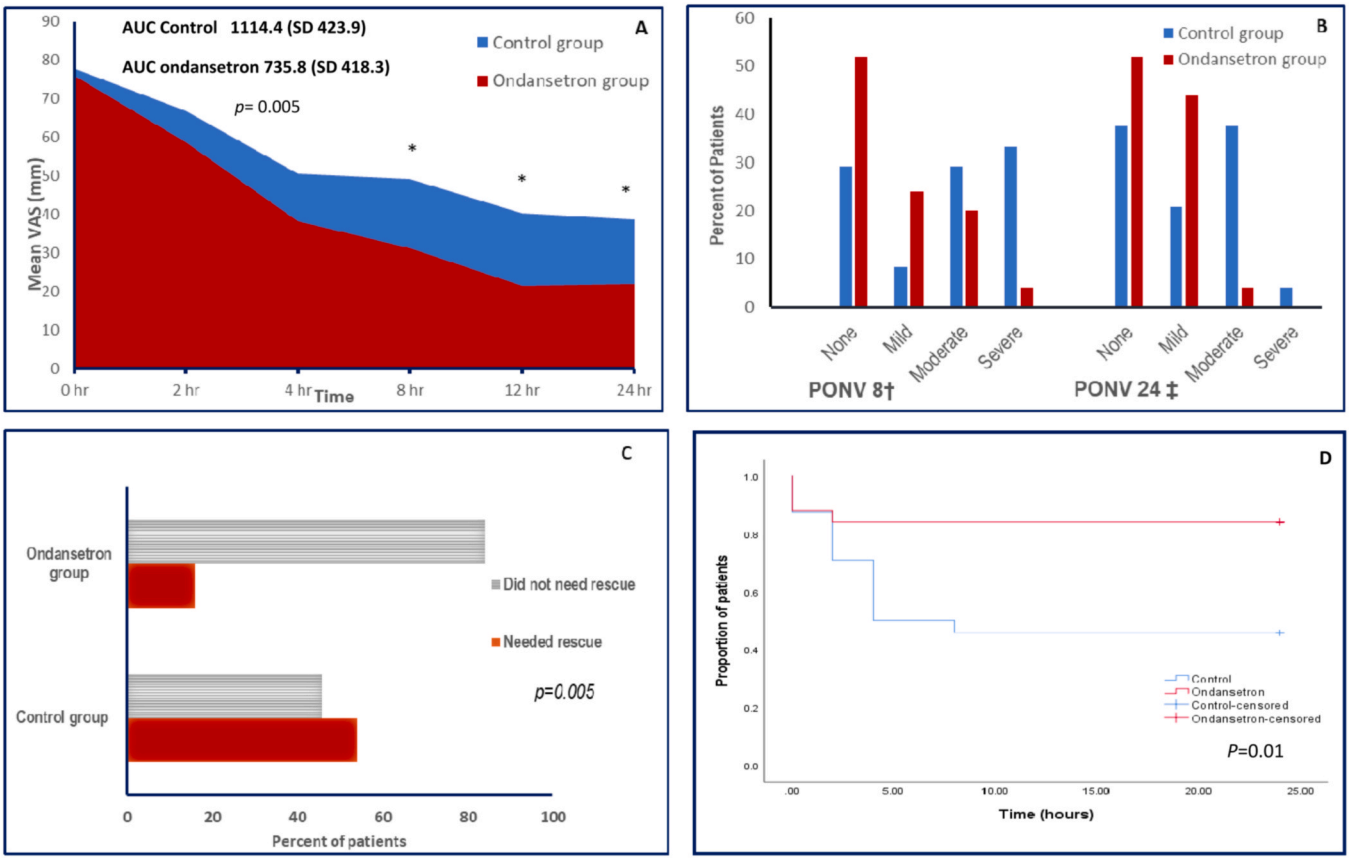

Fig. 2. (A) Area graph representing the mean VAS score at the different time intervals in the two groups; (B) Percentage of patients in the two groups who developed PONV with its different severities at 8, and 24 h post-surgery; (C) Percentage of patients who required and those who did not require diclofenac in the two groups; (D) Kaplan-Meier survival curve represents time to first rescue analgesic request. †$p = 0.007$; ‡ $p = 0.016$; AUC, area under the curve; SD, standard deviation.

use of opioids inwards, limiting the evaluation of the efficacy of ondansetron on opioid consumption.

Considering the excellent safety profile of ondansetron as an antiemetic, and the positive evidence of its local anesthetic action; thus, repurposing it as a local anesthetic agent represents an attractive novel option in the multimodal pain regimen in patients undergoing LC.

In conclusion, our results suggested that IP ondansetron might positively influence the analgesic efficacy of acetaminophen in patients undergoing LC. Further, studies with a larger sample size are recommended to include other painful procedures for longer periods to ensure the effectiveness of ondansetron in these settings. Regarding the differences between different 5-HT_3 blockers, additional studies are needed to evaluate whether our results can be generalized to other options of this class.

Conflict of interest statement

The authors declared no personal or funding conflict of interest.

Authorship

Guarantor of the article: Doaa H. Abdelaziz is acting as the submission's guarantor, taking responsibility for the integrity of the work, from inception to published article.

Author contributions

Sherif Boraii and Noha O. Mansour designed the study. Sherif Boraii, Tamer Omar, Amr Abdelraouf, and Doaa H. Abdelaziz performed the clinical trial. Doaa H. Abdelaziz and Noha O. Mansour analyzed and interpreted the data. Doaa H. Abdelaziz, Amr Abdelraouf, and Noha O. Mansour wrote and edited the paper and drew the figures. Sherif Boraii supervised the study and reviewed the manuscript. Mohamed Elnaem and Ejaz Cheema have designed the graphical abstract, revised the written work, the paper draft, and the critical revision of the final draft. All authors approved the final version of the manuscript.

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