Changes in Cytokine and Acute-Phase Protein Levels in Functional Endoscopic Sinus Surgery for Chronic Rhinosinusitis with Nasal Polyps: A Randomized Cohort Study

Vladimir Evgenevich Pavlov[1], **Yury S Polushin**[1], **Sergei Karpischenko**[2]

[1]Department of Anesthesiology and Intensive Care, the Pavlov First State Medical University of Saint Petersburg, Russia
[2]Department of Otorinolaringology, the Pavlov First State Medical University of Saint Petersburg, Russia

Abstract

Objective: This study aims to evaluate the dynamics of inflammatory markers (cytokines and acute-phase proteins), intraoperative bleeding intensity (BI), and postoperative pain severity (PS) in patients with chronic rhinosinusitis with nasal polyps in functional endoscopic sinus surgery (FESS) performed under general anesthesia and with the use of intravenous (IV) lidocaine or dexamethasone.

Methods: In this prospective, randomized, single-center, single-blinded cohort study, the clinical data and blood serum samples were collected from 52 patients after FESS, who were randomized into 3 groups: C (the control group, N = 26), D (with 0.1-0.15 mg/kg dexamethasone, N = 13), and L (with 1% IV lidocaine, N = 13). We analyzed the levels of interleukin (IL)-6, IL-10, IL-18, α1-antitrypsin (A1AT), and ferritin.

Results: The C group showed an increase in IL-6 and IL-6/IL-10. The D group demonstrated rising levels of IL-10 and a decrease in IL-6 and IL-6/IL-10. Bleeding intensity was lower in the L ($P < .001$) and D groups ($P < .05$) than in the control group. All 3 groups demonstrated relative changes in the levels of the markers within the normal range.

Conclusion: Changes in cytokine profile were insignificant, which may be attributed to the minimally invasive surgery technique. Dexamethasone led to an increase in IL-10 levels, decreased postoperative concentrations of IL-6, IL-6/IL-10, and IL18 and slightly curbed bleeding. Intravenous lidocaine had a moderate effect on preventing the rise of IL-6 and IL-6/IL-10, and it effectively decreased BI and postoperative PS.

Keywords: Acute-phase proteins, chronic rhinosinusitis with nasal polyps., cytokines, dexamethasone, lidocaine

Cite this article as:
Pavlov VE, Polushin YS, Karpischenko S. Changes in cytokine and acute-phase protein levels in functional endoscopic sinus surgery for chronic rhinosinusitis with nasal polyps: A randomized cohort study. *Eur J Rhinol Allergy* 2023;6(3):76-81.

Corresponding author:
Vladimir Evgenevich Pavlov
E-mail:
pavlov-vladimir2007@yandex.ru

Received: September 11, 2023
Accepted: October 13, 2023
Publication Date: December 20, 2023
DOI:10.5152/ejra.2023.23106

INTRODUCTION

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a hyperplastic inflammation of the sinus and nasal mucosa that considerably affects a patient's quality of life. Functional endoscopic sinus surgery (FESS) for CRSwNP involves the removal of polyps. Though it does not directly influence the cause and development of polyposis,[1] it is recommended for use when response to standard therapy is minimal, when polyps disrupt nasal breathing, or in cases of unilateral polyposis associated with a benign tumor or anatomic defect.[2,3] The anesthetic management in this type of procedure faces 2 notable challenges: the risk of significant intraoperative bleeding and pain in the treatment area after the surgery.[4,5] The general recommendation for reduction of intraoperative pain severity (PS) and inflammatory response is to use dexamethasone.[6] However, some studies indicate that the drug increases intraoperative bleeding[7,8] and note that the efficiency of this method is questionable.[9] An alternative solution may be intravenous (IV) lidocaine. It is known that intraoperative IV lidocaine boosts recovery and reduces PS in CRSwNP patients after the procedure without increasing the risk of bleeding.[10,11]

This study aims to evaluate the dynamics of inflammatory markers (cytokines and acute-phase proteins), intraoperative bleeding intensity (BI), and postoperative PS in patients with CRSwNP in FESS performed under general anesthesia (GA) and with the use of IV lidocaine or dexamethasone.

METHODS

A prospective, randomized, single-center, single-blinded cohort study of 52 FESS cases performed under GA and artificial mechanical ventilation was conducted in the ear, nose and throat clinic of Pavlov First Saint Petersburg State Medical University. The surgery was elective, and the subjects underwent a prior examination in accordance with the routine practice of the clinic. The severity of rhinosinusitis was assessed with a clinical scale developed by Friedman et al[12]; the assessment involved the analysis of computer tomography data for the nasal cavity and paranasal sinuses. Seventeen FESS procedures were accompanied by endoscopic endonasal septoplasty.

The study population included patients aged ≥18 years who had a chronic sinus condition (maxillary sinusitis, ethmoiditis, frontitis, or sphenoiditis) with polyps that could be treated via minimally invasive procedures.

The exclusion criteria were uncontrollable hypertension, severe coronary heart disease with frequent pain episodes, severe advanced atherosclerosis, allergies to local anesthetics, anticoagulant or antiplatelet therapy, clinical and laboratory abnormalities in the hemostatic profile, and systemic diseases that affect blood vessels (vasculitides, Wegener's granulomatosis, etc.).

All patients were randomized into 3 study groups. The C group (N = 26) was the control group, and its patients did not receive any anti-inflammatory treatment (non-steroid anti-inflammatory drugs or glucocorticoids (GCs)). The D group (N = 13) received IV dexamethasone (0.1-0.15 mg/kg) after anesthesia induction. The L group (N = 13) received 1% IV lidocaine (1 mg/kg at 1 mg/s) after preoperative cleansing at the start of the procedure; subsequently, the drug was continuously introduced with a syringe infusion pump at a rate of 2-3 mg/kg/h (without exceeding the limit of 300 mg/h) due to a high risk of intraoperative injury.[10,13]

Patients in both groups received the same type of GA: they were premedicated on the operating table with IV fentanyl (0.002-0.003 mg/kg) and IV atropine (0.005 mg/kg) if clinically indicated. Anesthesia was induced with IV propofol (2.0-3.0 mg/kg). For muscle relaxation, IV rocuronium bromide (0.4-0.6 mg/kg) was administered. After placing the laryngeal mask airway (LMA Classic; Teleflex Medical Europe, Athlone, Ireland), we started artificial mechanical ventilation with a tidal volume of 6-8 mL/kg and exhaled carbon dioxide ($P_{ET}CO_2$) monitoring. General anesthesia was supported with fentanyl (50-100 μg) and desflurane (4-12 vol%) to the minimal alveolar concentration (MAC) level of 0.8-1.4. At the beginning of each procedure, we performed infiltration anesthesia of the nasal cavity with a standard 3.4 mL solution of articaine hydrochloride with epinephrine hydrochloride (1 : 100 000). All FESS procedures were performed by the same surgeon, who did not know about terlipressin administration and evaluated BI on a 6-point scale of mean values (Fromme–Boezaart score). In this scale, 0 points indicate no bleeding in the surgical field, whereas 5 points indicate severe bleeding that completely reduces visibility and makes it impossible to continue the procedure.[14] Hemodynamic monitoring included heart rate (HR), noninvasive blood pressure (BP) with mean blood pressure (MBP), electrocardiography (ECG), pulse oximetry (SpO_2), and MAC of the anesthetic agent. Postoperative PS was evaluated with a visual analog scale (VAS) at 30, 60, and 180 minutes after the procedure. All patients were under post-operative supervision for at least 2 hours, and their HR, BP, ECG, and SpO_2 readings were closely monitored.

Main Points

- *Intensive bleeding may complicate inflammation during functional endoscopic sinus surgery (FESS).*
- *Though it does not reduce bleeding well, dexamethasone modulates the immune response better than lidocaine.*
- *The key factor in bleeding control with lidocaine is not prevention of inflammatory hyperemia but managing a patient's hemodynamic profile at each stage of the procedure.*
- *Low levels of cytokines at the end of FESS mean that the patient does not have a severe inflammation.*

The study complied with the international and ethical norms of the Declaration of Helsinki 2013: Ethical Principles for Medical Research Involving Human Subjects. The research was approved by the Internal Review Board of First Pavlov State Medical University of St. Petersburg (Date: May 30, 2022, Number: 263) and was performed with written voluntary informed consent from the patients.

Laboratory Tests

Blood samples were drawn twice: first preoperatively, after the insertion of a peripheral venous catheter before administration of the drugs, then postoperatively, from the intact vein right after a patient's awakening.

We evaluated the levels of interleukin (IL)-6, IL-10, IL-18 (enzyme-linked immunosorbent assay, diagnostic kits for ELISA, Vector-Best, Russia), α1-antitrypsin (A1AT), and ferritin (turbidimetric assay, A25 analyzer and reagents, Biosystems, Spain) in blood serum.

Statistical analysis was performed using StatTech version 2.8.8 (StatTech, Russia, RRID:SCR_023071). Quantitative values were tested for normality using the Shapiro–Wilk test. Quantitative values with a normal distribution were presented as mean (M) and SD with 95% CI. In cases of non-normal distribution, quantitative data were described as median (Me) and lower and upper quartiles (Q1-Q3), whereas categorical data were presented as absolute values and percentages. The comparison of 3 or more groups based on a quantitative parameter with anon-normal distribution was performed with the Kruskal–Wallis test, and post-hoc comparisons were made with Dunn's test with Holm's correction.

RESULTS

Demographic and clinical data of patients in the study groups are presented in Table 1.

The groups were balanced for sex ($P = .325$), age, and Friedman score for polyposis severity. The surgery duration and recovery time were the same for all the patients. Pain severity was significantly lower in the L group at 30 and 180 minutes after the procedure. Patients in the groups proved to have different degrees of comorbidity severity (Table 2).

The levels of cytokines and acute-phase proteins in all groups before and after FESS are demonstrated in Figure 1.

According to Figure 1, serum concentrations of cytokines (apart from IL-18) and acute-phase proteins did not exceed reference numbers in any group. However, the changes in their levels in all the groups before and after FESS were significant. Interleukin-6 levels rose in the C group after the procedure ($P < .001$), while in the L and D groups the changes were not significant. Patients in the D group experienced an increase in IL-10

Table 1. Demographic and Clinical Parameters of Study Groups

Parameter	Study Groups	Mean ± SD/ Median	95% CI/Q_1-Q_3	*P*
Age (years)	C	44.28 ± 12.72	39.03-49.53	.866[a]
	D	46.46 ± 13.77	38.14-54.78	
	L	45.15 ± 7.38	40.69-49.61	
BMI (kg/m^2)	C	27.11 ± 3.83	25.53-28.69	.356[a]
	D	24.66 ± 4.72	21.81-27.51	
	L	25.98 ± 6.89	21.82-30.15	
Friedman scale (score)	C	2	1-2	.129[b]
	D	3	1-3	
	L	2	2.00-3	
Surgery duration (minutes)	C	90	78-100	.969[b]
	D	89	75-110	
	L	95	70-110	
Recovery time (minute)	C	12	11-13	.359[b]
	D	12	12-14	
	L	12	12-14	
VAS 30 (score)	C	4	2-6	.003[b] $P_{C\text{-}L}$ = .004
	D	2	2-4	
	L	2	2-2	
VAS 60 (score)	C	2	2-4	.081[b]
	D	2	2-2	
	L	2	2-2	
VAS 180 (score)	C	2	2-4	.040[b] $P_{C\text{-}L}$ = .048
	D	2	2-2	
	L	2	2-2	

The data are presented in the form of the absolute value (percentage) [N (%)] and the median (lower quartile, upper quartile) [median (Q1; Q3)].
BMI, body mass index; VAS, visual analog scale.
[a]*F*-test.
[b]Kruskal–Wallis test.

Table 2. Comorbidity Severity in Study Groups

Comorbidity		Study Groups C	D	L	*P*
Asthma	Absent	15 (60.0)	6 (46.2)	9 (69.2)	.547
	Mild	6 (24.0)	2 (15.4)	1 (7.7)	
	Moderate	4 (16.0)	4 (30.8)	2 (15.4)	
	Severe	0 (0.0)	1 (7.7)	1 (7.7)	
Allergy	Absent	19 (76.0)	9 (69.2)	13 (100.0)	.105
	Present	6 (24.0)	4 (30.8)	0 (0.0)	
Aspirin triad	Absent	22 (88.0)	10 (76.9)	13 (100.0)	.189
	Present	3 (12.0)	3 (23.1)	0 (0.0)	

The data are presented in the form of N (%). The statistical method was Pearson's Chi-squared test.

(*P* = .002) after FESS. Postoperative levels of IL-18 dropped significantly in all groups. A decrease in A1AT serum concentration was significant in the C (*P* < .001) and L groups (*P* = .005), while its level dynamics in the D group was not significant. A drop in ferritin levels was observed only in the C (*P* < .001) and D groups (*P* = .017).

Hemodynamics and intraoperative BI values are presented in Table 3.

Median BI values in the C group did not differ significantly compared to each other. In the dexamethasone group, median BI changed between 30 and 60 minutes compared to the control group. In the L group, the operation field was already clear at 10 minutes of the procedure, and the BI was significantly lower compared to both the C and D groups. However, the differences in the parameter between the L and D groups leveled out at 30 minutes while remaining significantly lower than in the control group. Compared to the C group, HR in the L group was significantly lower at 30 and 60 minutes, and MBP at 10 and 30 minutes.

DISCUSSION

The development of polyposis is considered to be caused by bacterial or fungal colonization of the respiratory tract mucosa associated with disruptions in the innate immune response, including a decrease in antimicrobial factor expression and a breach of the epithelial barrier.[15] In that case, polyp growth is generally triggered by mediators of an allergy response (IL-5, IL-13, eotaxin-2, monocyte chemotactic protein-4,[16] histamine, and immunoglobulin E[3]), which is mediated by type 2 T helper cells. The cause of inflammation in a damaged tissue is different; it is mainly mediated by acute-phase proteins: tumor necrosis factor alpha (TNF-α), IL-1β, IL-6, IL-8, and interferon gamma (IFN-γ). Alarmins released from damaged cells stimulate their expression and act as damage-associated molecular patterns. Thus, inherent changes in the immune system may exacerbate postoperative inflammatory responses, affect PS and hyperemia, and consequently, increase BI. One of the ways to reduce inflammation is through IV administration of GCs (primarily dexamethasone).[17] According to some studies, IV lidocaine may also have a systemic anti-inflammatory effect. As Herroeder et al[18] state in their study on colorectal surgery, IL-6, IL-8, and IL-1 levels were lower in the IV lidocaine group compared to placebo. In animal models, lidocaine influences the very first stages of the systemic inflammatory response: it modulates migration, adhesion, and delivery of polymorphonuclear cells to the damaged tissue while inhibiting the production of reactive oxygen intermediates and the release of histamine. These properties of lidocaine lie in the blocking of G-protein-coupled receptors. By blocking these receptors, it inhibits inflammatory processes, including neutrophil sensitization and lysosomal degradation, the production of reactive oxygen intermediates, and the release of cytokines in both macrophages and glial cells. It also affects adhesion and migration of leucocytes in the endothelium by inhibiting the effect of intercellular adhesion molecules, transforming the cytoskeleton, or reducing the release of chemotactic factors. Lidocaine blocks the release of IL-1, TNF, and IL-8 in polymorphonuclear cells. It also decreases the levels of IL-6 and phospholipase A2—both agents disrupt the blood–brain barrier.[19] In our study, changes in cytokine profile in the L group may also be due to the fact that lower intraoperative BI reduces the extent of damage in FESS procedures. In a clear operating field, the procedure causes only local, minimal damage essential to the technique. Intensive bleeding and poor visibility of the surgical field increase the extent of tissue damage, which may exacerbate the inflammatory response. The VAS score in the L group was significantly lower at 30 and 180 minutes compared to the C group,

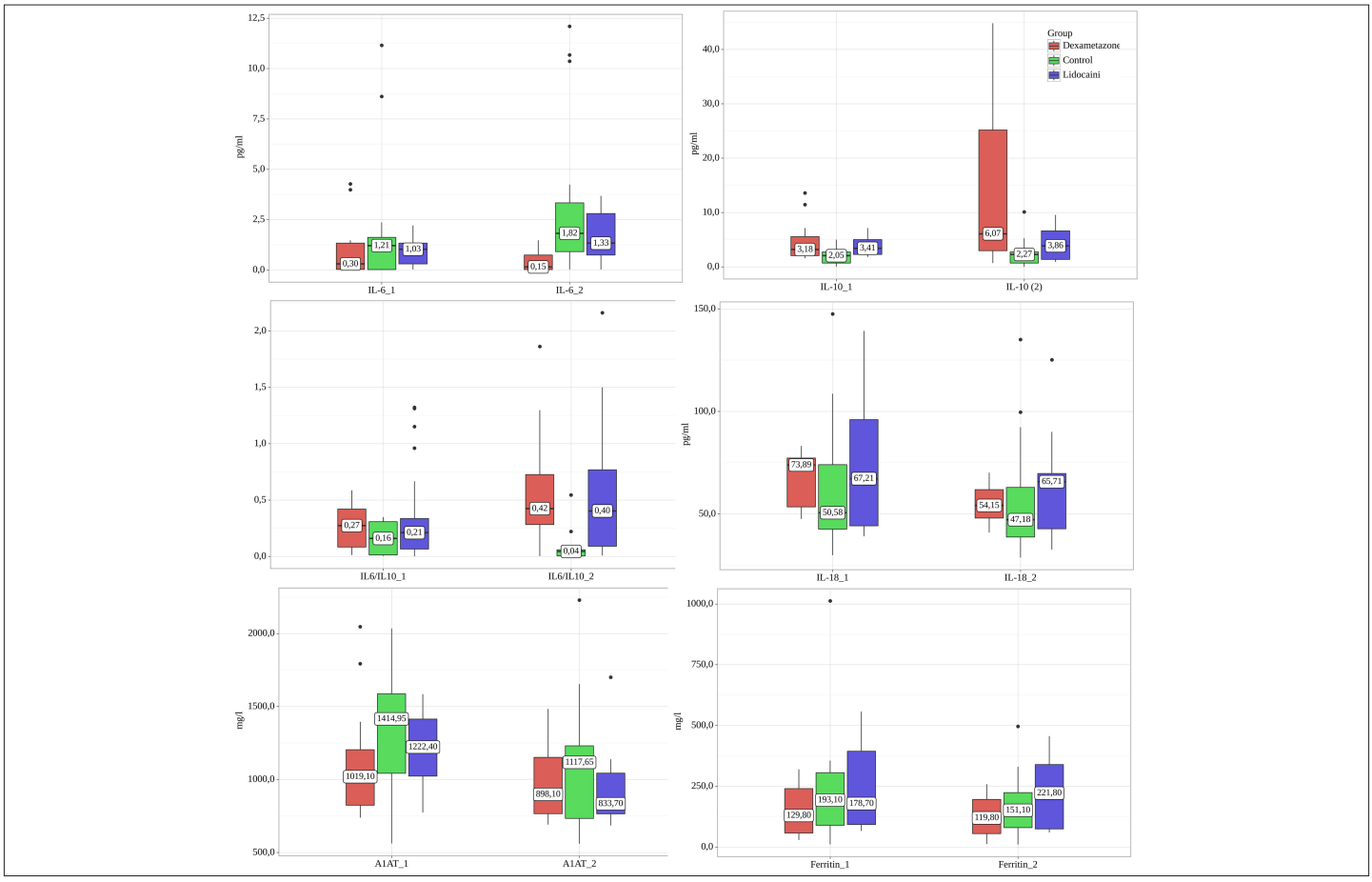

Figure 1. Levels of cytokines and acute-phase proteins before and after the procedure.

which may be attributed to the prolonged analgesic effect of lidocaine or its blood-saving and anti-inflammatory properties.

The C group showed a considerable rise in IL-6 levels. Interleukin-6 and IL-10, as well as their ratio, are extremely insightful parameters as they correlate with the rate of comorbidities and adverse outcomes.[17] According to some studies, the IL-6 to IL-10 ratio is correlated with the severity of chest and abdomen injuries,[20] systemic inflammatory response syndrome,[21] pneumonia,[22] and other conditions. The D group demonstrated zero levels of IL-6 and IL-6/IL-10, and their increase in the L group was not significant. The group comparison revealed that the extent of changes in IL-10 levels in the D group was significantly higher than in the other 2 groups, whereas the values of IL-6 and IL-6/IL-10 dropped significantly after the procedure compared to the control group. These changes may demonstrate that dexamethasone has a considerable immunomodulating effect and that the same properties in lidocaine are much less prominent. However, a considerable immunomodulating effect may have a downside: as proven by Sapan et al,[23] a sharp decrease in IL-6 and IL-6/IL-10 levels is just as unfavorable as their high concentration. The effect of an increase in IL-10 concentration is also complex: on the one hand, it limits the development of non-infectious complications;[24] on the other hand, it is associated with a higher risk of postoperative infection.[17] Low median levels of IL-6 and IL-10 in all groups are due to the fact that the FESS procedures were minimally invasive (endoscopic access, use of surgical instruments that do not cause inflammation, and use of a laryngeal mask) and elective.

The anti-inflammatory cytokine IL-18 belongs to the IL-1 family and shares properties and structural features with IL-1β. One of the main functions of IL-18 is the polarization of type 1 T helper cells and the production of IFN-γ.[25] Interleukin-18 is easier to analyze, thanks to its relative stability: its half-life is 16 hours,[26] whereas TNF-α and IL-1β remain stable for less than 20 minutes.[27] In our study, all groups demonstrated a decrease in median IL-18 levels postoperatively, with the changes being more pronounced in the D group. A drop in postoperative IL-18 concentration may be attributed to the increase in IL-18-binding protein levels as part of a negative feedback, which happens as a response to changing levels of IFN-γ in intraoperative inflammation.[25]

A postoperative decrease in A1AT was significant in the C and L groups and did not reach significance in the D group. The A1AT is an acute-phase protein that decreases protease levels and modulates the immune system; its concentration experiences a 2- to 5-fold increase at the inception of an inflammatory response.[28] In a few hours after the administration of anti-inflammatory agents, A1AT levels drop at first, then start to rise and peak on days 3-5.[29] The A1AT levels in the D group could be high because of immunosuppression facilitated by dexamethasone.

Unlike the L group, the C and D groups demonstrated a decrease in postoperative ferritin. In invasive procedures, low ferritin levels may be a sign of perioperative anemia from pre-existing conditions or bleeding.[30] Thus, the difference in preoperative and postoperative ferritin levels between the L group and the D and C groups is likely linked to a lower BI in the former.

Table 3. Bleeding Intensity and Hemodynamics at Different Timepoints

Parameter	Study Group	Me (Q25%-Q75%) at Different Timepoints		
		10 minutes	30 minutes	60 minutes
BI (score)	C	3.0 (3.0-4.0)	3.0 (2.0-4.0)	2.5 (2.0-3.0)
	D	3.0 (2.0-4.0)	2.0 (2.0-3.0)	2.0 (1.0-2.0)
	L	1.0 (1.0-2.0)	1.0 (1.0-2.0)	1.0 (1.0-2.0)
	P	< .001[a] $P_{C\text{-}L}$ < .001 $P_{L\text{-}D}$ = .003	< .001[a] $P_{C\text{-}L}$ < .001 $P_{C\text{-}D}$ = .030	< .001[a] $P_{C\text{-}L}$ < .001 $P_{C\text{-}D}$ = .021
HR (bpm)	C	78 (70-83)	72 (67-82)	73 (68-79)
	D	68 (65-77)	69 (63-77)	67 (61-70)
	L	71 (66-79)	64 (61-67)	56 (54-63)
	P	.192 $P_{C\text{-}D}$ = .297 $P_{C\text{-}L}$ = .410 $P_{D\text{-}L}$ = .741	.057 $P_{C\text{-}D}$ = .396 $P_{C\text{-}L}$ = .050[a] $P_{D\text{-}L}$ = .360	< .001[a] $P_{C\text{-}D}$ = .052 $P_{C\text{-}L}$ < .001[a] $P_{D\text{-}L}$ = .052
SBP (mm Hg)	C	106 (100-115)	104 (100-110)	110 (104-116)
	D	104 (99-113)	105 (102-109)	109 (104-116)
	L	104 (98-105)	101 (96-102)	103 (95-106)
	P	.303 $P_{C\text{-}D}$ = .756 $P_{C\text{-}L}$ = .378 $P_{D\text{-}L}$ = .581	.020[a] $P_{C\text{-}D}$ = .756 $P_{C\text{-}L}$ = .036[a] $P_{D\text{-}L}$ = .036[a]	.012[a] $P_{C\text{-}D}$ = .722 $P_{C\text{-}L}$ = .011[a] $P_{D\text{-}L}$ = .056
DBP (mm Hg)	C	62 (56-66)	63 (55-67)	55 (52-57)
	D	56 (49-63)	64 (57-67)	59 (55-64)
	L	52 (47-57)	55 (54-58)	58 (56-61)
	P	.004[a] $P_{C\text{-}D}$ = .051 $P_{C\text{-}L}$ = .006[a] $P_{D\text{-}L}$ = .468	.052 $P_{C\text{-}D}$ = .621 $P_{C\text{-}L}$ = .077 $P_{D\text{-}L}$ = .077	.032[a] $P_{C\text{-}D}$ = .090 $P_{C\text{-}L}$ = .090 $P_{D\text{-}L}$ = .959
MBP (mm Hg)	C	78 (72-80)	76 (71-81)	74 (70-78)
	D	72 (65-77)	77 (73-80)	76 (73-79)
	L	68 (65-75)	70 (68-71)	74 (69-76)
	P	.013[a] $P_{C\text{-}D}$ = .172 $P_{C\text{-}L}$ = .013[a] $P_{D\text{-}L}$ = .328	.020[a] $P_{C\text{-}D}$ = .562 $P_{C\text{-}L}$ = .034[a] $P_{D\text{-}L}$ = .030[a]	.317 $P_{C\text{-}D}$ = .512 $P_{C\text{-}L}$ = .570 $P_{D\text{-}L}$ = .420

The data are presented in the form of Median (Q1; Q3). The statistical method was Kruskal–Wallis test with Dunn's test for pairwise comparisons.

BI, bleeding intensity; DBP, diastolic blood pressure; HR, heart rate; MBP, mean blood pressure; SBP, systolic blood pressure.

[a]*P* < .05.

Prevention of intensive bleeding, which hinders visualization and increases complication risk, is vital for a safe and effective FESS procedure.[4] In our study, intraoperative BI in the L group at 10, 30, and 60 minutes was significantly lower than in the C group. In the D group, BI at 30 and 60 minutes was also reduced compared to the control group but to a lesser extent than in the L group. Though, as stated by Tirelly et al,[7] preoperative administration of GCs increased BI during the procedure, intraoperative dexamethasone had a mild hemostatic effect, which may stem from a lower severity of local inflammation as confirmed by previous studies.[4]

CONCLUSION

Changes in the cytokine profile of patients with CRSwNP undergoing FESS under GA were insignificant. Intraoperative dexamethasone affects the cytokine profile to a greater extent compared to intraoperative lidocaine. The effects of both drugs on bleeding control are equally inconsiderable; however, the onset of lidocaine action is more rapid.

Ethics Committee Approval: This study was approved by Ethics Committee of First Pavlov State Medical University of St. Petersburg (Date: May 30, 2022, Number: 263).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – V.P.; Design – V.P.; Supervision – Y.P, S.K.; Resources – V.P.; Materials – V.P.; Data Collection and/or Processing – V.P.; Analysis and/or Interpretation – V.P.; Literature Search – V.P.; Writing – V.P., Y.P., S.K.; Critical Review – Y.P., S.K.

Declaration of Interests: The authors have no conflict of interest to declare.

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

REFERENCES

1. Scadding GK, Durham SR, Mirakian R, et al. BSACI guidelines for the management of rhinosinusitis and nasal polyposis. *Clin Exp Allergy*. 2008;38(2):260-275. [CrossRef]
2. Ragab SM, Lund VJ, Scadding G. Evaluation of the medical and surgical treatment of chronic rhinosinusitis: a prospective, randomised, controlled trial. *Laryngoscope*. 2004;114(5):923-930. [CrossRef]
3. Tritt S, McMains KC, Kountakis SE. Unilateral nasal polyposis: clinical presentation and pathology. *Am J Otolaryngol*. 2008;29(4):230-232. [CrossRef]
4. Pavlov VE, Polushin YuS, Kolotilov LV. Anesthesiological possibilities of intraoperative bleeding control during endoscopic Rhinosinusurgical interventions. Article in Russian. *Vestn anesteziol reanimatol*. 2022;19(1):75-81. [CrossRef]
5. Hopkins C, Browne JP, Slack R, et al. Complications of surgery for nasal polyposis and chronic rhinosinusitis: the results of a national audit in England and Wales. *Laryngoscope*. 2006;116(8):1494-1499. [CrossRef]
6. Pundir V, Pundir J, Lancaster G, et al. Role of corticosteroids in Functional Endoscopic Sinus Surgery--a systematic review and meta-analysis. *Rhinology*. 2016;54(1):3-19. [CrossRef]
7. Tirelli G, Lucangelo U, Sartori G, et al. Topical steroids in rhinosinusitis and intraoperative bleeding: more harm than good? *Ear Nose Throat J*. 2020;99(6):388-394. [CrossRef]
8. Zhang T, Xu Y, Yao Y, et al. Randomized controlled trial: perioperative dexamethasone reduces excessive postoperative inflammatory response and ileus after surgery for inflammatory bowel disease. *Inflamm Bowel Dis*. 2021;27(11):1756-1765. [CrossRef]
9. Al-Qudah M, Rashdan Y. Role of dexamethasone in reducing pain after endoscopic sinus surgery in adults: a double-blind prospective randomized trial. *Ann Otol Rhinol Laryngol*. 2010;119(4):266-269. [CrossRef]
10. Павлов ВЕ, Каприщенко СА, Корячкин ВА. Способ снижения интраоперационного кровотечения при эндоскопических эндоназальных ринохирургических оперативных вмешательствах. Russian patent RU2752989C1; 2020.

11. Elaziz RAEA, Shaban S, Elaziz SA. Effects of lidocaine infusion on quality of recovery and agitation after functional endoscopic sinus surgery: randomized controlled study. *Open J Anesthesiol*. 2020;10(12):435-448. [CrossRef]
12. Friedman WH, Katsantonis GP, Sivore M, Kay S. Computed tomography staging of the paranasal sinuses in chronic hyperplastic rhinosinusitis. *Laryngoscope*. 1990;100(11):1161-1165. [CrossRef]
13. Pavlov VE, Kolotilov LV, Karpishchenko SA. Intravenous lidocaine in endoscopic sinus surgery. Article in Russian. *Anaes i reanim*. 2022;2(2):47-53. [CrossRef]
14. Kelly EA, Gollapudy S, Riess ML, Woehlck HJ, Loehrl TA, Poetker DM. Quality of surgical field during endoscopic sinus surgery: a systematic literature review of the effect of total intravenous compared to inhalational anesthesia. *Int Forum Allergy Rhinol*. 2013;3(6):474-481. [CrossRef]
15. Hulse KE, Stevens WW, Tan BK, Schleimer RP. Pathogenesis of nasal polyposis. *Clin Exp Allergy*. 2015;45(2):328-346. [CrossRef]
16. Stevens WW, Ocampo CJ, Berdnikovs S, et al. Cytokines in chronic rhinosinusitis. Role in eosinophilia and Aspirin-exacerbated respiratory disease. *Am J Respir Crit Care Med*. 2015;192(6):682-694. [CrossRef]
17. Rossaint J, Zarbock A. Perioperative inflammation and its modulation by anesthetics. *Anesth Analg*. 2018;126(3):1058-1067. [CrossRef]
18. Herroeder S, Pecher S, Schönherr ME, et al. Systemic lidocaine shortens length of hospital stay after colorectal surgery: a double-blinded, randomized, placebo-controlled trial. *Ann Surg*. 2007;246(2):192-200. [CrossRef]
19. Soto G, Naranjo González M, Calero F. Intravenous lidocaine infusion. [Perfusión de lidocaína intravenosa]. *Rev Esp Anestesiol Reanim (Engl Ed)*. 2018;65(5):269-274. [CrossRef]
20. Taniguchi T, Koido Y, Aiboshi J, Yamashita T, Suzaki S, Kurokawa A. The ratio of interleukin-6 to interleukin-10 correlates with severity in patients with chest and abdominal trauma. *Am J Emerg Med*. 1999;17(6):548-551. [CrossRef]
21. Taniguchi T, Koido Y, Aiboshi J, Yamashita T, Suzaki S, Kurokawa A. Change in the ratio of interleukin-6 to interleukin-10 predicts a poor outcome in patients with systemic inflammatory response syndrome. *Crit Care Med*. 1999;27(7):1262-1264. [CrossRef]
22. de Brito RC, Lucena-Silva N, Torres LC, Luna CF, Correia JB, da Silva GA. The balance between the serum levels of IL-6 and IL-10 cytokines discriminates mild and severe acute pneumonia. *BMC Pulm Med*. 2016;16(1):170. [CrossRef]
23. Sapan HB, Paturusi I, Jusuf I, et al. Pattern of cytokine (IL-6 and IL-10) level as inflammation and anti-inflammation mediator of multiple organ dysfunction syndrome (MODS) in polytrauma. *Int J Burns Trauma*. 2016;6(2):37-43.
24. Hsing CH, Wang JJ. Clinical implication of perioperative inflammatory cytokine alteration. *Acta Anaesthesiol Taiwan*. 2015;53(1):23-28. [CrossRef]
25. Dinarello CA. Interleukin 1 and interleukin 18 as mediators of inflammation and the aging process. *Am J Clin Nutr*. 2006;83(2):447S-455S. [CrossRef]
26. Hosohara K, Ueda H, Kashiwamura S, et al. Interleukin-18 induces acute biphasic reduction in the levels of circulating leukocytes in mice. *Clin Diagn Lab Immunol*. 2002;9(4):777-783. [CrossRef]
27. Biancofiore G, Bindi L, Miccoli M, et al. Balance of pro- and anti-inflammatory cytokines in cirrhotic patients undergoing liver transplantation. *Transpl Immunol*. 2013;28(4):193-197. [CrossRef]
28. Шевченко ОП. Белки острой фазы воспаления. Article in Russian. *Лаборатория*. 1996;1:10-17. Available at: http://www.clinlab.ru/win/LIBRARY/JOURNLAB/lab1/lab1ct1.htm.
29. Kueppers F. Genetically determined differences in the response of alpha-antitrypsin levels in human serum to typhoid vaccine. *Humangenetik*. 1968;6(3):207-214. [CrossRef]
30. Gómez-Ramírez S, Bisbe E, Shander A, Spahn DR, Muñoz M. Management of perioperative iron deficiency anemia. *Acta Haematol*. 2019;142(1):21-29. [CrossRef]