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Do Hipnotic Anesthetic Agents Used in Patients Undergoing Radical Prostatectomy Have An Effect on the Neutrophil/Lymphocyte Ratio? Retrospective Study

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What's known on the subject? and What does the study add?

Anesthetic agents and applications affect tumor pathophysiology and immunosuppression in the postoperative period. It was observed that anesthetic agents used in patients with cancers such as prostate cancer where there is increased inflammatory response in the early postoperative period. The probability of complications was higher in patients who received propofol with high preoperative neutrophil/lymphocyte ratio (NLR). In prostate cancer, preoperative high NLR (>1.7) may have a predictive value for bleeding, blood transfusion, and postoperative respiratory distress.

Abstract

Objective: Anesthetic agents and applications affect tumor pathophysiology and immunosuppression in the postoperative period. We evaluated the changes made by hypnotic anesthetic agents used during anesthesia on neutrophil/lymphocyte ratio (NLR) in patients undergoing radical prostate surgery and its relationship with short-term morbidity.

Materials and Methods: Age of patients who had radical prostatectomy, physical classification of the American Society of Anesthesiology, perioperative blood transfusion, drugs used during general anesthesia (intravenous, opioid, volatile anesthetic), duration of anesthesia, analgesics used in postoperative pain was examined. Preoperative, postoperative day-0 and day-2 NLR results were recorded.

Results: The data of 159 patients who underwent radical prostatectomy were assessed. The patients were divided into 2 groups; Group pentotal-sevoflurane/desflurane (PSD) (n=101) and Group propofol-sevoflurane/desflurane (PrSD) (n=58). There was no difference in terms of preoperative and postoperative 2 day NLR value, but the highest NLR values in the postoperative day 0 was found to be in Group PrSD. Postoperative complications were higher in Group PSD. However, preoperative NLR values of these complications were higher in Group PrSD. Erythrocyte (red blood cell) replacement patients were divided into 2 groups; between 0 and 2 units (n=147) and more than >2 units (n=12), their preoperative NLR ratios were 2.54 (0.7-16.3) and 3.3 (1.8-8.8) respectively. The cut value of NLR for bleeding was set at 1.77.

Conclusion: Increased NLR result is associated with immunosuppression and tumorigenesis, and is an easy and inexpensive technique. In prostate cancer, preoperative high NLR (>1.7) may have a predictive value for bleeding, blood transfusion, and postoperative respiratory distress.

Keywords: Radical prostatectomy, neutrophil/lymphocyte ratio, anesthetic agents

Introduction

Prostate cancer is the most commonly diagnosed malignant tumor in men across the world, but it is the second most common cause of cancer-related mortality and radical prostatectomy is the first choice in the treatment of localized prostate cancer (1). However, prostate cancer is a type of cancer with a frequency of relapses and metastases. The reasons for this include excessively aggressive behavior of the tumor, as well as perioperative factors that cause cancer cell dissemination due to tissue manipulation during surgery and immunosuppression (2). These perioperative factors include blood transfusion, postoperative pain, severe

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hypothermia, psychological stress, type of surgery, type of anesthesia (general, regional or combined), and cell-mediated immunity depression during surgery (2,3).

It is known that the anesthetic agent and method affect the pathophysiology of the tumor in the postoperative period. In particular, intravenous anesthetics (except propofol), opioids and volatile anesthetics have been reported to be involved in immunosuppression and angiogenesis (4). In addition, regional anesthesia is superior to general anesthesia in preventing cancer recurrence (5).

Inflammation is blamed for potentially causing prostate carcinogenesis and progression and the importance of the strategies aimed at the inflammatory process to prevent prostate cancer is emphasized (6). Recommended as an indicator of the inflammatory state of the host and the general immune response to various stress stimuli, neutrophil/lymphocyte ratio (NLR) is the ratio of the neutrophil count to the lymphocyte count in a peripheral blood sample (1,7). In addition, it has been specified that high NLR ratios before treatment are associated with poor prognosis in various types of cancer and high NLR (>2) ratios can be independent positive predictors of biochemical recurrence (7).

Based on the information that NLR is a marker of postoperative poor prognosis in patients undergoing radical prostate surgery, and that anesthesia practices worsen the prognosis in these patients due to immunosuppression, this study is intended to compare the changes caused by the hypnotic anesthetic agents used during anesthesia on NLR ratios and their relation with short-term morbidity.

Materials and Methods

Upon the approval no: 2020-29 from the hospital ethical committee, this study was conducted studied the retrospective records of the data pertaining to patients who performed radical prostatectomy with general anesthesia between January 2015 and January 2020. The blood transfusion in the past 12 weeks, those with antibiotic use due to acute infection or with steroid use due to an inflammatory disease, those administered neoadjuvant therapy for prostate cancer (hormone or radiotherapy) areas, those performed simultaneous biopsy or surgery on other organs were excluded from the study. Because NLR analysis in prostate cancer, transrectal prostate biopsy used during diagnosis may be sensitive to subclinical prostate inflammation and even systemic infection. Results may be affected by subclinical inflammations if adequate time has not elapsed between blood measurements and biopsy.

Age, body mass index, American Society of Anesthesiologists (ASA) physical status classification, perioperative blood transfusion, drugs used during general anesthesia (intravenous, opioid, and volatile anesthetic), duration of anesthesia, analgesics used for postoperative pain were also obtained from the patient records. The preoperative, postoperative day-0 and day-2 NLR ratios were calculated as the ratio of the number of neutrophils to the number of lymphocytes collected in a peripheral blood test. According to the NLR cut-off value, the presentcohort was divided into two groups: a high-NLR and a low-NLR group.

The patients underwent a routine general anesthesia protocol after routine non-invasive monitorization (electrocardiogram, non-invasive blood pressure, peripheral oxygen saturation, and esophageal temperature probe). In the induction of anesthesia, intravenous anesthetics (thiopental or propofol), muscle relaxants (rocuronium), and opioid (remifentanyl or fentanyl) were administered and then maintained using a volatile anesthetic (sevoflurane, desflurane). All patients underwent radical prostatectomy with laparotomy technique accompanied by retropubic incision in the supine position. At the end of the operation, the patients were administered paracetamol-tramadol for analgesic purposes.

Postoperative hospital stays in the intensive care unit and in hospital, as well as postoperative complications/problems were included in the records.

Statistical Analysis

Continuous data are given as mean ± standard deviation. Categorical data are given in percentages (%). Shapiro Wilk's test was used to investigate whether the data are normally distributed. Two way repeated measures ANOVA (one factor repetition) test was used for repeated measurements. The Pearson Exact chi-square was used to analysis for the categorical data. IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY:IBM Corp.) was used to perform the analyses. $P<0.05$ was considered the criterion for statistical significance. To determine the optimal cut value for NLR, the receiver operating characteristic of NLR for bleeding was analyzed.

Results

The data of 159 of 172 patients who underwent radical prostatectomy were assessed. Thirteen patients with missing data could not be included in the study. The mean age of the patients was 62.4±5.84 and according to the ASA 28% (n=46) of the patients were ASA I, 58% (n=93) ASA II, 12% (n=20) ASA III. The duration of anesthesia was 245±46.8/min and the discharge time was 9.84±6.15/day. 28% (n=45) of the patients needed intensive care in the postoperative period (Table 1). There was no statistically significant relation between NLR and

anesthesia duration (p=0.07), need for intensive care (p=0.414), and discharge time (p=0.922). 33.3% of the patients were at pT3a pathological stage and 30.2% of them were at the pT2 pathological stage.

The patients were divided into 2 groups according to the anesthetic agent administered during general anesthesia: thiopental-sevoflurane, thiopental-desflurane peritoneal-sevoflurane/desflurane (PSD) (n=101), pentotal-sevoflurane/desflurane (PrSD) (n=58). In the intergroup comparison, there was no difference in terms of preoperative NLR value [group PSD: 2.24 minimum-maximum (min-max): 0.44-16.3], group PrSD: 2.25 (min-max: 0.48-8.8), while the highest NLR values in the postoperative day 0 was found to be group PrSD ($p<0.05$) (Figure 1). NLR values on the 2nd postoperative day were similar in both groups [group PSD: 6.77 (min-max: 0.8-20), group PrSD:6.61 (min-max: 2.14-13.3)].

In the postoperative period, 69% of patients had no complications. Postoperative complications included fever (0.6%), arrhythmia (1.9%), electrolyte disorder (0.6%), hypertension (2.5%), bleeding (10.7%), coronary vasospasm (2.5%), respiratory distress (8,1%), perforation of the rectum (1.9%), wound site opening (0.6%) and edema of the legs (0.6%). In Table 2, the distribution of complications by anesthetic agents and preoperative NLR values are presented. The most common complication was bleeding, although it was seen more in group PSD, preoperative NLR value in the group was statistically significantly higher (2.55 versus 4.06). Other complications were higher in the group. However, preoperative NLR values of these complications were higher in group PrSD (Table 2). In addition, these complications postoperative day 0 NLR values were higher in group PrSD.

The cut value of NLR for bleeding was set at 1.77. The preoperative value was >1.77 in 61% of the patients with bleeding in the PSD group and 80% in the PrSD group (Figure 2).

During the perioperative period, patients were evaluated in two groups for red blood cell transfusion. These patients were evaluated as those with red blood cell transfusion between 0 and 2 units (n=147) and others with red blood cell transfusion of more than >2 units (n=12), and their preoperative NLR ratios were 2.54 (0.7-16.3) and 3.3 (1.8-8.8), respectively. This difference was statistically significant ($p<0.05$). Red blood cell transfusion was performed in 47 patients during the perioperative period. While 33 (70.3%) of these patients were in group PSD, 14 (29.7%) were in group PrSD. 35 of the patients in need of intensive care were in group PSD, while 11 patients were in group PrSD.

Table 1. Demographic data

	Mean	Standard deviation
Age	62.4	±5.84
BMI (kg/m^2)	22.53	±6.21
Gleason score	6.89	±1.02
Duration of anesthesia (minutes)	245	±46.8
Time of discharge (days)	9.84	±6.15

BMI: Body mass index

Discussion

In this study, we evaluated not only the long-term outcomes of preoperative, postoperative day-0 and day-2 NLR but also the association of prostate cancer patients with perioperative NLR and outcomes of hypnotic anesthetic agents in an analysis of 159 patients who underwent radical prostatectomy under general anesthesia. NLR values were higher on days 0 with PrSD administration. The most common complications in the postoperative period were bleeding and respiratory distress. The preoperative NLR values of these patients were found to be >1.77.

It has been found that a high NLR rate is correlated with poor prognosis in various organ cancers such as lung, stomach, colon and pancreas in many studies (8). The decreased lymphocyte ratio is associated with an immunosuppressive state, resulting in reduced efficacy in malignant tumor formation, progression and elimination. In prostate cancer NLR rate has been associated with early biochemical recurrence, clinicopathological features [pathological stage, Gleason score, preoperative prostate specific antigen (ng/mL), pathological lymph node, prostate capsule invasion, seminal vesicle invasion, surgical margin, nerve invasion] and poor prognosis in some studies (1,8).

Although many studies have been conducted to assess anesthesia techniques and oncological outcomes, the relationship between the surgery- or anesthesia-induced immunosuppression and the cancer recurrence has yet to be clarified (9). Wuethrich et al. (2)

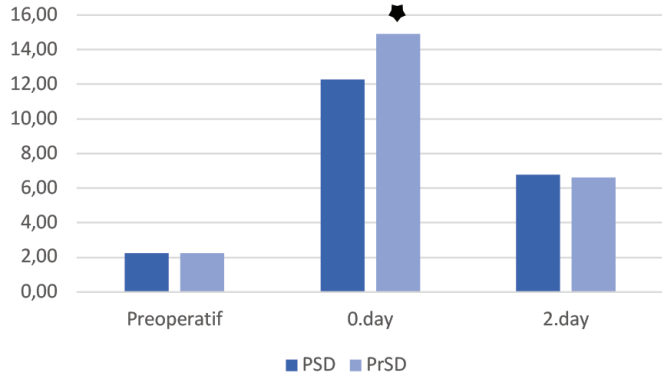

Figure 1. Perioperative NLR (median) values between groups

NLR: Neutrophil/lymphocyte ratio, PSD: Pentotal-sevoflurane/desflurane, PrSD: Propofol-sevoflurane/desflurane, *p<0.05

studied patients with advanced prostate cancer (stage pT3/4) who underwent retropubic radical prostatectomy surgery under perioperative epidural+general anesthesia or general anesthesia. The study reported no reduction in cancer progression or improvement in survival after radical prostatectomy in the epidural+general anesthesia group compared with the other general anesthesia group (postoperative opioid) in terms of recurrence during 14 years of observation. However, the study by Biki et al. (10) reported significantly less biochemical recurrence in the epidural+general anesthesia group compared to the general anesthesia group that was administered postoperative opioid. In their study, Lusty et al. (4) emphasized the role of regional anesthesia in reducing mortality in prostate cancer surgery, as the reason for this decrease in the use of opioid and volatile anesthetics in regional anesthesia applications, the reduction of surgical stress response and improvement of oncoimmunological responses directly through the anti-inflammatory effect of local anesthetics.

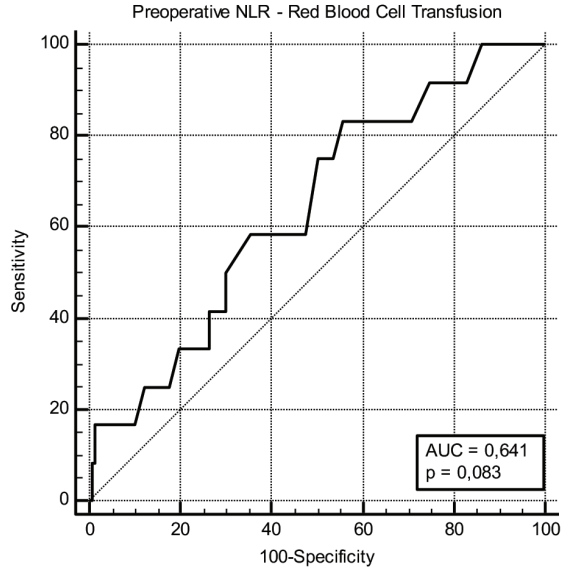

Figure 2. Preoperative NLR for the postoperative bleeding

NLR: Neutrophil/lymphocyte ratio, AUC: Area under the curve

The intravenous anesthetics of thiopental and ketamine suppress natural killer cell activity (9). Thiopental inhibits neutrophils function and suppresses activation of T-lymphocyte activation, as well as nuclear factor kappa B (NF-κB). Propofol increases the cytotoxic T lymphocyte activity, reduces pro-inflammatory cytokines and inhibits COX-2 and Prostaglandin E2 functions. In this case, reducing neuroendocrine responses due to surgery through hypothalamic-pituitary-adrenal axis and sympathetic nervous system suppression, propofol and regional anesthesia might cause less immunosuppression and relapse of certain types of cancer compared to volatile anesthetics and opioids (9). Opioids (especially morphine) reduce natural killer cell activity against cancer cells and increase tumor growth and angiogenesis upon activation of vascular endothelial growth factor (VEGF) (4). Inhalation agents suppress cell-mediated immunity, stimulate T-lymphocyte apoptosis and can contribute to tumor relapse by increasing angiogenesis with hypoxia-induced factor-1a activity (11). Looney et al. (12) observed that the group receiving sevoflurane-opioid anesthesia for breast cancer had an increased level of VEGF associated with angiogenesis compared with the group administered propofol-paravertebral anesthesia.

In this study, we classified the anesthetic agents administered into 2 groups. We did not add them to the assessment, as all patients received opioids and the effects of inhalation agents were similar. In all groups, the preoperative NLR value was above 2. The group with the highest postoperative NLR value was the PrSD group, which was statistically significant. Studies reported that propofol had no effect on immunosuppression, however, in our study, the values were higher in the propofol group. However, this height was only in the early postoperative period. Day 2 values were similar in both groups. This may be attributed to a single dose administration of propofol only in the induction of anesthesia. It may be more accurate to evaluate NLR values in longer-term infusion applications.

In patients with stomach cancer, short-term postoperative complications, intraoperative bleeding and blood

Table 2. Distribution of complications according to the anesthetic agents used

	PSD	PrSD	PSD Preoperative NLR (mean)	PrSD Preoperative NLR (mean)	p
Bleeding (n=18)	13	5	2.55	4.06	0.032
Respiratory distress (n=13)	9	5	2.75	2.10	0.13
Arhythmia (n=3)	2	1	2.65	4	0.028
Electrolyte disorder (n=1)	1	-	3.62	-	
Elevated blood pressure (n=4)	3	1	1.78	2.2	0.074
Swelling of the legs (n=1)	1	-	1.53	-	
Coronary spasm (n=4)	3	1	1.50	2.26	0.081

PSD: Pentotal-sevoflurane/desflurane, PrSD: Propofol-sevoflurane/desflurane

transfusion rates were reported to be higher in those with NLR >2 (13). The most common complications in this study were bleeding and respiratory distress. The complication incidence rate was higher in group PSD, but patients in group PrSD had higher preoperative NLR than those in group PSD. It was also seen that the NLR values of the patients who had blood transfusion were above 1.7, and the preoperative NLR was even higher in the patients who had more than 2 transfusions. Similarly, the number of patients staying in the intensive care unit and the number of transfused patients were higher in group PSD.

Study Limitations

The study had its limitations in itself. First, the data were collected from a single center and retrospectively, and the distribution among the groups was uneven. Although we excluded the factors that affect the NLR ratio, it is necessary to keep in mind that neutrophils and lymphocytes counts may also be affected by the agents used and their doses, as well as by comorbidity.

Conclusion

To conclude, was observed that anesthetic agents were used in patients with cancers such as prostate cancer, where there is an increased inflammatory response in the early postoperative period. Although this increase in propofol seems to be more, it would not be correct to link this increase only to propofol. In addition, the probability of complications was higher in patients who received propofol with high preoperative NLR. It seems rational to avoid the use of propofol in general anesthesia for patients with a high preoperative NLR value.

Additionally, preoperative high NLR (>1.7) may have a predictive value for bleeding, blood transfusion, and postoperative respiratory distress. However, there is a need for further prospective randomized controlled studies to clarify the effects of anesthesia on immunity, tumor recurrence, and survival.

Ethics

Ethics Committee Approval: Upon the approval no: 2020-29 from the hospital ethical committee, this the present study was conducted studied studying the retrospective records of the data pertaining to patients who performed radical prostatectomy with general anesthesia between January 2015 and January 2020 (Eskisehir Osmangazi University Ethics Committee).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.O., A.Ö., C.C., Concept: B.Y., Design: M.O., D.Ç., Data Collection or Processing: M.O., Ad.Ö., Analysis or Interpretation: M.O., D.Ç., Literature Search: M.O., Writing: M.O., D.Ç., B.Y.

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

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