Original Article

Effect of Lidocaine Infusion during General Anesthesia on Neutrophil-Lymphocyte-Ratio in Breast Cancer Patients Candidate for Mastectomy; a Clinical Trial

Elham Memary[1], Alireza Mirkheshti[1], Mahshid Ghasemi[1], Mehrdad Taheri[1], Ali Arhami Dolatabadi[1], Atiye Kaboudvand[1]

Abstract

Background: Considering the anti-inflammatory role of intravenous (IV) lidocaine, its analgesic properties, and its ability to reduce the need for opioids during and after surgery, in this study we decided to evaluate the effect of IV lidocaine infusion on levels of inflammatory factors based on neutrophil to lymphocyte ratio (NLR) in breast cancer surgery candidates.

Materials and Methods: The present study is a randomized clinical trial. All the patients with ASA: I, II breast cancer, who were candidates of mastectomy elective surgery were included. The patients were allocated to 2 groups of IV lidocaine and normal saline based on a random numbers table. After inducing anesthesia similar for all the patients, using 0.02 mg/kg midazolam, 2-4 µg/kg fentanyl, 1-2 mg/kg propofol and 0.5 mg/kg atracurium, either 1.5 mg/kg/hr IV lidocaine or the same volume of normal saline was infused intravenously. Glasgow prognostic score and NLR were calculated before and 6, 24, and 48 hours and 14 days after surgery.

Results: A total of 63 women suffering from breast cancer, with the mean age of 49.25±9.32 years, were included and allocated to lidocaine and control groups using simple randomization. There was no significant difference between the 2 groups regarding mean age (p=0.591), incision size (p=1.000), and duration of surgery (p=0.752). Using mixture model regression analysis and after adjusting the effect of baseline variables, a significant difference was detected between the groups regarding NLR during the follow-up period (p=0.006)

Conclusion: Based on the findings of the present study, it seems that NLR changes were smaller in breast cancer patients, who had received a lidocaine infusion during surgery, compared to the control group.

Keywords: Breast neoplasm; anesthesia, general; lidocaine; prognosis

1. Department of Anesthesiology, Imam Hosein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Corresponding Author:
Alireza Mirkheshti. Anesthesiology Research Center, Imam Hossein Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Tel: +982177567840;
Fax: +982177567840;
E-mail: alimirkheshti@yahoo.com

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Introduction

Breast cancer is one of the major causes of mortality due to cancer in women (1). It has been shown that a complex array of factors including hormones, genetic history, new genetic mutations, and chemo-physical environmental factors play a role in pathogenesis and development of breast cancer (2-4).

During the past decades, breast cancer has been widely studied from different aspects in most cancer research centers around the world, and the research is still ongoing (5). One aspect that has received much attention is the prognosis of this disease. Neutrophil to lymphocyte ratio (NLR) is one of the values used for this purpose. This scale is currently a sensitive one to evaluate systemic inflammatory response and an independent scale for prognostic outcome of cancer. It seems that systemic inflammatory response is the major cause of bad prognosis in cancer.

Cancer is abnormal growth of tumor cells; it seems that multiple inflammatory systems such as cytokines, chemokines, prostaglandins, and cyclooxygenases cause the growth in tumor cells by suppressing the immune system, inducing resistance to apoptosis and promoting angiogenesis, which is in fact the role of chronic inflammation for some types of cancer. Anesthesia procedure of cancer patients during surgery can affect the level of these inflammatory factors. Lidocaine is among the drugs used for induction of general anesthesia and has been proposed to have anti-inflammatory properties (6, 7). On the other hand, there have been reports of undesirable effects of opioid drug prescription during surgery on inflammatory factors' rate and cancer relapse after surgery (8, 9). Therefore, considering the anti-inflammatory role of intravenous (IV) lidocaine and its analgesic property, which reduces the need for opioids during and after surgery, in this study, we decided to assess the effect of IV infusion of lidocaine on NLR as a predictive inflammatory scale in candidates of elective breast cancer surgery.

Methods

The present study is a randomized clinical trial. All candidates for elective breast cancer surgery with ASA: I, II presents to Imam Hossein Hospital, Tehran, Iran, were included in the study. History of convulsion, mental illness or psychotropic drug consumption, hepatic diseases or hepatic enzyme dysfunction, kidney disorder, cardiac arrhythmia, hospitalization for more than 5 days, recent infection or infection of the surgery site in the past 14 days, allergy to lidocaine, fentanyl and propofol, history of blood transfusion in the past week or need for blood transfusion during or after surgery, operation duration longer than 4 hours, and drug abuse were exclusion criteria.

Intervention

In total, 70 cases were candidates for participation, 7 of them did not give consent and 63 participated. Figure 1 shows the flowchart of study participants. Patients were allocated to IV lidocaine and control groups using random numbers table. Blood sample of the patients was drawn for complete blood count (CBC) and different types of white blood cells (WBC) count. After induction of anesthesia for all patients through the same protocol using 0.02 mg/kg midazolam, 2-4 µg/kg fentanyl, 1-2 mg/kg propofol and 0.5 mg/kg atracurium, based on their group either 1.5 mg/kg/hr lidocaine or an equal volume of normal saline were intravenously infused. Maintaining anesthesia during surgery was done using propofol infusion based on keeping bispectral index: 40-60 and with a 100-200 µg/kg dose. All the patients were under full cardiovascular, bispectral index (BIS), and End tidal CO_2 monitoring. In case of tachycardia despite proper depth of anesthesia and circulation volume during operation, 1 µg/kg fentanyl was injected until hemodynamic was controlled. To control pain after surgery, for 48 hours, all the patients received Apotel ampule, with a dose of 1 gr in 6 hours, intravenously and 20µg/ml PCA fentanyl pump with bolus doses of 5.0 ml each 15 minutes. In lidocaine group, 2 mg/min lidocaine infusion and in control group, 2 mL/min normal saline infusion was done. When patients complained of severe pain with the visual analog scale (VAS) ≥4, 30 mg IV meperidine was injected and its dose was recorded for 48 hours. NLR was calculated before, and 6, 24, and 48 hours and 14 days after surgery.

Statistical analysis

Kolmogorov-Smirnov test and Q-Q plot were used to examine the normal distribution of data. To

describe the data we used mean, standard deviation (SD), median, frequency, and percentage. To compare the results between the two groups we used t-test, Mann Whitney and Chi-Square tests. To compare the results after adjusting for baseline values we used Analysis of Covariance (ANCOVA). To compare the trend of variable changes between the two groups we used Linear Mixed model analysis. All statistical analyses were performed by SPSS (IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.). P-value less than 0.05 was considered statistically significant.

Ethical considerations

This study was done after receiving a license from the ethics committee of Shahid Beheshti University of Medical Sciences by the number IR.SBMU.MSP.REC.1394.98. All the patients participated in the study after receiving a thorough explanation regarding the method of the study and giving written consent. Adherence to the declaration of Helsinki principles and maintaining patient data confidential were other measures taken to maintain

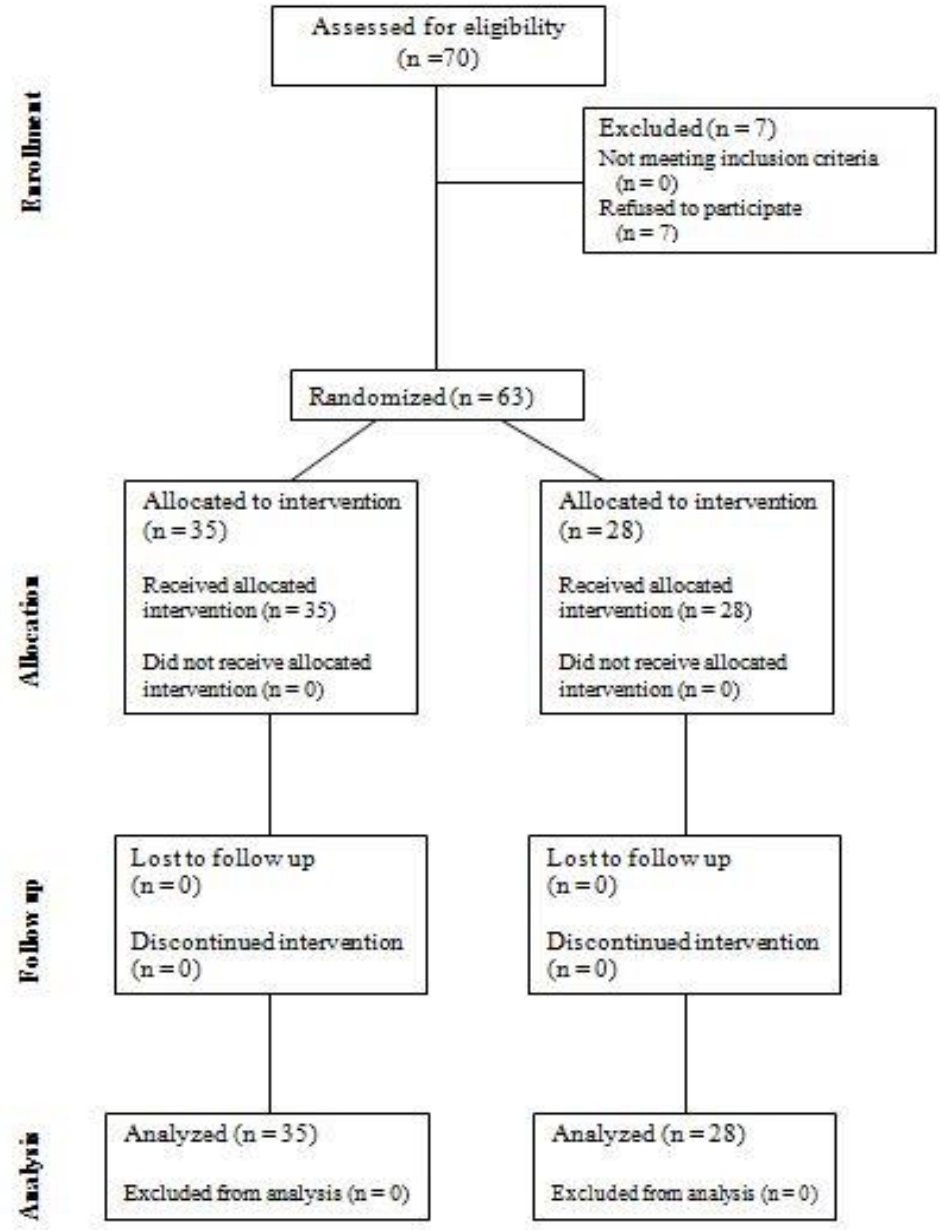

Fig. 1. CONSORT flowchart of studied patients.

ethics during the study. The protocol of this study is registered in the Iranian registry of clinical trials (www.IRCT.ir) under the code IRCT201608029593N5.

Results

A total of 63 women with the mean age of 49.25± 9.32 years suffering from breast cancer were included in the study. 28 were allocated to lidocaine group and 35 were in the control group. Mean age was 48.61±9.26 (range: 30-68) years in lidocaine group and 49.89±9.38 (range: 34-65) years in the control group. Independent t-test results showed that there is no statistically significant difference between the 2 groups (p=0.591). Regarding the type of surgery, all patients in both groups underwent mastectomy and no significance was found between the groups in terms of incision size (p=1.000) and duration of surgery (p= 0.752). Demographic data and baseline characteristics of the studied patients are reported in table 1.

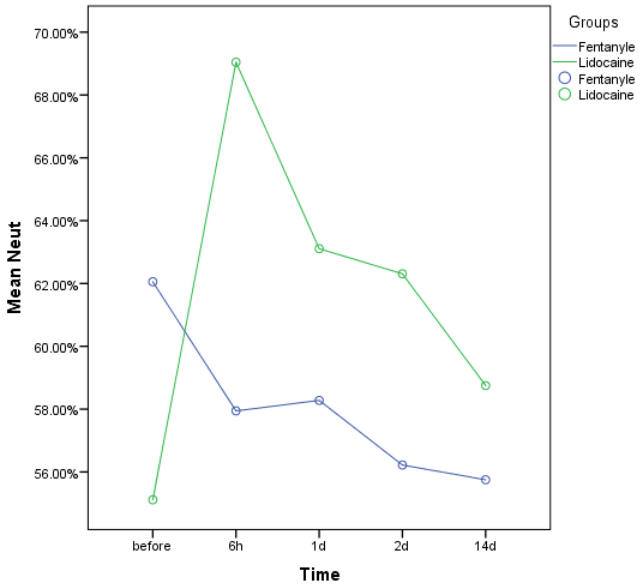

Fig. 2. Neutrophil percent changes during the study (p-value =0.006).

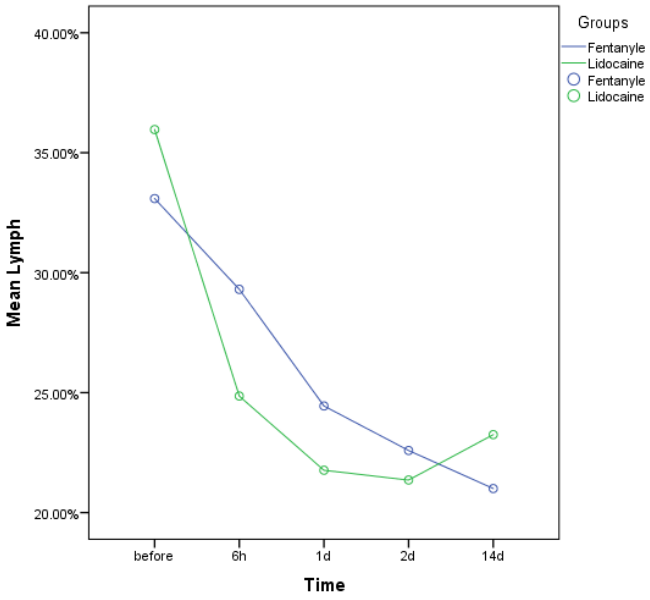

Fig. 3. Lymphocyte percent changes during the study (p-value =0.306).

Changes in neutrophil count

Using ANCOVA and after adjusting the effect of baseline neutrophil count, mean difference of NLR between the 2 groups was not significant (p=0.112). Mean difference of this ratio between the groups was significant 6 hours after surgery, but not 24 and 48 hours, and 14 days after the operation (Table 2). Using mixture model regression analysis and after adjusting the effect of baseline values of variables a statistically significant difference was detected between the 2 groups regarding NLR during the study period (p=0.006) (Figure 2).

Changes in lymphocyte count

Using ANCOVA and after adjusting the effect of baseline lymphocyte and neutrophil counts, mean difference of NLR between the 2 groups was not significant before surgery (p=0.505). Mean difference of this ratio between the groups was not significant 6, 24, and 48 hours, and 14 days after surgery (Table 3). Using mixture model regression analysis and after

Table 1: Baseline characteristics of studied patients.

Variable	Control Group	Lidocaine Group	P
	Mean ±standard Deviation		
Age (year)	49.89±9.38	48.61±9.26	0.591
Incision size (cm)	21.1±5.2	21.1±5.2	1.000
Duration of Surgery (minute)	2.5±0.2	2.4±0.6	0.101

Table 2: Neutrophil percent changes during the study.

Time	Fentanyl	Lidocaine	Difference	95% CI		P
	Mean ± SD			Lower	Upper	
0	62.06± 13.56	55.11 ± 9.25	6.94	-1.70	15.59	٠,112
6 hours	57.94± 8.40	69.04 ± 12.12	-11.09	-18.97	-3.22	0.003
1st day	58.28 ± 10.23	63.11 ± 5.90	-4.82	-11.10	1.44	0.118
2nd day	56.22 ± 11.38	62.31 ± 7.89	-6.08	-13.59	1.42	0.058
14th d	55.75 ± 12.65	58.75 ± 7.72	-3	-11.50	5.50	0.360

Table 3: Lymphocyte percent changes during the study.

Time	Fentanyl	Lidocaine	Difference	95% CI		P
	Mean ± SD			Lower	Upper	
0	33.09 ± 12.48	35.96 ± 11.22	-2.87	-11.57	5.82	0.505
6 hours	29.31 ± 8.15	24.86 ± 10.78	4.44	-2.38	11.27	0.054†
1st day	24.44 ± 6.08	21.76 ± 6.46	2.68	-1.86	7.22	0.067†
2nd day	22.59 ± 8.27	21.36 ± 11.64	1.23	6.09	8.55	0.567†
14th d	21 ± 8.29	23.25 ± 10.84	-2.25	-9.67	5.17	0.588†

† Based on t-test.
†Adjusted for the baseline value based on Analysis of Covariance (ANCOVA).

Table 4: Neutrophil-Lymphocyte-Ratio changes during the study.

Time	Fentanyl	Lidocaine	Difference	95% CI		P
	Mean ± SD			Lower	Upper	
0	1.83 ± 0.71	1.27 ± 0.29	0.95	-0.88	2.78	0.299†
6 hours	2.40 ± 1.01	2.38± 1.79	-1.28	-2.49	-0.06	0.011≠
1st day	2.82 ± 1.42	2.91 ± 0.89	-0.54	-1.19	0.11	0.027≠
2nd day	2.85 ± 0.89	3.19 ± 1.35	-0.88	-1.81	0.05	0.032≠
14th d	2.76 ± 0.66	2.37 ± 0.73	0.04	-0.82	0.91	0.705≠

† Based on t-test.
≠Adjusted for the baseline value based on Analysis of Covariance (ANCOVA).

adjusting the effect of baseline values of variables no statistically significant difference was detected between the 2 groups regarding NLR during the study period (p=0.306) (Figure 3).

Comparing changes in NLR

Using ANCOVA and after adjusting the effect of baseline lymphocyte and neutrophil counts, a mean difference of NLR between the 2 groups was found to be significant before surgery (p=0.005). Mean difference of this ratio between the groups was significant 6, 24, and 48 hours after operation, but not 14 days after surgery (Table 4). Using mixture model regression analysis and after adjusting the effect of baseline values of variables a statistically significant difference was detected between the 2 groups regarding NLR during the study period (p=0.006) (Figure 4).

Discussion

Based on the findings of the present study, NLR in patients receiving lidocaine infusion was significantly lower than the control group. Inflammation scores are among the important factors in cancer surgeries. Many findings show that inflammation is the cause of many cancers and is present in all malignant tumors. Recently, scores based on inflammation from peripheral blood like NLR have been proposed as prognosis markers in solid tumors (10). Although evidence in support of these markers as undesirable factors in gastrointestinal cancer is compelling, their effect in breast cancer is not fully understood. Therefore, in the present study we evaluated the effect of IV lidocaine infusion on NLR changes in breast cancer patients undergoing surgery.

The relationship between cancer, neutrophil and lymphocyte is not completely identified. It seems that increase in neutrophils or decrease in lymphocytes that lead to higher NLR result in heightened carcinogenesis. Researchers believe that activity of inflammatory mediators can promote proliferation, angiogenesis, and metastasis and overall, inflammatory environment is an ideal space for proliferation of cancer cells (11).

Various mechanisms have been proposed to justify the role of inflammation on cancer cell activities. Some believe that interaction between leukocytes and endothelial cells plays a key role in development of organ dysfunction (12, 13). Adhesion of activated leukocyte to endothelium is an important step in neutrophil mediated endothelial injury process that is marked by leukocyte migration, aggregation of leukocytes in tissues and increased permeability of vessels (14, 15). However, it has been observed that increase in neutrophil count alone does not affect prognosis and neither does decrease in lymphocyte count alone, only NLR plays a major role in prognosis and outcome of cancer patients (11, 16).

Research has shown that lidocaine decreases production of prostaglandins, leukotrienes, and thromboxanes of leukocytes (17). In addition, it leads to production of free radicals by neutrophil and prevents diffusion of anion superoxide (18, 19). Schmidt et al. in their study to determine the decreasing effect of lidocaine on microcirculatory disorders via prevention of leukocyte activation found that lidocaine reduces the changes resulting from endotoxin in leukocyte-endothelial cell adhesion and

macromolecular leakage. Therefore, lidocaine could play a therapeutic role in inflammation reduction following surgery on breast cancer (20). Findings of the present study are in line with previous studies and suggest that lidocaine has various inhibitory effects on neutrophil function and reduces adhesion of leukocytes to endothelium of small vessels and non-biologic surfaces and prevents leukocyte migration to inflamed areas (6).

Evidence shows that lidocaine has toxic effects on various cells, especially cancer cells. Recently, a study has shown that lidocaine regulates proliferation of human breast cancer cells via demetilation. Li et al. evaluated the effect of DNA demetilation in human breast cancer cells (MCF-7 and MDA-MB-231) on lidocaine effectiveness and the effect of demetilation on toxicity of these cells due to cisplatin (an anti-tumor agent commonly used for breast cancer). Their findings showed that lidocaine demetilates the whole genome, especially the promoter of tumor suppressor genes RARβ2 and RASSF1A. Using lidocaine leads to increased rate of apoptosis induced by cisplatin and higher toxicity due to it. Li et al. concluded that lidocaine causes demetilation of breast cancer cells as well as demetilation of RARβ2 and RASSF1A sensitized due to cellular toxicity of cisplatin (21). Lidocaine causes disorders in proliferation and differentiation and has cytotoxic effects on mesenchymal stem cells that play a key role in tumor growth and metastasis in vitro (22). In addition, lidocaine and tetracaine are inhibitors of kinesin locomotion and their administration leads to disintegration of microtubular lumps in breast cancer cells (23).

Existing studies deem the role of NLR significant in estimation of breast cancer patients' outcome (24). On the other hand, it has been found that lidocaine has considerable anti-inflammatory effects (6). Therefore, the present study aimed to evaluate the effectiveness of lidocaine administration on this inflammatory prognostic scale and was novel in this regard. However, the small sample size and short follow-up period were limitations of this study that definitely affect its generalizability. Therefore, multi center studies with acceptable sample size and longer follow-up period may challenge the findings of this study.

Conclusion

Based on the findings of the present study, it seems that NLR changes were smaller in breast cancer patients, who had received lidocaine infusion during mastectomy, compared to the control group.

Acknowledgment

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Conflicts of Interest

The authors hereby declare that there is no conflict of interest regarding the present study. It should be noted that the present article was extracted from the thesis of Dr. Atiye Kaboudvand to achieve her specialist degree in anesthesiology from Shahid Beheshti University of Medical Sciences.

References

1. Babu GR, Samari G, Cohen SP, Mahapatra T, Wahbe RM, Mermash S, et al. Breast cancer screening among females in Iran and recommendations for improved practice: a review. Asian Pac J Cancer Prev. 2011;12(7):1647-55.
2. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. cell. 2011;144(5):646-74.
3. Singh RR, Kumar R. Steroid hormone receptor signaling in tumorigenesis. Journal of cellular biochemistry. 2005;96(3):490-505.
4. Amani D, Khalilnezhad A, Ghaderi A, Niikawa N, Yoshiura K-i. Transforming growth factor beta1 (TGFβ1) polymorphisms and breast cancer risk. Tumor Biology. 2014;35(5):4757-64.
5. Matsumoto A, Jinno H, Ando T, Fujii T, Nakamura T, Saito J, et al. Biological markers of invasive breast cancer. Japanese journal of clinical oncology. 2016;46(2):99-105.
6. Caracas HCPM, Maciel JVB, de Souza MMG, Maia LC. The use of lidocaine as an anti-inflammatory substance: a systematic review. journal of dentistry. 2009;37(2):93-7.
7. WAL S, Vaneker M, Steegers M, Berkum Bv, Kox M, LAAK J, et al. Lidocaine increases the anti-inflammatory cytokine IL-10 following mechanical ventilation in healthy mice. Acta Anaesthesiologica Scandinavica. 2015;59(1):47-55.
8. Tavare AN, Perry NJ, Benzonana LL, Takata M, Ma D. Cancer recurrence after surgery: direct and indirect effects of anesthetic agents. International journal of cancer. 2012;130(6):1237-50.
9. Colonna S, Werner TL. Breast Cancer Bone Metastases. Metastatic Bone Disease: Springer; 2016. p. 45-54.
10. Kemal Y, Yucel I, Ekiz K, Demirag G, Yilmaz B, Teker F, et al. Elevated serum neutrophil to lymphocyte and platelet to lymphocyte

ratios could be useful in lung cancer diagnosis. Asian Pacific journal of cancer prevention: APJCP. 2013;15(6):2651-4.
11. Minardi D, Scartozzi M, Montesi L, Santoni M, Burattini L, Bianconi M, et al. Neutrophil-to-lymphocyte ratio may be associated with the outcome in patients with prostate cancer. SpringerPlus. 2015;4(1):1.
12. BONE RC. Inhibitors of complement and neutrophils: a critical evaluation of their role in the treatment of sepsis. Critical care medicine. 1992;20(6):891-8.
13. Redl H, Nikolai A, Kneidinger R, Schlag G. Endothelial and leukocyte activation in experimental polytrauma and sepsis. Behring Institute Mitteilungen. 1993(92):218-28.
14. Garutti I, Rancan L, Simón C, Cusati G, Sanchez-Pedrosa G, Moraga F, et al. Intravenous lidocaine decreases tumor necrosis factor alpha expression both locally and systemically in pigs undergoing lung resection surgery. Anesthesia & Analgesia. 2014;119(4):815-28.
15. Lan W, Harmon D, Wang J, Ghori K, Shorten G, Redmond P. The effect of lidocaine on in vitro neutrophil and endothelial adhesion molecule expression induced by plasma obtained during tourniquet-induced ischaemia and reperfusion. European journal of anaesthesiology. 2004;21(11):892-7.
16. Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. Journal of the National Cancer Institute. 2014;106(6):dju124.
17. Cook VL, Shults JJ, McDowell MR, Campbell NB, Davis JL, Marshall JF, et al. Anti-inflammatory effects of intravenously administered lidocaine hydrochloride on ischemia-injured jejunum in horses. American journal of veterinary research. 2009;70(10):1259-68.
18. Azuma Y, Shinohara M, Wang P-L, Suese Y, Yasuda H, Ohura K. Comparison of inhibitory effects of local anesthetics on immune functions of neutrophils. International journal of immunopharmacology. 2000;22(10):789-96.
19. Berger C, Rossaint J, Van Aken H, Westphal M, Hahnenkamp K, Zarbock A. Lidocaine reduces neutrophil recruitment by abolishing chemokine-induced arrest and transendothelial migration in septic patients. The Journal of Immunology. 2014;192(1):367-76.
20. Schmidt W, Schmidt H, Bauer H, Gebhard MM, Martin E. Influence of lidocaine on endotoxin-induced leukocyte-endothelial cell adhesion and macromolecular leakage in vivo. The Journal of the American Society of Anesthesiologists. 1997;87(3):617-24.
21. Li K, Yang J, Han X. Lidocaine sensitizes the cytotoxicity of cisplatin in breast cancer cells via up-regulation of RARβ2 and RASSF1A demethylation. International journal of molecular sciences. 2014;15(12):23519-36.
22. Lucchinetti E, Awad AE, Rahman M, Feng J, Lou P-H, Zhang L, et al. Antiproliferative Effects of Local Anesthetics on Mesenchymal Stem CellsPotential Implications for Tumor Spreading and Wound Healing. The Journal of the American Society of Anesthesiologists. 2012;116(4):841-56.
23. Yoon JR, Whipple RA, Balzer EM, Cho EH, Matrone MA, Peckham M, et al. Local anesthetics inhibit kinesin motility and microtentacle protrusions in human epithelial and breast tumor cells. Breast cancer research and treatment. 2011;129(3):691-701.
24. Chen J, Deng Q, Pan Y, He B, Ying H, Sun H, et al. Prognostic value of neutrophil-to-lymphocyte ratio in breast cancer. FEBS open bio. 2015;5(1):502-7.