Rev Bras Anestesiol. 2019;69(1):42–47

REVISTA
BRASILEIRA DE
ANESTESIOLOGIA

Publicação Oficial da Sociedade Brasileira de Anestesiologia
www.sba.com.br

SCIENTIFIC ARTICLE

The relationship between neutrophil to lymphocyte ratio and postoperative pain in total knee and hip arthroplasty

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Received 20 November 2017; accepted 18 July 2018
Available online 13 August 2018

KEYWORDS
Neutrophil to lymphocyte ratio;
Postoperative pain;
Lower extremity arthroplasty;
Total knee arthroplasty;
Total hip arthroplasty

Abstract
Background and objectives: Neutrophil to lymphocyte ratio is a simple, cost-effective and easily applicable inflammation indicator that is being used frequently in mortality, morbidity and prognosis studies in the recent years. We evaluated the relationship between neutrophil to lymphocyte ratio and postoperative pain in patients undergoing total hip arthroplasty and total knee arthroplasty.
Material and methods: We included 101 patients who preferred spinal anesthesia and intravenous patient-controlled analgesia in accordance and divided them into two groups, total hip arthroplasty and total knee arthroplasty. We recorded demographic information, duration of operation, length of hospital stay, analgesics consumption, neutrophil to lymphocyte ratio results and postoperative pain using Visual Analog Scale.
Results: The morphine consumption of the patients was as follows in group total hip arthroplasty and total knee arthroplasty: at the 4th hour: 7.38 mg, 7.80 mg; 8th hour: 12.19 mg, 13.29 mg; 12th hour: 16.94 mg, 19.18 mg; 24th hour: 25.97 mg, 27.98 mg; 48th hour: 36.38 mg, 39.59 mg. The Visual Analog Scale scores of the patients was as follows in group total hip arthroplasty and total knee arthroplasty: at the 4th hour: 4.10, 4.51; 8th hour: 3.02, 3.43; 12th hour: 2.29, 2.55; 24th hour: 1.90, 1.87; 48th hour: 1.08, 1.13. In group total hip arthroplasty, we found a statistically significant association between postoperative neutrophil to lymphocyte ratio and the Visual Analog Scale values on the 48th hour in a positive direction ($r = 0.311$; $P = 0.031$; $P < 0.05$).
Conclusion: Neutrophil to lymphocyte ratio can be accepted as a relatively objective method for the diagnosis of postoperative pain.

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https://doi.org/10.1016/j.bjane.2018.07.005

PALAVRAS-CHAVE
Relação neutrófilo/linfócito;
Dor pós-operatória;
Artroplastia de extremidade inferior;
Artroplastia total de joelho;
Artroplastia total de quadril

Relação entre a proporção neutrófilo/linfócito e a dor pós-operatória em artroplastia total de joelho e quadril

Resumo
Justificativa e objetivos: A proporção entre neutrófilo/linfócito é um indicador de inflamação simples, custo-efetivo e de fácil aplicação que vem sendo utilizado com frequência em estudos de mortalidade, morbidade e prognóstico nos últimos anos. Avaliamos a relação entre a proporção neutrófilo/linfócito e a dor pós-operatória em pacientes submetidos à artroplastia total de quadril e artroplastia total de joelho.
Material e métodos: No total, 101 pacientes que preferiram a raquianestesia e a analgesia venosa controlada pelo paciente foram incluídos e divididos em dois grupos neste estudo: artroplastia total de quadril e artroplastia total de joelho. Os dados demográficos e os tempos de operação, internação hospitalar e consumo de analgésicos e os resultados da proporção neutrófilo/linfócito e da dor pós-operatória foram registrados usando uma escala visual analógica.
Resultados: O consumo de morfina dos pacientes submetidos à artroplastia total de quadril e artroplastia total de joelho nas horas 4, 8, 12, 24 e 45 foi de, respectivamente: 7,38 mg e 7,80 mg; 12,19 mg e 13,29 mg; 16,94 mg e 19,18 mg; 25,97 mg e 27,98 mg; 36,38 mg e 39,59 mg. Os escores obtidos na escala visual analógica dos pacientes submetidos à artroplastia total de quadril e artroplastia total de joelho nas horas 4, 8, 12, 24 e 48 foram, respectivamente, os seguintes: 4,10 e 4,51; 3,02 e 3,43; 2,29 e 2,55; 1,90 e 1,87; 1,08 e 1,13. Na artroplastia total do quadril, uma associação estatisticamente significativa foi encontrada entre a proporção neutrófilo/linfócito no pós-operatório e os valores da escala visual analógica na 48ª hora em uma direção positiva ($r = 0{,}311$; $p = 0{,}031$; $p < 0{,}05$).
Conclusão: A proporção neutrófilo/linfócito pode ser aceita como um método relativamente objetivo para o diagnóstico da dor pós-operatória.

Introduction

Anesthetic techniques and postoperative pain management are very important for the total joint arthroplasty (TJA) patients. Metabolic, endocrine, and inflammatory response due to uncontrolled pain can increase mortality and morbidity.[1] Insufficient analgesia blocks rehabilitation and aggressive physiotherapy which is critical to sustain the range of joint motion, increases the risk of thromboembolism and duration of hospital stay. Therefore, lower extremity arthroplasty patients require active and successful postoperative pain management.[2] Postoperative pain can be developed due to different factors. There are many studies made with factors related to surgery, preoperative pain, demographic characteristics, and physiological factors.[3] Surgical trauma causes acute phase response. Acute phase response allows tissue injury to be controlled, limits infection and initiate the healing process.[4] During the inflammatory response, changes occur on the ratio of leukocytes level in blood. Relative lymphopenia accompanies neutrophil. The neutrophil to lymphocyte ratio (NLR) is suggested to be a simple indicator for inflammatory response.[5] NLR has frequently been used in recent years for many mortality, morbidity, and prognosis studies as an inflammatory indicator just because it is simple, cheap, and easy to use.[6]

In this study, we aimed to evaluate the association of acute pain relationship with the neutrophil to lymphocyte ratio for elective lower extremity arthroplasty operations.

Materials and methods

This observational prospective study has been approved by the Clinical Studies Ethical Committee of Istanbul University, Faculty of Medicine. The study was conducted between April–September 2014 in Orthopedics Clinic of Istanbul Faculty of Medicine.

Sample Size Analysis was performed using the Power and Sample Size Program (P.S version 3.1.2). We predicted 20% reduction in NLR and we need at least 98 patients for $\alpha = 0.05$ and power = 0.80. When possible drop-outs (20%) are added, a total of 117 requirements are calculated.

We included ASA I–III patients between ages of 18 and 90 that were scheduled for elective lower extremity TJA under spinal anesthesia. We excluded patients with active infection, malignity diagnosis, chronic inflammatory disease history or corticosteroid use. Patients who had emergent trauma operations were also excluded from the study. We informed patients regarding anesthetic techniques and postoperative analgesia options. Patients who preferred spinal anesthesia and intravenous (i.v.) patient-controlled analgesia (PCA) for postoperative analgesia method in accordance with their consent taken preoperative anesthesia visit were taken to surgery room, and included in the study. Age, sex, height, and weight of patients were recorded. Neutrophil, lymphocyte levels were recorded from preoperative peripheral blood hemogram samples and NLR were calculated from the results.

Table 1 Evaluation of demographic data by operation type.

	Total hip arthroplasty ($n=48$)	Total knee arthroplasty ($n=53$)	p
	Mean ± SD	Mean ± SD	
Age (years)	58.67 ± 12.28	65.43 ± 9.42	0.002[a,c]
Body mass index (kg m^{-2})	28.96 ± 6.13	32.89 ± 5.56	0.001[a,c]
Operation time (min)	150.10 ± 27.61	126.89 ± 18.66	0.001[a,c]
Length of hospital stay (day)	7.29 ± 1.89	7.17 ± 1.85	0.744[a]
Sex			
Female	34 (70.8%)	46 (86.8%)	0.084[b]
Male	14 (29.2%)	7 (13.2%)	

SD, standard deviation.
[a] Student *t*-test.
[b] Yates Continuity Correction.
[c] $P<0.01$; *$P<0.05$.

Patients were given intrathecal 15 mg hyperbaric bupivacaine via 25G atraumatic spinal needle from the L3–4 or L4–5 intervertebral space for spinal anesthesia in the sitting position accordingly with routine practice in the clinic. For prophylaxis, i.v. cefazolin 1 g and i.v. ranitidine 50 mg for H_2 receptor blocker were administered. Preoperative periarticular, intraarticular injection were not applied. Operation time was recorded.

For postoperative analgesia, we prepared i.v. PCA with 0.3 mg.mL^{-1} morphine solution routinely for all patients. Basal infusion was set as 0.3 mg.h^{-1}, bolus dose as 1 mg and lock out time as 15 min without program loading dose. In cases that pain control could not be achieved, 2 mg morphine was applied as rescue analgesia. Nonsteroidal anti-inflammatory drugs (NSAIDs) administration was prohibited.

Patients were assessed on postoperative 4, 8, 12, 24 and 48th hour using Visual Analog Scale (VAS). Total morphine consumption on 4, 8, 12, 24 and 48th hour was recorded. We obtained neutrophil, lymphocyte levels from peripheral blood hemogram samples at 1st postoperative hour for all patients.

Statistical analysis

NCSS (Number Cruncher Statistical System) 2007&PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) were used for statistical analysis. Student *t*-test was used for two group comparisons of parameters with normal distribution, Mann–Whitney *U* test was used for two group comparisons of parameters without normal distribution in comparison of descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) as well as quantitative data. Yates Continuity Correction test was used for comparison of qualitative data. Significance was evaluated at $P<0.01$ and $p<0.05$.

Results

In the study were included 126 patients; 25 were excluded from follow-up due to insufficient data and postoperative NSAIDs use. The study was carried out with total 101 cases of which 79.2% ($n=80$) women and 20.8% ($n=21$) men between April and September 2014 in Orthopedics Clinic of Istanbul University, Faculty of Medicine. Demographical data can be seen in Table 1.

In Table 1, statistically significant differences were found between the age distributions of the cases according to the operation type ($P=0.002$, $P<0.01$). The mean age of patients having total knee arthroplasty (TKA) is higher than the patients having total hip arthroplasty (THA). Statistically differences were found between body mass index (BMI) of the patients according to the operation type ($P=0.001$, $P<0.01$). BMI of TKA group are higher than those of THA. There was a statistically significant difference between surgical durations of cases in terms of surgery types ($P=0.001$; $p<0.01$). Operation time of patients having THA was significantly higher than the ones having TKA.

There was no significant difference between VAS values and morphine consumption levels given at 4, 8, 12, 24 and 48th hours in terms of surgery type ($P>0.05$) (Tables 2 and 3).

Although we did not demonstrate any significant difference ($P<0.05$) between preoperative NLR according to surgery types; there was statistically significant difference between postoperative NLR ($P=0.004$; $P<0.01$) (Table 4).

Postoperative NLR for THA group was significantly higher than the TKA group. Average increase of 7.20 ± 7.17 units in postoperative NLR was found to be statistically significant when compared to preoperative NLR for patients with THA ($P=0.001$; $P<0.01$). Similarly, average increase of 4.43 ± 5.13units in postoperative NLR was found to be statistically significant when compared to preoperative NLR for patients with TKA ($P=0.001$; $P<0.01$). There was statistically significant difference between postoperative and preoperative NLR changes of patients according to the surgery types ($P=0.018$; $P<0.05$). Changes in patients with THA were significantly higher than the ones with TKA.

We did not detect any statistically significant difference between preoperative NLR and 4, 8, 12, 24 and 48th hour VAS scores for patients having THA ($P>0.05$). There was no statistically significant difference between preoperative NLR and 4, 8, 12, 24 and 48th hour VAS scores for the patients having TKA ($P>0.05$) (Table 5).

Table 2 Evaluation of Visual Analog Scale scores according to operation type.

VAS	Total hip arthroplasty ($n = 48$) Mean ± SD	Total knee arthroplasty ($n = 53$) Mean ± SD	p
4th hour	4.10 ± 3.16 (4.00)	4.51 ± 2.52 (4.00)	0.341[a]
8th hour	3.02 ± 2.47 (2.00)	3.43 ± 2.33 (3.00)	0.272[a]
12th hour	2.29 ± 2.19 (2.00)	2.55 ± 2.36 (2.00)	0.581[a]
24th hour	1.90 ± 2.21 (1.00)	1.87 ± 1.81 (1.00)	0.655[a]
48th hour	1.08 ± 1.61 (0.00)	1.13 ± 1.35 (1.00)	0.376[a]

SD, standard deviation; VAS, Visual Analog Scale.
[a] Mann–Whitney *U*-test.

Table 3 Evaluation of morphine consumptions according to operation type.

Morphine	Total hip arthroplasty ($n = 48$) Mean ± SD	Total knee arthroplasty ($n = 53$) Mean ± SD	p
4th hour	7.38 ± 3.82	7.80 ± 4.03	0.593[a]
8th hour	12.19 ± 5.22	13.29 ± 6.23	0.340[a]
12th hour	16.94 ± 7.16	19.18 ± 8.49	0.157[a]
24th hour	25.97 ± 10.55	27.98 ± 11.27	0.358[a]
48th hour	36.38 ± 12.41	39.59 ± 14.06	0.228[a]

SD, standard deviation.
[a] Student *t*-test.

Table 4 Preoperative and postoperative neutrophil to lymphocyte ratio assessment according to surgery type.

	Total hip arthroplasty ($n = 48$)	Total knee arthroplasty ($n = 53$)	*P*-value
Preoperative NLR	3.03 ± 2.43 (2.46)	2.75 ± 2.64 (2.24)	0.355[a]
Postoperative NLR	10.24 ± 6.85 (8.35)	7.18 ± 4.54 (5.83)	0.004[a,b]

NLR, neutrophil to lymphocyte ratio.
[a] Mann–Whitney *U*-test.
[b] $P < 0.05$.

Table 5 Association between Visual Analog Scale scores and preoperative neutrophil to lymphocyte ratio according to surgery type.

		Total hip arthroplasty ($n = 48$)		Total knee arthroplasty ($n = 53$)	
Relation of preoperative NLR and VAS		r	p	r	p
VAS	4th hour	−0.011	0.939	−0.071	0.614
	8th hour	−0.050	0.736	−0.051	0.718
	12th hour	−0.185	0.209	−0.055	0.695
	24th hour	−0.034	0.820	−0.150	0.282
	48th hour	0.234	0.110	0.017	0.905

r, Spearman's correlation coefficient; NLR, neutrophil to lymphocyte ratio; VAS, Visual Analog Scale.

Table 6 did not present any statistically significant difference between postoperative NLR and 4, 8, 12, 24 and 48th hour VAS scores for patients having THA ($p > 0.05$). The relation of 31.1% in a positive direction (VAS value increases as postoperative NLR increases) between postoperative NLR and 48th hour VAS scores for patients having THA were found to be statistically significant ($r = 0.311$; $p = 0.031$; $p < 0.05$) (Fig. 1).

Discussion

In this study, we demonstrated the relation between NLR, labeled as an indicator of inflammatory process in many studies, and pro-inflammatory cytokines known to have an effect on pain formation. We have not found any difference about morphine consumption and VAS used as pain indicators and preoperative NLR. However significant relation between

Table 6 Association between Visual Analog Scale scores and postoperative neutrophil to lymphocyte ratio according to surgery type.

		Total hip arthroplasty ($n = 48$)		Total knee arthroplasty ($n = 53$)	
Relation of postoperative NLR and VAS		r	p	r	p
VAS	4th hour	−0.041	0.783	−0.104	0.459
	8th hour	0.141	0.340	−0.057	0.685
	12th hour	0.113	0.446	0.015	0.914
	24th hour	0.229	0.117	0.080	0.569
	48th hour	0.311	0.031[a]	−0.029	0.839

NLR, neutrophil to lymphocyte ratio; VAS, visual analog scale; r, Spearman's correlation coefficient.
[a] $P < 0.05$.

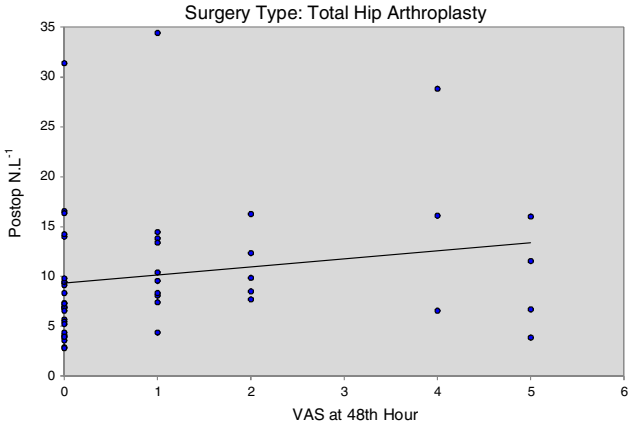

Figure 1 Association between Postoperative NLR (neutrophil to lymphocyte ratio) and 48th hour VAS (Visual Analog Scale) pain values for total hip arthroplasty cases.

postoperative NLR and 48th hour VAS values has been found for the THA group. Appropriate management of postoperative pain provides patient with early mobilization, shorter hospital stay, lower costs and increased patient satisfaction. One of the main goals of postoperative pain management is to provide sufficient pain control with the lowest doses of analgesics. By this means frequency of side effects of analgesics can be minimized. Therefore, there is no similar study in literature to ours – as far as we know, we have not had the chance to compare our results with a similar study. However, we have concluded that the difference between the patients' groups (THA and TKA) in our study may arise from the duration of surgery. There was statistically significant difference at an advanced level between duration of surgeries of cases according to the surgery types ($p = 0.001$; $p < 0.01$). Duration of surgeries for the THA patients was significantly higher than the TKA patients.

Surgical incision is a traumatic stimulus that triggers systemic neuroendocrine and local inflammatory responses with sympathetic nervous system.[7] Surgical trauma causes acute phase response. Acute phase response allows tissue injury to be controlled, limits infection and initiates the healing process.[4] As physiological response of leucocytes in circulation to stress causes an increase in the number of neutrophils and a decrease in the number of lymphocyte; the ratio of these two subgroups are used as inflammation indicator in intensive care practice.[8-11] Neutrophils, activated by tissue destruction, releases enzymes such as myeloperoxidase, acid phosphatase and elastase.[12-14] The ratio of leucocytes in circulation changes during the inflammatory response. The number of leucocytes decreases relatively and elevated NLR may serve as the cost-effective and readily available prognostic marker.[15] This biomarker can be used as practical predictor in the daily clinical work.[16] When evaluated with sepsis scores such as APACHE 2 (Acute Physiology and Chronic Health Evaluation II) and SOFA (Sepsis-related Organ Failure Assessment), this ratio has been found to be correlated well with the severity and prognosis of disease and is called as neutrophil lymphocyte stress factor.

Akilli et al. divided the 373 patients, who presented to emergency department and required intensive care unit follow up, into 4 groups in their study that analyzed the patients' in-hospital and 6 months follow up prospectively in terms of mortality. Significant difference was found in in-hospital and 6th month mortality ratio in accordance with NLR increase.[17] Proinflammatory cytokines are generally produced by active macrophages and plays role in increase of inflammatory reactions. There are a lot of evidence that pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α play a role for process of pathological pain formation.[18] Cytokines and prostaglandins are important inflammatory mediators that have an effect on pain receptors. They can affect to pain receptors either directly or make prostaglandin release that activate pain receptors for some cases.[19] Release of TNF-α and IL-1β causes the formation and release of other cytokines included IL-6.[20] IL-6 is the main cytokine causing acute phase response. IL-6 reaches peak release postoperative between 4 and 48th hours.[21] Cytokine formation reflects the level of tissue formation. Released amounts of IL-6 changes accordingly with the duration of surgery, mechanic ventilation in intensive care unit and prevalence of trauma.[22] In the light of the information that IL-6 levels were affected from duration of surgery, we have concluded that the reason why a correlation between NLR increase and VAS was observed in the THA group but was not observed in the TKA group was the duration of surgery. IL-6, the main cytokine causing acute phase response, reached peak release postoperative between 4th and 48th hours; and that, the inflammation reached its peak point at 48th hour in the cases included in our study and the

significant difference of the relation between the NLR and VAS at this peak point, was seen to be compatible with the literature.[21] The limitation of our study was the absence of a tool that measures inflammatory response to assess pain and the markers of inflammatory response have not been evaluated. Further studies shall be done.

Conclusions

We have observed the relation between NLR which is an inflammation indicator, and pain. The significant difference in positive direction at the 48th hour for the patients in THA group is a promising opportunity for pain control. It can be accepted as a relatively objective method for effective analgesia especially for the patients who cannot verbalize pain such as geriatric patients, patients with dementia or intubated patients. Nevertheless, there is still need for a prospective randomized study with large numbers of patients to have a certain conclusion on this issue.

Conflicts of interest

The authors declare no conflicts of interest.

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