Original Article

HEALTH SCIENCES
MEDICINE

DOI: 10.32322/jhsm.1348328
J Health Sci Med. 2023;6(5):1047-1051

Role of hemogram parameters as predictive markers for propofol injection pain in reproductive and postmenopausal women: a prospective study

Ömer Taşargöl[1], Halil Cihan Köse[2]

[1]Department of Anesthesiology and Reanimation, Doctor Burhan Nalbantoglu State Hospital, Nicosia, Cyprus
[2]Department of Algology, Kocaeli City Hospital, Kocaeli, Turkey

Cite this article as: Taşargöl Ö, Köse HC. Role of hemogram parameters as predictive markers for propofol injection pain in reproductive and postmenopausal women: a prospective study. *J Health Sci Med.* 2023;6(5):1047-1051.

Received: 22.08.2023 ◆ **Accepted**: 08.09.2023 ◆ **Published**: 28.09.2023

ABSTRACT

Aims: In clinical practice, propofol injection pain (PIP) is a frequent condition that clinicians could face every day. The aim of this prospective study was to investigate the correlation between PIP and hemogram parameters in reproductive and postmenopausal women.

Methods: In this prospective study, 40 reproductive and 40 postmenopausal female patients who underwent elective surgery were enrolled. Baseline data including age, weight, height, hemogram parameters, neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and systemic immune inflammatory score (SII) were recorded preoperatively. The pain was classified as 0: no pain, 1: mild pain, 2: moderate pain, 3: severe pain. Patients were previously informed about the questioning of pain scores during propofol.

Results: The proportion of patients experiencing PIP in postmenopausal (n=16;40%) group was significantly higher than those in the reproductive group (n=6;15%) (p=0.009). When reproductive and postmenopausal groups were compared according to the presence or absence of pain, no difference was found between the groups in terms of hemogram ratios and platelet indices (p>0.05). The NLR, PLR and SII ratios were not significant in predicting the presence of PIP.

Conclusion: The findings of our study showed that the occurrence of PIP in postmenopausal women was higher compared to women in reproductive age. Hemogram values, NLR platelet, PLR and SII ratios were not significantly associated with the presence of PIP.

Keywords: Propofol, pain, neutrophil, hemogram, postmenopausal

INTRODUCTION

Propofol is one of the most used hypnotic agents for the induction and maintenance of general anesthesia, procedural sedation, and sedation in intensive care units.[1,2] While the risk of severe complications related to propofol injection, such as propofol-related infusion syndrome is rare, milder side effects are more prevalent. Amongst these side effects, the preeminent and commonly encountered adverse circumstance for clinicians is the manifestation of propofol injection pain (PIP).[3]

The pain experienced during propofol injection is considered to result from various factors, including damage to the inner lining of blood vessels, differences in osmolality, abnormal pH levels, and stimulation of pain receptors and nerve endings in veins. These factors are considered to contribute to the pain experienced during injection, although the underlying cause is not well-established.[3,4] The incidence of PIP ranges from 28% to 90% and is known to create a negative memory of the anesthesia experience for individuals.[3-5] The majority of research conducted on the topic of PIP has primarily concentrated on mitigating discomfort through the administration of agents like lidocaine, ephedrine, ondansetron and ketamine prior to the injection.[5-8] Nevertheless, in recent years, a limited number of studies have also been undertaken to explore the predictive factors associated with PIP in various patient populations.[9,10]

The neutrophil- lymphocyte ratio has been shown to have a relationship with the perception of postoperative pain and pain in chronic diseases. Therefore, aimed to determine if there was a link between pain on propofol injection (POPI) and various hemogram parameters

Corresponding Author: Halil Cihan Köse, halilcihankose@hotmail.com

and ratios. This prospective study aimed to investigate the potential correlation between PIP and hemogram parameters and derived ratios, including the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and systemic immune inflammation score (SII), in a cohort of reproductive and postmenopausal women undergoing elective surgery. The objective was to assess whether hematological markers could serve as an indicator of pain in this patient population.

METHODS

This prospective study was carried out with the permission of Doctor Burhan Nalbantoglu State Hospital Ethics Committee (Date: 18.07.2023, Decision No: 1.01-25/23). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

In this prospective study, a cohort comprising 40 reproductive and 40 postmenopausal female patients who underwent elective surgery at a tertiary hospital in July and August 2023 was planned to enroll. All participants provided informed consent. The study specifically focused on patients scheduled under general anesthesia for elective procedures in the fields of orthopedics, abdominal surgery, urology, otolaryngology, or plastic surgery, and classified as American Society of Anesthesiology (ASA) physiological score I or II. Exclusion criteria included hematological, oncological, or endocrinological diseases, a history of chronic drug or steroid use within the last three months, upper-lower respiratory tract infection within the last three weeks, and regular alcohol consumption, as these factors could potentially impact their surgical outcomes. Patients with a history of psychiatric illness and those requiring tranquilizers due to severe anxiety prior to surgery were also excluded from the study, as these factors may influence their pain perception.

Prior to the surgical procedure, relevant information was gathered from the patients, including age, weight, length, and various indicators from their hemogram. These indicators included white blood cell count, neutrophil count, lymphocyte count, platelet count, as well as platelet indices such as mean platelet volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT). Additionally, the levels of hemoglobin and hematocrit were measured. All hemograms were performed using the Sysmex XT 1800i device manufactured by Sysmex Corporation in Kobe, Hyogo, Japan. Using this data, calculations were made to determine the neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), and systemic immune inflammation score (SII). The SII was derived using the formula SII = Platelet (P) x Neutrophil (N) / Lymphocyte (L) counts. The primary outcome was the association between presence of the PIP and hemogram parameters. Secondary outcomes included hemogram derivated parameters and the comparison of the presence of the PIP between two study groups. The study design and process are depicted in the flow diagram (**Figure 1**).

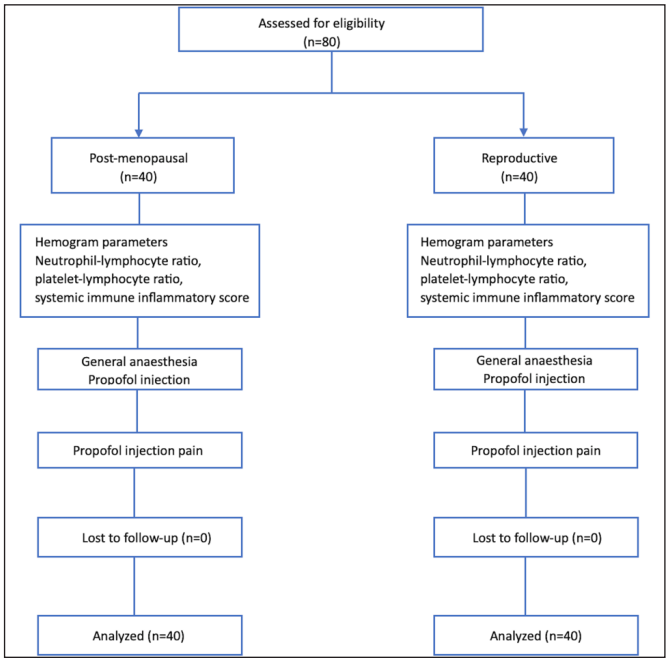

Figure 1: Flow diagram of the study

Patients underwent routine monitoring (including electrocardiography, pulse oximetry, and noninvasive blood pressure). Intravenous access was performed on the dorsum of the hand with a 20 gauge cannula. A face mask was used to deliver 6 lt/min of fresh oxygen and fraction of inspired oxygen (FiO2) for three minutes before induction. Prior to propofol injection, patients were informed about the possibility of experiencing pain. The anesthesiologist utilized McCririck and Hunter's verbal rating score (VRS) to evaluate the intensity of pain.11 The pain was categorized into four groups: 0 (no pain), 1 (mild pain), 2 (moderate pain), and 3 (severe pain). A solution containing 200 mg/20 mL of 1% propofol and 2 mL of 2% lidocaine (40 mg) was prepared in a 50 mL syringe. The patients' baseline heart rate and blood pressure were measured, and the infusion of propofol was initiated at a rate of 18.3 mL/min until a dosage of 2.5 mg/kg was achieved. The anesthesiologist regularly assessed the patients' pain levels every five seconds until they became unconscious. Additionally, the patients' heart rate and blood pressure were recorded after the induction of anesthesia.

In this study, a blinded researcher conducted a comparison between hemogram parameters and pain perception scores. To analyze the data, the statistical software SPSS 16.0 was employed. The hemogram parameters were assessed using an independent sample

t-test if they followed a normal distribution. However, if the distribution was not normal, the Mann-Whitney U test was used instead. For categorical evaluations, the Chi-square test with Yates correction was applied. The cut-off levels for parameters were determined through the analysis of the receiver operating characteristic curve. A significance level of $p < 0.05$ was considered statistically significant.

RESULTS

In this study, a total of 80 consecutive patients, 40 in each group (reproductive and post-menopausal), were evaluated. While the mean age was 36.87±7.56 years in the reproductive group, it was 60.55±3.50 years in the postmenopausal group. The descriptive data of the groups such as age, weight and height are presented in Table 1.

Table 1. Descriptive characteristics of patients

	Reproductive (n:40)	Post-Menopause (n:40)	p
Age (years)	36.87±7.56	60.55±3.50	NA
ASA I/II	28/12	11/29	0.0001
Length (cm)	165.75±5.28	161.20±4.93	0.0001
Weight (kg)	68.72±8.39	78.5±6.48	<0.0001
BMI (kg/cm²)	25.03±2.99	30.28±3.04	<0.0001
Type of surgery			
General surgery	17 (42.5%)	19 (47.5%)	
Orthopedics	9 (22.5%)	12 (30%)	
Neurosurgery	5 (12.5%)	4 (10%)	0.689
Otolaryngology	7 (17.5%)	3 (7.5%)	
Plastic surgery	2 (5%)	2 (5%)	

American Society of Anesthesiology class: ASA, Body Mass Index: BMI

When the groups were compared in terms of complete blood count results and obtained rates, there was no statistical difference between the groups (Table 2). The distribution of pain densities according to age groups is presented in Table 3 and this distribution was found to be statistically different ($p<0.05$). When the groups were classified as pain (+) and no pain, a statistical difference was found after Yates' correction ($p=0.024$) and this significance was due to the number of patients with pain in the postmenopausal group. When reproductive and postmenopausal patients are grouped according to the presence or absence of pain, no difference was found between the groups in terms of hemogram ratios and platelet indices ($p>0.05$) (Table 4).

In both groups, the NLR, PLR, and SII ratios were not significant in predicting PIP. Area under the curve for NLR, PLR, and SII related to the PIP, and cut-off values of each predictor with sensitivity and specificity values for PIP was shown in Table 5. However, no significant result was present for cut-off values in predicting PIP.

Table 2. Laboratory results of patients

	Reproductive (n:40)	Post-Menopause (n:40)	p
WBC	8.97±4.45	9.16±3.78	0.837
HGB	12.56±2.29	12.20±1.76	0.432
HCT	37.44±6.15	36.14±2.02	0.207
PLT	308.4±73.07	302.95±127.95	0.815
PDW	12.03±2.10	12.27±2.06	0.607
MPV	10.30±0.97	10.52±0.89	0.293
PCT	0.31±0.07	0.31±0.11	0.999
NEUT#	6.08±4.43	6.05±3.85	0.974
LYMPH#	2.18±0.93	2.37±1.52	0.502
NLR	3.67±4.32	3.31±3.25	0.674
PLR	173.23±102.03	166.41±152.22	0.814
SIII	1320.02±2188.56	1255.28±2506.63	0.901

White Blood Cell: WBC; Hemoglobin: HGB; Hematocrit: HCT; Platelet: PLT; Platelet Distribution Width: PDW; Mean Platelet Volume: MPV; Plateletcrit: PCT; Neutrophil Count: NEUT#; Lymphocyte Count: LYMPH#; Neutrophil Lymphocyte Ratio: NLR; Platelet Lymphocyte Ratio: PLR; Standard Derivation: SD; Systemic Immune Inflammation Score: SII; Number of Individuals:

Table 3. Pain density levels according to groups

	VRS-0 (n)	VRS-1 (n)	VRS-2 (n)	VRS-3 (n)	p
Reproductive	16	15	7	2	0.009
Post-Menopause	6	11	16	7	

McCririck and Hunter's Verbal Rating Score: VRS

Table 4. Evaluation of hemogram ratios and platelet indices when reproductive and postmenopausal patients are grouped according to the presence or absence of pain

Reproductive	No-Pain (n:16)	Pain (+) (n:24)	p
NLR	2.89±2.35	4.03±5.24	0.356
PLR	156.76±87.20	177.39±109.02	0.522
SIII	817.58±644.79	1617.47±2757.71	0.183
PLT	287.53±51.76	323.20±82.84	0.126
PDW	12.12±2.07	12.09±2.13	0.964
MPV	10.23±1.18	10.37±0.85	0.664
PCT	0.29±0.05	0.33±0.08	0.083
Post-Menopause	**No-Pain (n:6)**	**Pain (+) (n:34)**	**p**
NLR	4.06±2.72	3.25±3.36	0.580
PLR	193.31±124.44	165.41±158.54	0.673
SIII	1161.05±825.47	1288±2702.82	0.826
PLT	292.42±46.85	304.02±137.73	0.689
PDW	11.07±1.35	12.42±2.15	0.147
MPV	10.15±0.34	10.57±0.95	0.062
PCT	0.29±0.05	0.31±0.12	0.459

Neutrophil Lymphocyte Ratio: NLR; Platelet Lymphocyte Ratio: PLR; Standard Derivation: SD; Systemic Immune Inflammation Score: SII; Platelet: PLT; Platelet Distribution Width: PDW; Mean Platelet Volume: MPV; Plateletcrit: PCT; Number of Individuals: n; No-Pain: VRS-0, Pain (+): VRS-1-2-3

Table 5. ROC analysis for NLR, PLR and SII parameters

Factor	AUC (95% CI)	Cut-off	p	Sensitivity (%)	Specificity (%)
Reproductive					
NLR	0.497 (0.309-0.606)	2.73	0.978	66.7	50
PLR	0.487 (0.299-0.675)	124.50	0.890	46.8	68.8
SII	0.482 (0.298-0.666)	747.46	0.847	58.3	50
Post-Menopause					
NLR	0.537 (0.223-0.850)	4.40	0.776	88.2	50
PLR	0.525 (0.225-0.824)	156.74	0.850	70.6	50
SII	0.529 (0.230-0.849)	1131.90	0.762	85.3	50

Neutrophil Lymphocyte Ratio: NLR; Platelet Lymphocyte Ratio: PLR; Confidence Interval: CI ; Systemic Immune Inflammation Score: SII; Area under the curve: AUC

DISCUSSION

The findings from our study revealed a higher occurrence of PIP in postmenopausal women compared to women in reproductive age. However, it is important to note that the presence of this pain cannot be accurately predicted by analyzing hemogram parameters and the derived indices obtained from the hemogram.

Several variables, including vein diameter at the site of propofol injection, injection rate, lipid composition of the commercial formulation, and other factors, may influence the occurrence of PIP. On the other hand, chronic inflammation in the patient was also associated with the pain perception.[9,12] In our study, we also investigated the relationship between propofol injection-related pain and hemogram-derived parameters, which increase in acute or chronic inflammation, but could not determine it.

We conducted a study that was methodologically quite similar to this study, but only included male patients.[9] In that study, we detected a linear correlation between PIP and NLR,PLR and SII. In our study, however, we could not determine a correlation between these parameters and the presence of PIP, in which case one of the effective factors may be gender per se. Hanci et al.[13] found a relationship between the phase of the menstrual cycle of women and the presence of PIP in their study. It has been previously revealed that lymphocyte count increases in the premenstrual period compared to other periods of the menstrual cycle.[14] In our study, we did not standardize our patients in the reproductive period in terms of menstrual phase, and therefore we could not achieve homogenization in our data. We also know that there are serious differences in leukocyte composition in the postmenopausal period compared to the reproductive period.[15] Given the variations observed in hemogram data and the influence of multiple factors, it is plausible that the examined relationship could not be conclusively determined. This discrepancy can be attributed to the inherent differences in hemogram profiles between individuals of reproductive age and those in the post-menopausal stage. It is possible that a definitive association between PIP and pain perception could be established by conducting investigations within more homogenous groups.

Moreover, the current literature does not provide clear evidence regarding the association between hemogram parameters and the perception of acute or chronic pain. Some studies have identified a linear correlation between parameters such as NLR and pain perception, while others have observed a reverse correlation or no correlation at all.[11,16,17] Moreover, it is important to note that several articles investigated these parameters as predictors of treatment outcomes and mortality rates.[18-20]

In our study, we clearly found that the perception of pain associated with propofol injection was more pronounced in postmenopausal women. In a study comparing extracorporeal shock wave lithotripsy-related pain in postmenopausal and reproductive women, it was reported that postmenopausal women felt less pain.[21] However, in a study investigating musculoskeletal pain and the reproductive life stage, no relationship was found between pain and reproductive life stage.[22] When examining the relationship between pain perception and the reproductive life stage of women, it is crucial to consider the specific type, mechanism, and source of pain as distinct factors. Currently, the mechanism underlying PIP remains unknown, and it is possible that conducting studies with larger sample sizes may yield more conclusive findings. Thus, it is imperative to approach the investigation of PIP with a comprehensive understanding of its various dimensions in order to obtain meaningful and reliable results.

Our study has several limitations, some of which have been discussed earlier. One significant limitation is the lack of evaluation of women of reproductive age based on the specific phase of the menstrual cycle. Additionally, postmenopausal cases were not standardized, presenting another limitation. Furthermore, the absence of a randomized controlled trial introduces potential bias. Moreover, the classification of patients based on verbal statements rather than utilizing techniques such as hormone measurements to determine reproductive life stage is another limitation. Implementing such techniques would provide more precise and reliable data. Demographic data was different between the groups, different results can be obtained with more similar descriptors with matching to the propensity score. Lastly, no previous studies investigated the association between PIP and hemogram parameters, therefore, we could

not calculate power analysis according to the previous studies. However, this study could provide data for a sample size calculation for future trials.

CONCLUSION

In the present prospective study, our objective was to investigate the relationship between pain experienced during propofol injection and the reproductive life stage of women. Our findings indicate that postmenopausal women exhibit a higher incidence of pain compared to women of reproductive age. Furthermore, our analysis suggests that the use of hemogram and hemogram parameters alone is not sufficient to accurately predict the occurrence of pain in this context. These results highlight the need for further research to identify more reliable predictors and develop effective interventions for pain management during propofol injection in postmenopausal women.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Doctor Burhan Nalbantoglu State Hospital Ethics Committee (Date: 18.07.2023, Decision No: 1.01-25/23).

Informed Consent: Written informed consent was obtained from patients.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

REFERENCES

1. Wakai A, Blackburn C, McCabe A, et al. The use of propofol for procedural sedation in emergency departments. *Cochrane Database Syst Rev.* 2015;2015(7):CD007399.
2. Zhi Y, Li W. Effects of total intravenous anesthesia with etomidate and propofol on postoperative cognitive dysfunction. *Physiol Res.* 2023;72(2):251-258.
3. Desousa KA. Pain on propofol injection: causes and remedies. *Indian J Pharmacol.* 2016;48(6):617-623.
4. Nishimoto R, Kashio M, Tominaga M. Propofol-induced pain sensation involves multiple mchanisms in sensory neurons. *Pflugers Arch.* 2015;467(9):2011-2020.
5. Lang BC, Yang CS, Zhang LL, Zhang WS, Fu YZ. Efficacy of lidocaine on preventing incidence and severity of pain associated with propofol using in pediatric patients: A PRISMA-compliant meta-analysis of randomized controlled trials. *Medicine.* 2017;96(11):e6320.
6. Ayatollahi V, Behdad S, Kargar S, Yavari T. Comparison of effects of ephedrine, lidocaine and ketamine with placebo on injection pain, hypotension and bradycardia due to propofol injection: a randomized placebo controlled clinical trial. *Acta Med Iran.* 2012;50(9):609.
7. Gilani MT, Bameshki A, Razavi M. Efficacy of ephedrine in the prevention of vascular pain associated with different infusion rates of propofol. *Anesth Essays Res.* 2014;8(3):345-348.
8. Zahedi H, Maleki A, Rostami G. Ondansetron pretreatment reduces pain on injection of propofol. *Acta Med Iran.* 2012;50(4): 239-243.
9. Tasargol O. A Prospective study on the predictability of propofol injection pain. *Cureus.* 2020;12(2):e6945.
10. Miniksar OH, Yuksek A. Effects of preoperative anxiety levels and the D-type personality on propolol injection pain. *North Clin Istanb.* 2022;9(1):1-7.
11. McCrirrick A, Hunter S. Pain on injection of propofol: the effect of injectate temperature. *Anaesthesia.* 1990;45:443-444.
12. Daoudia M, Decruynaere C, Le Polain de Waroux B, Thonnard JL, Plaghki L, Forget P. Biological inflammatory markers mediate the effect of preoperative pain-related behaviours on postoperative analgesics requirements. *BMC Anesthesiol.* 2015;15:183.
13. Hanci V, Ayoğlu H, Yilmaz M, et al. Effect of menstrual cycle on the injection pain due to propofol. *Eur J Anaesthesiol.* 201;27(5):425-427.
14. Facchinetti F, Borella P, Valentini M, Fioroni L, Genazzani AR. Premenstrual increase of intracellular magnesium levels in women with ovulatory, asymptomatic menstrual cycles. *Gynecol Endocrinol.* 1988;2(3):249-256.
15. Chen Y, Zhang Y, Zhao G, et al. Difference in leukocyte composition between women before and after menopausal age, and distinct sexual dimorphism. *PLoS One.* 2016;11(9):e0162953.
16. Canikli Adıgüzel Ş, Akyurt D, Bahadır Altun H, Tulgar S, Ültan Özgen G. Can neutrophil-lymphocyte ratio, platelet-lymphocyte ratio, or systemic immune inflammation index be an indicator of postoperative pain in patients undergoing laparoscopic cholecystectomy? *Cureus.* 2023;15(1):e33955.
17. Canbolat N, Buget MI, Sivrikoz N, Altun D, Kucukay S. [The relationship between neutrophil to lymphocyte ratio and postoperative pain in total knee and hip arthroplasty]. *Braz J Anesthesiol.* 2019;69(1):42-47.
18. Yigit Y, Yilmaz S, Ozbek AE, Karakayali O, Cetin B, Halhalli HC. Can platelet indices reduce negative appendectomy rates? *Cureus.* 2019;11(3):e4293.
19. Furuncuoğlu Y, Tulgar S, Dogan AN, Cakar S, Tulgar YK, Cakiroglu B. How obesity affects the neutrophil/lymphocyte and platelet/lymphocyte ratio, systemic immune-inflammatory index and platelet indices: a retrospective study. *Eur Rev Med Pharmacol Sci.* 2016;20(7):1300-1306.
20. Tulgar YK, Cakar S, Tulgar S, Dalkilic O, Cakiroglu B, Uyanik BS. The effect of smoking on neutrophil/lymphocyte and platelet/lymphocyte ratio and platelet indices: a retrospective study. *Eur Rev Med Pharmacol Sci.* 2016;20(14):3112-3118.
21. Islamoglu E, Tas S, Karamik K, Yalcinkaya S, Tokgoz H, Savas M. Does extracorporeal shock wave lithotripsy-related pain get affected by menstrual cycle and menopause? *Urolithiasis.* 2019;47(6):575-581.
22. Frange C, Hirotsu C, Hachul H, et al. Musculoskeletal pain and the reproductive life stage in women: is there a relationship? *Climacteric.* 2016;19(3):279-284.