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Comparison of the effects of low-flow and normal-flow anesthesia on intracranial pressure, cerebral oxygenation and bispectral index in laparoscopic cholecystectomy operation

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Abstract. – OBJECTIVE: Pneumoperitoneum in laparoscopic surgeries can raise intracranial pressure (ICP). Low-flow anesthesia offers benefits such as improved clearance, temperature preservation, fluid reduction, cost savings, and lower emissions. However, the impact of low-flow anesthesia on ICP during laparoscopic cholecystectomy remains unclear. This study aimed to compare the effects of low-flow anesthesia (0.75 l/min) to those of normal-flow anesthesia (1.5 l/min) on optic nerve sheath diameter (ONSD) in laparoscopic cholecystectomy patients.

PATIENTS AND METHODS: A total of 80 elective laparoscopic cholecystectomy patients were included in the study. Patients were randomly allocated (1:1) into two study groups: a low-flow anesthesia group and a normal-flow group. ONSD, BIS, left and right rSO_2, SAP, DAP, MAP, HR, SpO_2, $EtCO_2$, peak inspiratory pressure (P-Peak), Mini-Mental State Exam (MMSE), and duration of surgery were recorded.

RESULTS: The results showed that low-flow anesthesia (0.75 l/min) during laparoscopic cholecystectomy had a preventive effect on the increase in ONSD at 30 minutes (T4) into the operation ($p = 0.014$). BIS values of left and right rSO2 during the preoperative and intraoperative periods were similar.

CONCLUSIONS: In conclusion, low-flow anesthesia during laparoscopic cholecystectomy may benefit ICP by preventing an increase in ONSD.

Key Words:

Laparoscopic cholecystectomy, Intracranial pressure, Low-flow anesthesia, Normal-flow anesthesia, Optic nerve sheath diameter.

Introduction

The use of laparoscopic surgery is widespread, with laparoscopic cholecystectomy being one of the most frequently performed procedures. There are numerous advantages to laparoscopic cholecystectomy over open surgery, including a decreased complication rate, less post-operative pain, and a shorter hospital stay. However, during laparoscopic surgeries, the pneumoperitoneum is known to raise intracranial pressure (ICP), reduce cerebral blood flow (CBF), and, as a consequence, cause cerebral hypoxia[1,2].

Increased intra-abdominal pressure, decreased cerebrospinal fluid (CSF) absorption, obstruction of lumbar venous plexus drainage, increased pressure in the vascular compartment of sacral spaces, and cerebral vasodilation brought on by hypercarbia are some of the mechanisms accounting for the increased in ICP during laparoscopy[3]. The most accurate way to measure and monitor ICP is intraventricular and intraparenchymal catheterization. However, invasive ICP monitoring during laparoscopic surgery is nearly difficult because of significant complications like hemorrhage, infection, and equipment trouble[4,5]. Cerebrospinal fluid connects the optic nerve sheath, which is an outgrowth of the cerebral dura mater, to the intracranial subarachnoid space. The diameter of the sheath that protects the optic nerve likewise grows larger in response to elevated ICP[6]. Recently, ultrasound-guided ONSD measurement has become a simple and reliable method for estimating elevated ICP[4,7].

Reduced cerebral perfusion pressure is a direct result of increased ICP. This induces brain parenchymal ischemia and delayed recovery from anesthesia. Therefore, in the event of elevated intracranial pressure (ICP), like after laparoscopic cholecystectomy, near-infrared spectroscopy (NIRS), a non-invasive and continuous monitoring technique, is used to evaluate cerebral perfusion adequacy and predict regional tissue oxygenation[8,9]. One of the most dreaded problems is awareness during general anesthesia. Individu-

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als differ in the duration and degree of their consciousness and recall of intraoperative experiences. While intense awareness episodes are uncommon, they can create anxiety and post-traumatic stress, resulting in unfavorable psychological and cognitive outcomes[10]. Various techniques and monitoring methods are used during anesthesia to reduce the risk of awareness. One such technique is the use of bispectral index (BIS) monitoring. BIS is a method that allows for the depth of sedation and anesthesia to be measured by analyzing the electrical activity of the brain[11]. There are various potential upsides to low-flow anesthesia. It lessens emissions of greenhouse gases and the expense of healthcare while increasing mucociliary clearance, maintaining core body temperature, and decreasing fluid loss by as much as 75%. It also enhances the dynamics of the air we breathe[12-14]. During laparoscopic procedures, the use of low-flow anesthesia has been proposed as a potential strategy to mitigate the increase in ICP and minimize the risk of cerebral hypoxia[15-17]. Nevertheless, the impact of low-flow anesthesia on ICP during laparoscopic cholecystectomy remains poorly investigated and insufficiently understood.

The primary goal of this study was to evaluate the differences in ONSD between patients undergoing laparoscopic cholecystectomy under low-flow anesthesia (0.75 l/min) and normal-flow anesthesia (1.5 l/min). We aimed to test whether ONSD is affected more beneficial by low-flow anesthesia (0.75 l/min) than by standard-flow anesthesia (1.5 l/min). The secondary objectives included measuring regional cerebral oxygen saturation (rSO_2) and BIS throughout the operation and assessing cognitive function in the post-operative 24th hour.

Patients and Methods

Ethical approval for this single-center, prospective, randomized controlled trial was provided by the Clinical Ethics Committee of Necmettin Erbakan University (2023/4146) on January 20, 2023. The study protocol was registered in the international database ClinicalTrials.gov (NCT05946200). Patients were randomly assigned 1:1 to receive either low-flow or standard anesthesia. Patients were informed of the study and given the opportunity to participate when they arrived at the operating room for their scheduled procedure. Patients had to fall within the 18-65 age range and have an ASA physical status of I or II to be considered for inclusion. Underage participants, pregnant women, people with acute or chronic eye disease, people taking medicines known to impact ICP, and people with a history of alcohol or drug misuse were all disqualified.

Preoperative Procedures

The patients were taken into surgery without any sort of sedation. Electrocardiography (ECG), peripheral oxygen saturation (SpO_2), and non-invasive arterial blood pressure were all monitored during the procedure as part of the normal monitoring protocols. Ocular ultrasonography was also used to record the right and left ONSD measurements. All patients had their rSO_2 measured using NIRS, and BIS monitoring was utilized to gauge how deeply they were sedated. Sensors for NIRS and BIS were placed under the hairline on the right and left frontal lobes and taped in place to prevent light from reaching them.

Randomization

A computerized randomization table made by an independent researcher assigned patients equally to a low-flow group (LG, n = 40) and a normal-flow group (NG, n = 40). Patients in the low-flow group had their fresh gas flow reduced from 4 l/min to 0.75 l/min after the first 10 minutes. In contrast, patients in the normal-flow group were given 4 l/min of fresh gas for the first 10 minutes, with the flow rate afterward being maintained at 1.5 l/min. A tidal volume of 8 ml/kg of ideal body weight was used for all patients being mechanically ventilated at a rate of 12-14 breaths per minute. Minimum alveolar concentration (MAC) values were calculated as a function of age and shown in terms of their impact on the volume of air breathed in. All surgeries were performed by the same general surgeon using the same protocol. Pneumoperitoneum was induced in all patients by insufflation with carbon dioxide (CO_2) at a pressure of 12 mmHg. A head elevation of 30 degrees was chosen as the gold standard for the reverse Trendelenburg posture.

General Anesthesia

All patients were given general anesthesia following the same standardized approach by a seasoned anesthesiologist. Rocuronium bromide (0.6 mg/kg IV) was administered after anesthesia was produced with propofol (2 mg/kg IV) and fentanyl (2 mcg/kg IV). Following endotracheal intubation, minute ventilation was used to keep the end-tidal carbon dioxide ($EtCO_2$) between 35 and 40 mmHg. An intravenous dose of ondansetron (4 mg) was given during the induction of anesthesia to reduce the risk of nausea and vomiting after surgery. In addition, 5-25 milligrams of ephedrine hydrochloride were administered intravenously if the patient's mean arterial pressure (MAP) dropped by 25% or more. Atropine was given intravenously at 0.01 mg/kg whenever the patient's heart rate (HR) fell below 40 beats per minute (bpm). When sevoflurane was inhaled in a 0.5 O_2 oxygen-air mixture, anesthesia persisted in both groups. At the start of the skin sutures, sevoflurane was turned off and replaced with 4 l of oxygen per minute in the fresh gas flow for both groups. After the procedure was finished, the patient was given intravenous tramadol (1 mg/kg 1).

Perioperative Measurements and Observations

The predetermined time points of the study were defined as follows. T0: in the supine position before anesthesia induction; T1: 5 min after endotracheal intubation in the supine position; T2: 5 min after pneumoperitoneum; T3: 5 min after the reverse Trendelenburg position; T4: 30 min after endotracheal intubation; T5: 5 min after desufflation (anesthetized, before awakening in the supine position); and T6: after extubation.

At each time point, we measured the ONSD, BIS values, left rSO_2 ($LrSO_2$), and right rSO_2 ($RrSO_2$) and recorded the SAP, DAP, MAP, HR, SpO_2, $EtCO_2$, and P-Peak. A Mini-Mental State Examination (MMSE) was conducted on patients preoperatively and in the post-operative 24th hour. In addition to the recorded parameters, we also noted the duration of the surgical procedure.

Statistical Analysis

Our study set intended to investigate if ONSD was affected more by low-flow management or normal-flow anesthetic. A minimum of 38 subjects per group with an ONSD measurement shift of 0.3 mm or more was required for clinically meaningful findings. The sample size was determined using statistics from a previous study[18]. Multivariate observational analysis was used on the data. For the latent variables, descriptive statistics were calculated. Means and standard deviations were determined for the continuous values, whereas frequencies and percentages were assessed for the categorical variables. For the fixed factors, mixed-effect models were developed. We looked at group, time, and group-time interaction. To compare the continuous variables between the two groups, a *t*-test was used. Bivariate correlation analysis was used to compare the values for ONSD among the three measurements. The least-square means were compared when the group-time interaction was significant. The SPSS statistics program [Statistics for Windows, Version 22.0. (BM Corp., Armonk, NY, USA)] was employed for the data analysis. $p < 0.05$ was considered statistically significant.

Results

A total of 85 patients were enrolled in this study. Three patients were excluded for meeting the exclusion criterion of a BMI value over 40 kg/m^2, so 82 patients were analyzed and randomly allocated to the LG or the NG. Two patients were excluded from the analysis because their ONSDs could not be measured. Thus, 80 patients were included in the analysis (Figure 1). All the patients underwent surgery for laparoscopic cholecystectomy, with no mortality until discharge time.

The average age for the NG was 52.77 years, while for the LG, the mean age was 46.80 years. The study included 21 males/19 females for the NG and 22 males/18 females for the LG, with an average BMI of 29.55 kg/m^2 for the NG and an average of 29.09 kg/m^2 for the LG. Eighteen patients in the NG were in ASA physical status I, and the remaining 22 were in status II. For the LG, 11 were in ASA physical status I, and the remaining 29 were in status II. We did not find any statistically significant changes regarding demographic variables or ASA status (Table I).

The mean operation time for laparoscopic cholecystectomy was 52.00 min for the NF group and 51.45 min for the LF group. We also performed and recorded preoperative and post-operative MMSE tests. However, we did not find any statistically significant differences in the operation time and MMSE from the preoperative period through the post-operative period between the groups (Table I).

The ONSD measurements taken during the study protocol are listed in Table II. Some changes were noted in ONSD during the study. When comparing times, ONSD was greater in T4 (numerically $p = 0.003$ and $p = 0.014$) when we used linear and multivariable regression analyses regarding co-morbidities with the adjusted R-square.

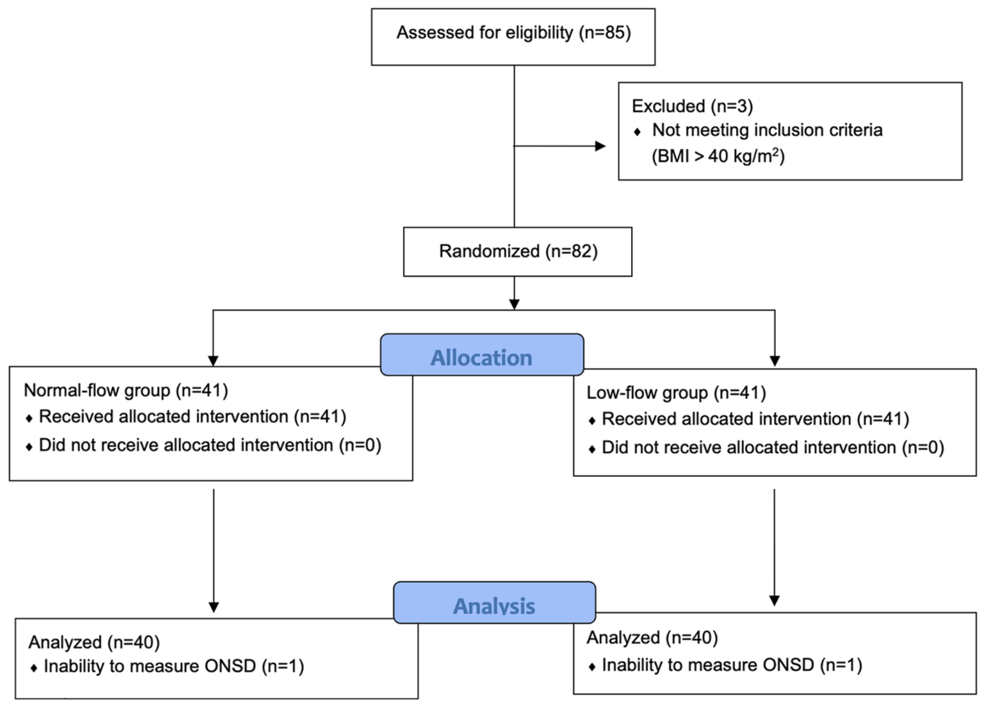

Figure 1. CONSORT flow diagram.

Table I. Demographic variables and clinical data of the study.

Variable	NG (n = 40) mean ± SD	LG (n = 40) mean ± SD	*p*
Age (years)	52.77 ± 12.98	46.80 ± 14.69	0.058
Gender (n)	21 male/19 female	22 male/18 female	0.823
BMI (kg/m^2)	29.55 ± 4.16	29.09 ± 5.55	0.673
ASA (n)	ASA 1(18)/ASA 2(22)	ASA 1(11)/ASA 2(29)	0.104
Operation time (min)	52.00 ± 5.97	51.45 ± 5.31	0.665
MMSEPreop	26.70 ± 0.68	26.80 ± 0.60	0.492
MMSEPostop	26.10 ± 0.87	25.67 ± 0.88	0.479

Table II. Optic nerve sheath diameter (ONSD) values.

Variable	NG (n = 40) mean ± SD	LG (n = 40) mean ± SD	R-square	Adjusted R-square	*p*
T0	3.70 ± 0.23	3.70 ± 0.14	0.678	0.647	0.623
T1	4.14 ± 0.30	4.11 ± 0.18			0.065
T2	4.81 ± 0.36	4.27 ± 0.27			0.447
T3	4.65 ± 0.33	4.05 ± 0.24			0.301
T4	4.67 ± 0.29	4.00 ± 0.24			*0.014
T5	4.21 ± 0.26	3.85 ± 0.22			0.963
T6	3.88 ± 0.24	3.75 ± 0.13			0.194

NG: normal-flow group, LG: low-flow group, T0: in the supine position before anaesthesia induction, T1: 5 min after endotracheal intubation in the supine position, T2: 5 min after pneumoperitoneum, T3: 5 min after the reverse Trendelenburg position, T4: 30 min after endotracheal intubation, T5: 5 min after desufflation (anaesthetised, before awakening in the supine position), and T6: after extubation. *$p < 0.05$.

Table III. Mean values of cerebral oximetry (%) for the right and left cerebral hemispheres.

Variable	NG (n = 40) mean ± SD (right/left)	LG (n = 40) mean ± SD (right/left)	R-square	Adjusted R-square	p right	p left
T0	70.87 ± 7.37/71.82 ± 7.55	67.67 ± 9.52/69.72 ± 7.20	0.179	0.185	0.723	0.991
T1	82.15 ± 9.11/83.25 ± 8.49	78.80 ± 10.93/81.47 ± 9.82			0.173	0.394
T2	78.25 ± 9.44/79.07 ± 9.22	74.27 ± 10.94/77.17 ± 10.14			0.861	0.951
T3	75.82 ± 9.36/76.65 ± 9.35	71.02 ± 9.80/74.65 ± 9.36			0.123	0.409
T4	76.57 ± 7.51/74.35 ± 13.42	73.01 ± 9.92/73.85 ± 8.79			0.790	0.556
T5	76.62 ± 8.96/76.47 ± 8.73	71.52 ± 9.41/73.62 ± 7.98			0.858	0.686
T6	82.85 ± 8.84/82.25 ± 8.43	76.70 ± 6.80/78.40 ± 6.74			0.120	0.702

NG: normal-flow group, LG: low-flow group, T0: in the supine position before anaesthesia induction, T1: 5 min after endotracheal intubation in the supine position, T2: 5 min after pneumoperitoneum, T3: 5 min after the reverse Trendelenburg position, T4: 30 min after endotracheal intubation, T5: 5 min after desufflation (anaesthetised, before awakening in the supine position), and T6: after extubation.

No statistically significant difference was observed between the two groups' $RrSO_2$ and $LrSO_2$ measurements ($p > 0.05$) at all time points (Table III). There was no statistically significant change in BIS values between the two groups prior to surgery (T0) or during surgery (T1, T2, T3, T4, T5, and T6) ($p > 0.05$; Table IV).

We analyzed the primary outcomes using a regression test to determine the differences between normal-flow and low-flow anesthesia on ONSD. Thus, we discovered a sizable variation in the R-squared value depending on the chosen flow approach (R-square = 0.678, adjusted R-square = 0.647, regression test constant $p = 0.001$ [Figure 2A]). We also analyzed the secondary outcomes by using regression tests for the NIRS (right/left) and BIS parameters between the normal and low-flow groups. We found that the R-square number affected the NIRS (right/left) and BIS parameters (numerically, R-square = 0.179, adjusted R-square = 0.185; R-square = 0.460, adjusted R-square = 0.336 [Figures 2B-D]).

We analyzed the remaining secondary outcomes by dividing them into two main subjects, one of which included hemodynamic variables and the other of which included respiratory variables. Through this approach, no statistically significant changes were detected in heart rate or MAP when using linear regression analysis (numerically, $p = 0.207$ and $p = 0.786$). Regarding respiratory variables, we did not find any statistically significant changes for $EtCO_2$, SpO_2, and airway pressure peak (P-Peak) through the linear regression analysis (numerically, $p = 0.809$, $p = 0.697$, and $p = 0.422$).

Table IV. Bispectral index (BIS) values.

Variable	NG (n = 40) mean ± SD	LG (n = 40) mean ± SD	R-square	Adjusted R-square	p
T0	93.95 ± 4.70	95.37 ± 2.04	0.460	0.336	.238
T1	49.45 ± 6.38	46.90 ± 5.44			.988
T2	49.75 ± 5.49	47.07 ± 4.84			.124
T3	51.22 ± 5.36	47.40 ± 5.18			.165
T4	51.47 ± 4.96	48.80 ± 5.02			.719
T5	52.07 ± 5.83	48.82 ± 5.57			.088
T6	90.85 ± 4.73	92.47 ± 2.81			.747

NG: normal-flow group, LG: low-flow group, T0: in the supine position before anaesthesia induction, T1: 5 min after endotracheal intubation in the supine position, T2: 5 min after pneumoperitoneum, T3: 5 min after the reverse Trendelenburg position, T4: 30 min after endotracheal intubation, T5: 5 min after desufflation (anaesthetised, before awakening in the supine position), and T6: after extubation.

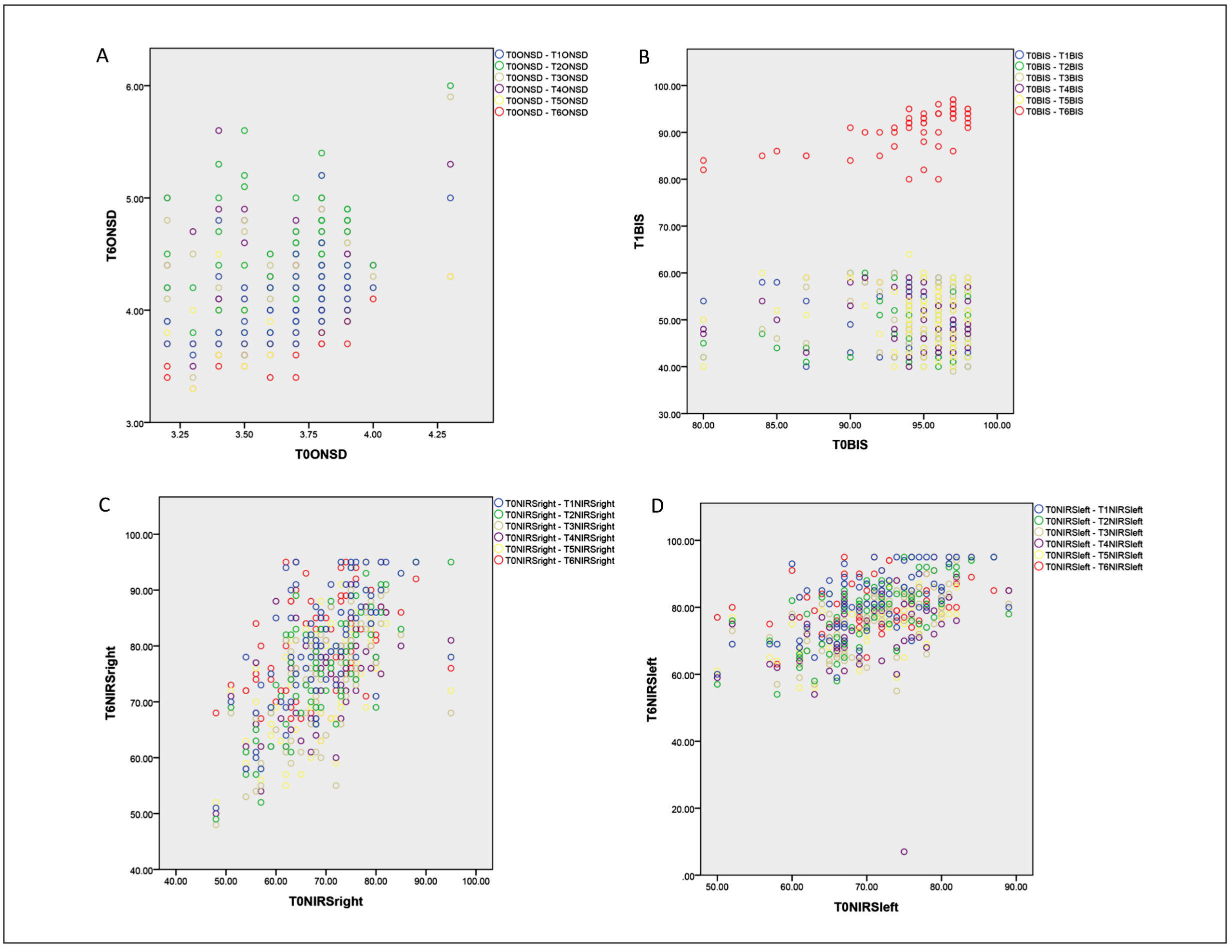

Figure 2. ONSD, BIS and NIRS variables. **A**, Correlation between times from T0 to T6 for ONSD values. **B**, Correlation between times from T0 to T6 for BIS parameters. **C**, Correlation between times from T0 to T6 for the right side of NIRS parameters. **D**, Correlation between times from T0 to T6 for the left side of NIRS parameters.

Discussion

The findings of the present study indicate that low-flow anesthesia (at a flow rate of 0.75 l/min) had a preventive effect on the rise of ONSD at T4 (30 min into operation) during laparoscopic cholecystectomy.

Pneumoperitoneum during laparoscopic procedures is known to increase ICP[19]. Recently, it was found that measuring ONSD with ultrasound is a simple and accurate way to predict elevated ICP[4]. Yashwashi et al[20] demonstrated that high-pressure pneumoperitoneum, as opposed to low-pressure pneumoperitoneum, causes a significant increase in ICP during laparoscopic cholecystectomy. The authors further noted that ICP monitoring could be achieved through the measurement of ONSD using ultrasound examination, which is a completely non-invasive method. Their findings demonstrated that the application of higher pressures in the abdominal cavity during laparoscopic cholecystectomy could result in elevated ICP. Demirgan et al[21] examined the outcome of putting patients in the reverse Trendelenburg position before pneumoperitoneum in those undergoing laparoscopic cholecystectomy in a different study. The findings of this study demonstrated that the application of this position prior to pneumoperitoneum resulted in the prevention of an increase in ONSD during laparoscopic cholecystectomy. Yanatma et al[22] investigated the effect of positive end-expiratory pressure (PEEP) application on ONSD during laparoscopic cholecystectomy. In this study, the researchers aimed to determine whether the use of 10 cmH_2O PEEP would lead to any notable changes in ONSD when compared to the absence of PEEP application. The results of the study revealed that there was no significant change in ONSD in the PEEP-applied group compared to the non-applied group. Despite these developments, our literature search did not yield any studies investigating the impact of low-flow anesthesia on ONSD in laparoscopic cholecystectomy operations.

We measured ICP using ONSD during laparoscopic cholecystectomies and compared the results between low-flow and normal-flow anesthesia. T4 ONSD was significantly different between the low-flow and normal-flow groups, according to the results. Specifically, at the 30th minute of the operation, the ONSD values in the LG were much lower than those in the NG. The results of this study imply that low-flow anesthesia may have a beneficial influence on ICP dynamics after laparoscopic cholecystectomy, as ONSD readings at this time period are lower in the LG than in the NG. For surgical treatments, having lower ONSD in the LG is preferable since it suggests lessening of increased intracranial pressure (ICP). Utilizing low-flow anesthesia helps to maintain stable levels of carbon dioxide (CO_2) and ventilation[23], which in turn can help mitigate the rise in ICP and minimize the risk of cerebral hypoxia.

Cerebral oximeters utilize NIRS to acquire continuous and non-invasive measurements of cerebral oxygenation levels[24]. In addition, awareness during general anesthesia is considered one of the most feared complications[10]. The administration of low-flow anesthesia with small doses of inhaled anesthetics may lead to an increased likelihood of patients experiencing awareness and recall during the procedure, as the concentrations of volatile anesthetics may be insufficient to maintain complete unconsciousness[25,26]. Recently, with the implementation of BIS monitoring during anesthesia, the incidence of awareness has reached acceptable levels[27]. In their study comparing low-flow and normal-flow anesthesia in morbidly obese patients undergoing laparoscopic bariatric surgery, Akbas et al[28] investigated the impact of these variables on anesthesia depth, brain oxygen saturation, and other vital signs. The results indicated that there were no statistically significant differences between the low-flow and normal-flow anesthesia groups. These findings support the conclusion that there is no significant difference in effectiveness between low-flow and normal-flow anesthesia for laparoscopic bariatric surgery in morbidly obese patients. According to the study conducted by Kupisiak et al[11] the use of both low-flow and high-flow rate general anesthesia demonstrated similar outcomes in terms of cerebral oxygen saturation, depth of anesthesia, and hemodynamic stability in patients undergoing laparoscopic cholecystectomy. Similarly, in our study, we conducted a thorough evaluation of cerebral oxygen saturations at various time points during the entire preoperative and intraoperative periods (T0, T1, T2, T3, T4, T5, and T6). We found no statistically significant variation in cerebral oxygen saturation during the entire surgical procedure. Also, the BIS values of both groups were tracked and compared continuously before, during, and after surgery. None of the measured intervals revealed statistically significant differences in BIS values between the groups. There was also no significant difference in BIS values between the low-flow and normal-flow groups, suggesting that both approaches can provide the same level of depth of anesthesia. The MMSE is a valuable tool for assessing post-anesthesia cognitive changes in clinical settings. Its widespread use is attributed to its reliability, practicality, and ease of administration. The presence and severity of postoperative cognitive dysfunction can be influenced by various factors, including the type of anesthesia administered and the specific drugs used during the procedure[29-31]. In a study, Sandeep[32] examined the effects of sevoflurane during low-flow and medium-flow anesthesia on cognitive function and recovery in patients undergoing elective laparoscopic cholecystectomy. According to their findings, the MMSE scores of the patients in both groups did not exhibit significant differences. The researchers arrived at the conclusion that patients who undergo elective laparoscopic cholecystectomy can recover their normal cognitive function and recuperation times regardless of the fresh gas supply utilized during anesthesia, based on the obtained result. Similarly, our study also found that the MMSE scores of patients in both the low-flow and normal-flow anesthesia groups did not show any significant differences. These findings show that patients undergoing elective laparoscopic cholecystectomies do not significantly differ in cognitive function whether they are given low-flow or normal-flow anesthetic. Therefore, both methods might be regarded as secure and efficient in terms of protecting patients' cognitive abilities.

Limitations

Some limitations of the present study should be mentioned. First, the study had a small sample size, which could affect the generalizability of the findings and limit the statistical power to detect significant differences. The second limitation is that the research was only done in one location. Thus, the findings may not apply to other healthcare systems or populations. Third, the study focused on short-term outcomes and did not assess the long-term effects of low-flow anesthesia on patients' recovery, complications, or cognitive function beyond the immediate postoperative period. Fourth, the study did not include a control group receiving high-flow anesthesia, which could provide a more comprehensive comparison between different anesthesia techniques.

Conclusions

The present study demonstrated that low-flow anesthesia during laparoscopic cholecystectomy might have beneficial effects on ICP dynamics by preventing the rise of ONSD at a specific time point.

Conflict of Interest

The authors have no relevant financial or non-financial interests to disclose.

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Authors' Contribution

All authors contributed to the study's conception and design. Material preparation, data collection, and analysis were performed by Aydın Mermer. The first draft of the manuscript was written by Aydın Mermer and Betül Kozanhan. Aydın Mermer and Betül Kozanhan reviewed and edited previous versions of the manuscript. All authors read and approved the final manuscript.

Ethics Approval

The study protocol was approved by the Ethics Committee of Necmettin Erbakan University (Approval Number: 2023/4146).

Informed Consent

Informed consent was obtained from all individual participants included in the study.

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Data Availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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