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Is the reduced risk of post-operative nausea and vomiting in low flow anesthesia applications associated with pre-operative neutrophil/lymphocyte ratio values?

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Ethics Committee Approval
The study was approved by the Malatya Turgut Ozal University Clinical Research Ethics Committee (date: April 28, 2022, number: 2022/19).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: Post-operative nausea and vomiting (PONV) are defined as nausea and/or vomiting occurring within the first 24 h after surgery and are often observed in the first 2 h after surgery. Only a few previous studies on the use of low fresh gas flow that reduces inhaler agent consumption in laparoscopic cholecystectomy patients at high risk of PONV have been published. Our study aimed to determine the incidence of PONV in the first 30 min and again at 24 h in cases of laparoscopic cholecystectomy in which we applied low fresh gas flow (1 L/min). In addition, we wanted to predict whether the pre-operative neutrophil/lymphocyte ratio (NLR) ≥2 is a risk factor for PONV in our patients to whom we applied low fresh gas flow.
Methods: For our prospective cohort study, 80 cases between the ages of 18 and 65, had American Society of Anesthesiologists (ASA) scores of I and II, and who had been scheduled to undergo elective laparoscopic cholecystectomy were included in the study. The NLR limit (calculated by dividing the neutrophil count obtained from the complete blood count before surgery by the lymphocyte count) calculated in the pre-operative period after a patient's informed consent was obtained was accepted as 2 [5]. Patients were classified into two groups: (1) NLR-I with NLR <2 and (2) NLR-II with NLR ≥2. Premedication was not used in either group.
Results: A total of 80 patients were included in the study. They were divided into two groups for classification purposes: (1) NLR-I (n=40) and (2) NLR-II (n=40). The characteristics of the patients in both groups, such as gender distribution, ASA scores, smoking status, mean age, and body mass index (BMI) values, were not different. Sevoflurane consumption in the groups was similar (P=0.169). The time required to complete surgery was longer in the NLR-II group (P=0.025). Nausea/vomiting and antiemetic use were similar in the NLR-I and NLR-II groups in which low fresh gas flow was applied in the first 30 min and 24 h (P=0.500). Although nausea/vomiting was more common in the female and non-smoking group in the first 30 min and 24 h, it was not statistically significantly different from males and smoking groups (P=0.325). However, nausea/vomiting was more common and significantly different in the ASA II versus the ASA I group (P=0.046). The time required to complete surgery was longer, and sevoflurane consumption was higher in patients with nausea and vomiting (P=0.001).
Conclusions: Pre-operative NLR as classified by the two groups was not associated with an increase in the risk of PONV in patients to whom we applied low fresh gas flow. A decrease in sevoflurane consumption due to low fresh gas flow may lead to a reduction in the risk of PONV in at-risk patients.

Keywords: postoperative nausea and vomiting, low fresh gas flow, neutrophil-lymphocyte ratio

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Introduction

Post-operative nausea and vomiting (PONV) are described as nausea and/or vomiting occurring within the first 24 h following surgery with most cases occurring within the first 2 h [1]. Its prevalence has been reported to be around 44%–83% in different studies. The incidence after laparoscopic cholecystectomy is as high as 46% to 72% [2]. PONV leads to a decrease in patient comfort and satisfaction after a one-day laparoscopic cholecystectomy procedure and infrequently results in dehydration, electrolyte imbalances, suture separation, aspiration of gastric contents, esophageal rupture, and hemorrhaging. PONV leads to prolongation of hospital stays and increases procedure-related costs [3]. Important risk factors for PONV include patient-related, anesthetic, and surgical factors [4]. However, PONV has been thought to increase this risk due to it associated inflammation. The neutrophil/lymphocyte ratio (NLR) is a cost-effective parameter that can be used in the follow-up of inflammatory diseases and the limiting value of this ratio has been accepted as 2 [5]. Research has been published that demonstrates a link between the NLR and PONV [6]. A wide range of antiemetics have been studied for the prevention and treatment of PONV [7]; however, none of the available antiemetics are completely effective. Combined antiemetic treatments have been recommended to prevent PONV, particularly in high-risk patients [8,9]. All of these factors have led to the emergence of new studies. However, a few previous studies on the use of low fresh gas flow that reduces inhaler agent consumption in laparoscopic cholecystectomy patients at high risk of PONV have been published.

In our study, we aimed to determine the antiemetic requirement and the incidence of PONV in the first 30 min and 24 h in cases of laparoscopic cholecystectomy in which we applied low fresh gas flow (1L/min). We also wanted to predict whether pre-operative NLR is a risk factor for PONV in the patients to whom we applied low fresh gas flow.

Materials and methods

Ethical approval was received from the Malatya Turgut Ozal University Clinical Research Ethics Committee and dated April 28, 2022 with number 2022/19 for our prospective cohort study. Eighty cases with scores of I/II based on the American Society of Anesthesiologists (ASA) status and those between the ages of 18 and 65 who had been scheduled to undergo elective laparoscopic cholecystectomy were included in the study. Those with a history of PONV and those with hematological problems were excluded from the study. The NLR limit value (calculated by dividing the neutrophil count obtained from the complete blood count as measured before surgery by the lymphocyte count) calculated in the pre-operative period after a patient's informed consent was obtained was accepted as 2 [5]. Patients were divided into two groups for classification purposes: (1) NLR-I (n=40) with NLR <2 and (2) NLR-II with NLR ≥2 (n=40). Premedication was not applied to either group. After a patient was taken to the procedure room, electrocardiography (ECG), heart rate/minute (HR /min.), systolic arterial pressure (SAB-mmHg), diastolic arterial pressure (DAB-mmHg), mean arterial pressure (OAB-mmHg), and peripheral oxygen saturation (SpO_2) were monitored. Age, gender, height, weight, body mass index (BMI), ASA score, smoking status, comorbid diseases, and NLR values of all patients were recorded pre-operatively. Intravenous anesthesia with lidocaine (1 mg/kg), propofol (2 mg kg), fentanyl (1 µg/kg), and vecuronium (0.1 mg/ kg) was administered to both patient groups, and after adequate anesthesia depth was achieved following induction, patients were intubated with the appropriate endotracheal tube and connected to the anesthesia device. End-tidal carbon dioxide ($EtCO_2$), sevoflurane amount, and oxygen flow were continuously monitored after intubation. Fresh gas flow was then adjusted to 1 L min after which 80% O_2 + 20% nitrous oxide3 (N_2O) and 2%–3% sevoflurane were administered. Tramadol (1 mg/kg) for post-operative pain treatment and metoclopramide (10 mg) for PONV were administered. We applied 5 cmH_2O positive-end expiratory pressure (PEEP) to prevent atelectasis during the operation and we managed to keep the bispectral index (BIS) value around 40–50 for the depth of anesthesia throughout the operation. Sugammadeks (Bridion 200 mg/ 2 mL, MerckSharp and DohmeCorp, USA) was used to reverse neuromuscular blockade and patients were transferred to post-operative intensive care after extubation. Sevoflurane consumption, time to complete surgery, nausea, vomiting, and antiemetic requirements of the patients were recorded in the first 30 min in post-operative intensive care and at the first 24 h in the relevant clinic.

Statistical analysis

The conformity of continuous variables such as age, BMI, sevoflurane consumption, and time to complete surgery in the study to normal distribution was evaluated graphically and using the Shapiro–Wilks test. It was determined that age and BMI variables conformed to the normal distribution, and sevoflurane consumption and surgical completion time variables did not conform to such a distribution. Mean, standard deviation (SD) and median (interquartile range [IQR]) values were given in the representation of the descriptive statistics of the variables.

Independent sample t-test was used to compare age and BMI values based on NRL grouping. In addition, the Mann–Whitney U test was used to compare sevoflurane consumption and surgical completion time values based on NLR grouping. The cross tables were created for the comparison of gender, ASA, smoking status, and NLR grouping, and number (n), percentage (%) and chi-squared test statistics were determined. In the comparison of nausea/vomiting conditions between the NLR-I and NLR-II groups, cross tables were created, and number (n), percentage (%) and Fisher's exact test statistics were determined. For statistical analysis and calculations IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and MS-Excel 2007 programs were used. Statistical significance level was accepted as P <0.05.

Results

A total of 80 patients were included in the study. They were divided into two groups for classification purposes: (1) NLR-I (n=40) and (2) NLR-II (n=40). The characteristics of the patients in both groups, such as gender distribution, ASA scoring, smoking status, mean age, and BMI values were not different (P=0.999) as shown in Table 1 and Figure 1.

Sevoflurane consumption values in the groups were similar (P=0.169). The time required to complete surgery was longer in the NLR-II group (P=0.025) as shown in Table 1 and Figure 2.

Table 1: Characteristic features of neutrophil/lymphocyte ratio I and II (NLR-I and NLR-II) groups

	NLR <2	NLR ≥2	*P*-value
Gender			
Female, n (%)	28 (70.0)	28 (70.0)	0.999*
Male, n (%)	12 (30.0)	12 (30.0)	
ASA			
ASA I, n (%)	11 (27.5)	11 (27.5)	0.999*
ASA II, n (%)	29 (72.5)	29 (72.5)	
Smoking			
No, n (%)	26 (65.0)	26 (65.0)	0.999*
Yes, n (%)	14 (35.0)	14 (35.0)	
Age (years), mean (SD)	48.08 (13.46)	46.05 (13.96)	0.511
BMI, mean (SD)	29.31 (4.31)	28.70 (4.19)	0.523
Sevoflurane consumption (ml), mean (SD) (median)	15.68 (2.03) (15.50)	16.23 (1.82) (16.00)	0.169
Duration of surgery (min), mean (SD) (median)	46.88 (5.82) (47.00)	49.93 (6.08) (49.00)	0.025ⱡ

* χ^2 Chi-squared test, ⱡ Independent Sample T-Test, Mann–Whitney U test, SD: standard deviation

Figure 1: Distribution of age and body mass index (BMI) values among the neutrophil/lymphocyte ratio I and II (NLR-I and NLR-II) groups

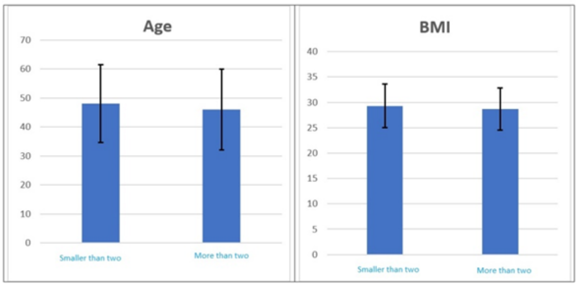
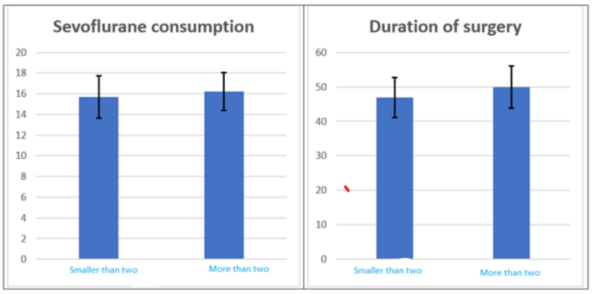


Figure 2: Sevoflurane consumption and duration of operation between NLR-I and NLR-II groups



Nausea/vomiting and antiemetic use were similar in the NLR-I and NLR-II groups in cases in which low fresh gas flow was applied in the first 30 min and at 24 h (*P*=0.500) as shown in Table 2. Although PONV was more common in the female gender and non-smoking group in the first 30 min and at 24 h, PONV was not significantly different than in any other affected patient (*P*=0.325). However, PONV was more common in the ASA II group and was statistically significantly different from the ASA I group (*P*<0.05) as shown in Table 3. The time to complete surgery was longer, and sevoflurane consumption was higher in patients with PONV (*P*=0.001) as shown in Table 3 and Figures 3 and 4.

Table 2: Nausea/vomiting relationship with NLR

	NLR <2 n (%)	NLR ≥2 n (%)	*P*-value
In the first 30 min Nausea/vomiting and antiemetic requirement			
No	36 (90.0)	35 (87.5)	0.500
Yes	4 (10.0)	5 (12.5)	
In 24 h Nausea/vomiting and antiemetic requirement			
No	37 (92.5)	35 (87.5)	0.356
Yes	3 (7.5)	5 (12.5)	

Fisher's exact test

Table 3: The effects of gender, American Society of Anesthesiologists (ASA) score, body mass index (BMI) and smoking status on nausea and vomiting

		In the first 30 min Nausea/vomiting (Yes/No)	In 24 h Nausea/vomiting (Yes/No)
Gender n (%)	**Female**	6 (10.7)/50 (89.3)	5 (8.9)/51 (91.1)
	Male	3 (12.5)/21 (87.5)	3 (12.5)/21 (87.5)
	***P*-value**	0.544	0.450
ASA n (%)	**ASA I**	0 (0.0)/22 (100.0)	0 (0.0)/22 (100.0)
	ASA II	9 (15.5)/49 (84.5)	8 (13.8)/50 (86.2)
	***P*-value**	0.046	0.066
Smoking n (%)	**Yes**	2 (7.1)/26 (92.9)	2 (7.1)/26 (92.9)
	No	7 (13.5)/45 (86.5)	7 (13.5)/45 (86.5)
	***P*-value**	0.325	0.325
BMI	**(median)**	30.70 (5.65)/28.79 (4.02)	31.46 (5.53)/28.74 (4.02)
	***P*-value**	0.206*	0.084*
Sevoflurane consumption	**(median)**	19.78 (1.48)/15.46 (1.36)	20.13 (1.13)/15.49 (1.36)
	***P*-value**	<0.001ⱡ	<0.001ⱡ
Duration of surgery (min)	**(median)**	60.33 (4.30)/46.89 (4.41)	61.63 (1.99)/46.93 (4.39)
	***P*-value**	<0.001ⱡ	<0.001ⱡ

* Independent Sample T-Test, ⱡ Mann–Whitney U Test, Fisher's exact test

Figure 3: Consumption of sevoflurane with nausea and vomiting in the first 30 min and at 24 h

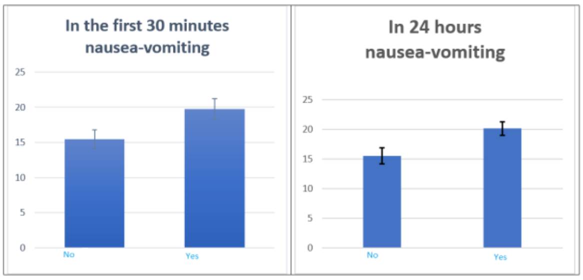
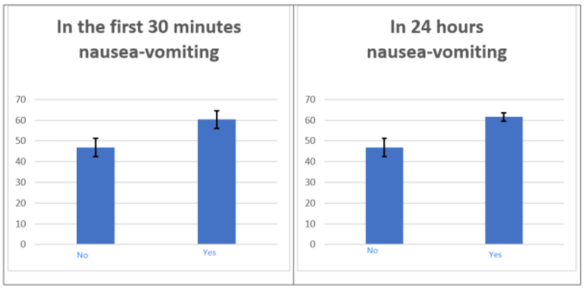


Figure 4: The duration of the operation in patients with nausea and vomiting in the first 30 min and at 24 h



Discussion

The study was conducted prospectively with 80 patients (24 [30%] males and 56 [70%] females) between the ages of 18 and 65 who had been scheduled for elective laparoscopic cholecystectomy. There was similar between the NLR-I and NLR-II groups in terms of gender distribution, ASA score, smoking, mean age and BMI values. In the literature, NLR ≥2 has been shown to be a risk factor for nausea-vomiting [4,6]. However, in our study, it was determined that this risk was significantly reduced with the use of low fresh gas flow. In addition, increased sevoflurane consumption was observed to be correlated with increased PONV. This result indicates that the anesthesia method we applied with low fresh gas flow led to a reduction in the risk of PONV.

Female gender, previous history of PONV and/or car sickness, non-smoking status, and post-operative opioid use are important risk factors associated with the patient predicted to have PONV [10]. A comprehensive meta-analysis of 22 studies addressing risk factors for PONV each involving 500 patients, female gender and non-smoking status were the strongest predictors of PONV among patient-specific risk factors, whereas BMI, and ASA scores were not statistically significant [3]. BMI was not statistically significant in our study. However, PONV was more common in the ASA II risk group. We think that the existing co-morbidities of the patients in the ASA II risk group had a negative effect on this situation. In addition, although PONV was more common in female patients and non-smokers in our study, female gender and non-smoking status were not identified as risk factors for PONV.

Important risk factors for PONV also include anesthetic and surgical factors. In a comprehensive meta-analysis study in 2012, only three of the 13 surgical categories have been shown to be statistically significant. It has been stated that laparoscopic cholecystectomy, in particular, was the strongest predictor of PONV followed by laparoscopic interventions and gynecological surgery [3]. It has previously been emphasized that antiemetics should be used prophylactically in patients with a high risk of PONV who are undergoing surgery, such as laparoscopic cholecystectomy [11]. Due to the high risk of PONV in our patient group, prophylactic antiemetics were administered. In a study involving 5123 patients, it was shown that 59% of untreated surgical patients complained of nausea and vomiting, while at the same time, only 17% of the patient group who were given antiemetic prophylaxis and avoided emetogenic effects during anesthesia complained of nausea and vomiting [12]. In a study by Erhan et al. [13] that consisted of 80 patients who underwent laparoscopic cholecystectomy, the overall incidence of PONV was 75% with placebo, 35% with ondansetron, 30% with granisetron, and 25% with dexamethasone. In our study, we administered 10 mg of metoclopramide prophylactic to patients with a high risk of PONV, and our PONV rates were 10% in the NLR-I group and 12.5% in the NLR-II group, both of which were quite low. The low consumption of inhalers due to the anesthesia method we applied with low fresh gas flow suggests that this method can lead to a reduction in the risk of PONV.

The use of inhalation agents was identified as the major dose-dependent risk factor for vomiting in the early post-operative interval (0–2 h) in a study enrolling 1180 patients. It was discussed that in the delayed post-operative period (2–24 h), it would be prudent to avoid inhalation anesthesia rather than add an antiemetic to prevent or treat delayed vomiting [14]. In another study, it was shown that the main anesthetic triggers for PONV were inhalation agents, and no significant differences were found between the type of agent [15]. Again, in the study conducted by Apfel et al. [3] in 2012, it was shown that the use of inhalation agents, which is an anesthesia-related risk factor, is the strongest predictor of PONV followed by the duration of anesthesia. The results of our study are also significant in terms of increased antiemetic requirement, increased PONV risk with high sevoflurane consumption, and prolonged surgical time in the early post-operative period (first 30 min) and in the delayed post-operative 24-h period.

In a study by Nelskyla et al. [16] in 2001 with 62 patients, they found that optimized application of sevoflurane with BIS monitoring led to a reduction in PONV and allowed for early recovery in patients who underwent outpatient gynecological laparoscopy. In our study, in which we applied low fresh gas flow with BIS monitoring and optimum sevoflurane consumption, our PONV incidence was quite low.

Opinions differ as to the effect of nitrous oxide (N_2O) use on PONV. In a study conducted by Taylor et al. [17] with 50 patients who underwent laparoscopic cholecystectomy, the incidence of PONV was similar in the group with and without N_2O. However, Apfel et al. [15] mentioned the relative risk for N_2O. A recent study by Peyton et al. [18] revealed that the risk of PONV due to N_2O was time dependent. We think that the use of N_2O, which produced a surgical time of 50 min less than other agents, only had a limited effect on PONV in our study.

The fourth consensus guidance on the management of PONV in adults and children was updated in 2020 by Gan et al. [19] focuses on risk assessment, key-risk prevention, and pharmaco-prophylaxis. In our patient group with a high risk of PONV, we managed to reduce the consumption of inhaler agents, which is one of the key-risks for PONV, by applying low fresh gas flow under BIS monitoring. In addition, the incidence of PONV was found to be very low after prophylactic antiemetic administration.

NLR and platelet to lymphocyte ratio (PLR) are pre-operative inflammatory markers [20]. NLR and PLR can be measured easily and inexpensively and can quickly provide the necessary information for interventions within the first few hours after hospitalization [21]. In their study by Arpaci et al. [22] consisting of 64 patients, it was found that the risk of PONV was significantly higher in patients with NLR ≥2. They have suggested that NLR could be an indicator for PONV, and antiemetic prophylaxis could be given after evaluating the NLR ratio. In another study with 80 patients, the patients were classified into two groups based on their pre-operative NLR values. The need for antiemetics and the risk of PONV was found to be significantly higher in the patient group with NLR ≥2 in the recovery room and at 24-h [6]. In our study, although the patient group with NLR ≥2 had a higher rate of antiemetic requirement and PONV risk in the first 30 min and at 24 h than the NLR<2 group, the difference between these two groups was not statistically significant. Our study suggests that decreased inhalation agent consumption due to low flow anesthesia leads to a reduction in the risk of PONV; thus, high NLR values do not appear to be correlated with an increase in the risk of PONV. However, due to the small number of patients, this result needs to be supported by more comprehensive studies.

Limitation

The fact that our study was conducted in a single center in addition to the relatively small number of patients were restrictive factors. We think that future studies need to be done more comprehensively and prospectively.

Conclusions

Pre-operative NLR was not associated with an increased risk of PONV in patients to whom we applied low fresh gas flow. Decreased sevoflurane consumption due to low fresh gas flow may lead to a reduction in the risk of PONV in at-risk patients.

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