Carotid surgery affects plasma kynurenic acid concentration: A pilot study

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Background: An increase in plasma kynurenic acid (KYNA) concentration has been observed following surgery, inflammation, and cerebral pathologies. The aim of the present study was to analyze the changes in plasma KYNA concentration in patients undergoing carotid surgery (CS).

Material/Methods: Adult patients undergoing elective carotid endarterectomy (CEA) or carotid angioplasty with stent placement (CAS) were studied. Plasma KYNA concentrations were analyzed before surgery and at 4 time points after CS. The amount of inflammation was measured as neutrophil-lymphocyte ratio (NLR).

Results: Forty patients (10 female and 30 male) aged 55–86 years of age were evaluated in this study. In patients with unstable carotid plaque, the plasma KYNA concentration was higher than in patients with stable carotid plaque. Moreover, the NLR was significantly higher in patients with unstable carotid plaque undergoing CEA than in patients undergoing CAS. Plasma KYNA concentration increased after surgery in patients undergoing CEA and CAS. There was a strong correlation between plasma KYNA concentration and NLR in patients with postoperative neurological disorders.

Conclusions: CS increases plasma KYNA concentration, and changes in plasma KYNA concentration can indicate neurologic outcomes in patients undergoing CS.

MeSH Keywords: **Kynurenic Acid • Angioplasty • Endarterectomy, Carotid**

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Background

The kynurenine pathway is the main route for tryptophan metabolism, and kynurenic acid (KYNA) is one of the biologically active metabolites in this pathway. Physiologically, the normal plasma KYNA concentration ranges between 25 and 60 nmol/L [1–4]. Several pathologic conditions such as inflammation, sepsis and septic shock, stroke and cerebral ischaemia, Alzheimer's disease, multiple sclerosis, epilepsy, and depression affect plasma KYNA concentrations [1–4,6,7]. An increase in the plasma KYNA concentration has also been observed following thoracic and cardiovascular surgery [8]. Elevated KYNA levels correlate with postoperative neuropsychological deficits in cardiac surgery patients [8]. Moreover, the KYNA concentration correlates with infarct volume and predicts fatal outcome [6,7,9]. However, the effect of carotid surgery on plasma KYNA concentration has not been documented.

Carotid surgery is an evidence-based treatment for the prevention of carotid-related cerebrovascular complications. Unfortunately, carotid endarterectomy (CEA) or carotid angioplasty stenting (CAS) may disturb cerebral circulation, leading to various cerebral injuries, including carotid surgery-related stroke. These pathologies elevate mortality, morbidity, and hospital costs and significantly impair quality of life. Moreover, rapid improvement of cerebral circulation and increases in oxygen supply may disturb brain function and affect the kynurenine pathway. The aim of the present study was to analyze the changes in plasma KYNA concentrations in patients undergoing carotid surgery.

Material and Methods

The study was approved by the Committee for Bioethics at the Medical University of Lublin, and written informed consent was obtained from all patients. Patients scheduled for elective carotid surgery due to stenosis were included in this study. Computed tomography angiography and color duplex ultrasound examination were used to determine the severity of carotid stenosis. Patients who received routine shunting or required general anaesthesia were excluded from analysis. According to the Society of Vascular Surgery, CEA is performed in all symptomatic patients with carotid stenosis of 50% to 90% and asymptomatic patients with stenosis of 60% to 99%. Moreover, CEA was performed in patients older than 70 years with long lesion (greater than 15 mm), preocclusive stenosis, or lipid-rich plaques. Carotid angioplasty stenting should be reserved for symptomatic patients with stenosis of 50% to 99% at high risk for CEA for anatomic or medical reasons or for patients with severe uncorrectable coronary artery diseases, chronic heart failures, or/and chronic obstructive pulmonary diseases [10,11]. A stenosis was classified as

symptomatic if the patients were treated for transient ischemic attack (TIA), stroke, a cerebrovascular ischemic event or ocular ischemic symptoms within 1 year before surgery and if the event was confirmed by computed tomography or/and magnetic resonance imaging and neurological examination.

Anesthesia

On the day before surgery, all patients were pre-medicated with a single 2 mg oral dose of estazolam (Estazolam, Polfa, Pl). Before the induction of anaesthesia, all patients were routinely monitored with respect to electrocardiography and arterial pressure. The arterial pressure was measured directly in an arterial artery, and the arterial catheter was inserted under local anesthesia just before induction of anesthesia. The choice of anesthesia depended on the type of surgery: regional anesthesia was performed in patients scheduled for CEA, and local anesthesia was performed in CAS patients. For regional anesthesia, the deep and superficial cervical plexus were blocked using 0.5% bupivacaine hydrochloride (Bupivacaine, Polfa, Pl) at the dose of 5 mg and 2% lidocaine hydrochloride (Xylocaine, Polafa, Pl) at the dose of 10 mg. The local anesthesia was performed using 0.5% bupivacaine hydrochloride at the dose of 1-2 mg injected subcutaneously.

Surgery

In all patients, dual anti-platelet treatment with acetylsalicylic acid (Aspirin, Bayer DE) at the daily dose of 75 mg and clopidogrel (Pharmathen S.A., GR) at the daily dose of 75 mg was initiated at least 3 days before the procedure. CEA was performed through a longitudinal arteriotomy, running from the carotid bifurcation to the anterolateral surface of the internal carotid artery (ICA). The carotid artery was clamped, and the arteriotomy was closed with primary sutures. All procedures were performed without shunting. CAS was performed using femoral catheterization. Access to the common carotid artery was achieved with a 7-Fr 80-cm-long sheath. The carotid lesions were crossed with a 0.014 filter EPD guide wire (Abbott Vascular, USA). The filter EPD deployment was performed in a non-tortuous distal internal carotid artery (ICA) segment. The lesions received stents with tapered X-Act Abbott Stent System components (Abbott Vascular, USA). Additional dilation of the lesion with balloon angioplasty was performed if angiographic residual stenosis after stent placement was more than 30%.

Study protocol and patient distribution

Plasma KYNA concentrations were measured at 5 time points: 1) before anaesthesia and surgery (baseline value), 2) 1 h after surgery, 3) 6 h after surgery (in the evening after surgery), 4) on the morning of postoperative day 1, and 5) on the morning of postoperative day 2. The white blood cell (WBC) count

was measured at time points 1, 4, and 5. The neutrophils/lymphocyte ratio (NLR) was used as a marker of inflammation severity [12,13] and was measured at time points 1, 4, and 5. To examine KYNA levels, blood samples were collected from the radial artery and immediately centrifuged (2500 r/min). The plasma obtained was frozen at –20°C. Plasma KYNA concentrations were measured fluorometrically. Blood plasma was deproteinated with 50% trichloroacetic acid and centrifuged. The resulting supernatant was applied to a cation-exchange resin (Dowex 50 W+, Sigma). The eluted KYNA was subjected to HPLC (Hewlett Packard 1050 HPLC system: ESA catecholamine HR-30, 3 µm, C_{18} reverse-phase column) and quantified fluorometrically (Hewlett Packard 1046A fluorescence detector: excitation 344 nm, emission 398 nm) [14]. The KYNA results are expressed as pmol/ml.

Patients were assigned to one of three groups based on the type of carotid surgery: patients with unstable carotid plaque treated by CEA under regional anaesthesia (UCP-CEA), patients with stable carotid plaque treated with CEA under regional anaesthesia (SCP-CEA) and patients treated with CAS under local anaesthesia (CAS).

Statistical analysis

The means and standard deviations (SD) were calculated for parametric data. The value at time point 1 was regarded as baseline. Categorical variables were compared using the χ^2 and Fisher exact tests, and the Yates correction was applied. The unpaired Student's t-test was used to analyze variables with a normal distribution. Non-parametric data were statistically analyzed using the Wilcoxon signed-rank test and the Kruskal-Wallis ANOVA test for initial detection of differences. A P<0.05 was considered to be statistically significant. The sample size was determined by Statistica 9 software. The power of all statistical tests was determined by G*Power software $(1 – \beta)$.

Results

Forty adult patients (10 female and 30 male) aged 55–86 years were examined in this study. Thirty patients (75%) were symptomatic and 10 (25%) were asymptomatic. There were 26 patients (65%) treated for right internal carotid artery stenosis (RICAS). There were 26 patients (65%) treated with CEA (19 patients treated for RICAS and 7 patients treated for left internal carotid artery stenosis (LICAS)) and 14 patients (35%) treated with CAS (8 patients treated for RICAS and 6 patients treated for LICAS). Unstable carotid plaque with inflammation was found in 15 CEA patients (57.7%). The mean duration of surgeries was 58±14 min in the CEA group (60±16 min in UCP-CEA group and 57±13 min in SCP-CEA group) and 60±17 min in the CAS group. The mean duration of carotid artery clamping
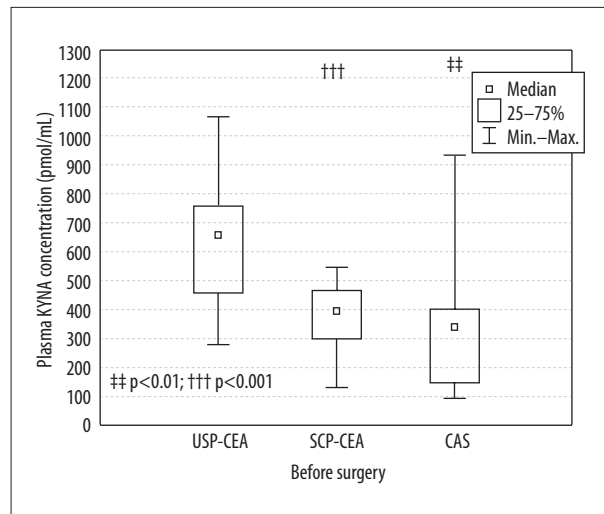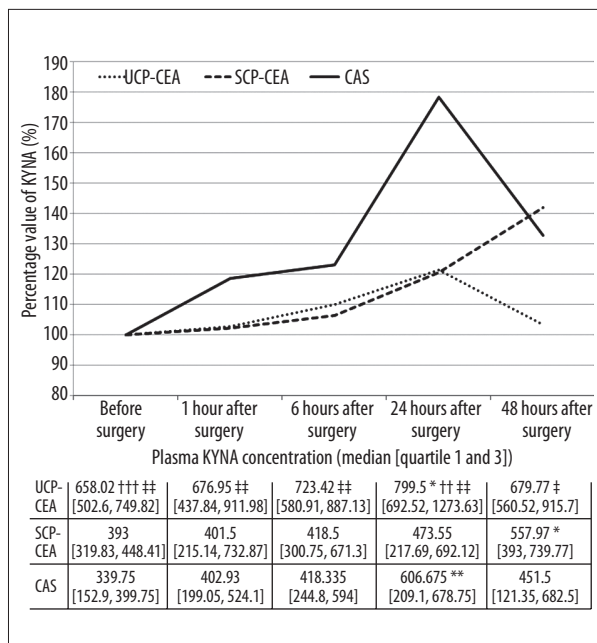

Figure 1. The difference between plasma kynurenic acid (KYNA) concentration before anesthesia and surgery in carotid endarterectomy (CEA) patients with unstable carotid plaque with inflammation (UCP-CEA) and CEA patients with stable carotid plaque (SCP-CEA), as well as in patients receiving carotid angioplasty stents (CAS). ‡‡ p<0.01 – significant difference between UCP-CEA group and CAS group, ††† P<0.001 – significant difference between UCP-CEA group and SCP-CEA group (Mann-Whitney U test).

was 14±8 min. Patients were treated with carotid duplex ultrasound examination at postoperative day 30, and none showed evidence of stent thrombosis or/and restenosis. An uncomplicated postoperative period was noted in 32 patients (80%). Postoperative neurological disorders were observed in 8 patients on the first and/or second postoperative day. Stroke was diagnosed in 4 CEA patients (10.3%). There were 2 strokes in the UCP-CEA group and 2 in the CAS group (17.6%). Transient ischemic attack (TIA) was noted in 3 patients. There was 1 TIA in the UCP-CEA group, 2 in the SCP-CEA group, and 1 in the CAS group. One of the stroke patients in the UCP-CEA group died on postoperative day 10.

The median baseline value of plasma KYNA concentration was significantly higher in CEA patients with unstable carotid plaque with inflammation than in CEA patients with stable carotid plaque before surgery (Figure 1). The median value of plasma KYNA concentration did not differ significantly between the SCP-CEA group and the CAS group (Figure 2).

In patients treated with CAS, the plasma KYNA concentration increased at time point 4 (Figure 2). The plasma KYNA concentration increased at time point 4 in patients with unstable carotid plaque undergoing CEA, whereas in patients with stable carotid plaque, the KYNA concentration increased at time point 5 (Figure 2). Plasma KYNA concentrations were significantly higher in the UCP-CEA group than in the SCP-CEA group

Figure 2. Changes in the percentage of plasma kynurenic acid (KYNA) concentration in patients with unstable carotid plaque undergoing carotid endarterectomy (UCP-CEA), patients with stable carotid plaque undergoing carotid endarterectomy (SCP-CEA) and carotid angioplasty stenting (CAS). Time points: 1) before anaesthesia and surgery (baseline), 2) 1 h after surgery, 3) 6 h after surgery (in the evening after surgery), 4) on the morning of postoperative day 1, and 5) on the morning of postoperative day 2. * p<0.05, ** p<0.01 – significant differences in plasma KYNA concentration in comparison with baseline (Wilcoxon test), †† p<0.01 and ††† p<0.001 – significant differences in plasma KYNA concentration between UCP-CEA group and STP-CEA group; ‡ p<0.05 and ‡‡ p<0.01 – significant differences in plasma KYNA concentration between UCP-CEA group and CAS group (Mann-Whitney U test).

at time points 1 and 4. Moreover, the KYNA concentrations were higher in UCP-CEA group than in the CAS group at all postoperative time points. There were no differences between the SCP-CEA group and the CAS group (Figure 2).

In patients with postoperative neurological disorders, the plasma KYNA concentrations were significantly higher than in patients with an uncomplicated postoperative period from time points 2 to 5 (Table 1).

The changes in WBC and NLR are presented in Table 2. The NLR was significantly higher in the UCP-CEA group than in the CAS group before surgery (p<0.01). The WBC count weakly correlated with the plasma KYNA concentration in the SCP-CEA group (p<0.01, r=0.51). There was a strong positive correlation between NLR and plasma KYNA concentration in patients with postoperative neurological disorders (p<0.001, r=0.79).

Discussion

In this study the effect of anesthesia and surgery on plasma KYNA content in patients undergoing CEA and CAS was studied. The data show that the baseline value of plasma KYNA concentrations determined before surgery were higher in patients with unstable carotid plaque undergoing CEA than in patients with stable carotid plaque undergoing CEA and patients undergoing CAS. Independent of the baseline KYNA level, the concentration increased during the postoperative period in all studied groups. The plasma KYNA concentration increased on the first postoperative day in patients with unstable carotid plaque undergoing CEA and in patients undergoing CAS. However, for patients with stable carotid plaque undergoing CEA, the KYNA increase was noted on the second postoperative day. Higher plasma KYNA concentrations were observed at all studied time points in patients with unstable carotid plaque undergoing CEA compared to patients with stable carotid plaque undergoing CEA and CAS patients. Moreover, higher plasma KYNA concentrations were noted in patients with postoperative neurological disorders. The KYNA value strongly correlated with the degree of inflammation as measured by NLR.

The baseline plasma KYNA concentration was significantly higher in patients with unstable carotid plaque treated with CEA. Notably, unstable carotid plaque with inflammation was found in 57.7% of these patients. An increase in the plasma KYNA concentration was documented during inflammation [2,15], sepsis and septic shock [16,17], and HIV-1 infection [18]. Elevated KYNA content was also noted locally in patients with tick-borne encephalitis and other infections of the central nervous system [3,5,19]. Interestingly, the content of KYNA in synovial fluid is lower in inflammatory rheumatoid arthritis and spondyloarthropathies compared to non-inflammatory osteoarthritis [20]. Local inflammation cannot be excluded as a main reason for higher plasma KYNA concentration in unstable carotid plaque detected in CEA patients. The higher NLR in the UCP-CEA group observed in our study may confirm this assumption. Several authors showed significantly higher concentrations of tumor necrosis factor alpha (TNF-α), interferon gamma (IFN-γ), and interleukin 17α (IL-17α) in unstable carotid plaques with local inflammation than in uncomplicated plaques [21,22]. Moreover, circulating cytokines strongly correlate with the severity of carotid artery plaque formation [23]. Several cytokines, particularly interferon alpha (IFN-α), IFN-γ, IL-1, IL-12, IL-18, and TNF-α, induced indoleamine 2,3-dioxygenase (IDO) activity [24–26]. Importantly, TNF-α up-regulated IDO activity by 300% [26]. It is reasonable that elevated cytokine levels stimulate IDO activity and substantially increase tryptophan catabolites, including KYNA. Therefore, we can conclude that the elevated plasma KYNA concentration in the UCP-CEA patients may result from plaque inflammation.

Table 1. Plasma kynurenic acid (KYNA) concentration (expressed in pmol/mL) in patients with uncomplicated postoperative period (group A) and patients with postoperative neurologic disorders (group B).

Patients	Value	Time points				
		Before surgery	1 h after surgery	6 h after surgery	24 h after surgery	48 h after surgery
Group A (n=32)	Median [quartile 1 and 3]	399.75 [193.5, 556.58]	392.63 [225, 671.64]	468.05* [267, 642.11]	625.5** [252, 704.72]	515.63 [218, 682.91]
Group B (n=8)	Median [quartile 1 and 3]	558.71 [391.16, 889.5]	789.91 [549.75, 951.38]	831.6 [720, 907.13]	1245.13* [1146.75, 1421.78]	945.5* [894.21, 1158.72]
Intergroup differences		NS	p<0.05	p<0.05	p<0.001	p<0.001

Time points: 1/ before anaesthesia and surgery (baseline value), 2/ one hour after surgery, 3/ six hours after surgery (in the evening after surgery), 4/ on the morning of postoperative day 1, 5/ on the morning of postoperative day 2. * p<0.05; ** p<0.01 – significant differences in comparison with baseline value (Wilcoxon test), NS – non statistically significant, (intergroup differences – Mann-Whitney U test).

Table 2. The amount of white blood cells (WBC) and the neutrophils/lymphocyte ratio (NLR) measured at time points 1, 4 and 5 (median value and [quartile 1 and 3]).

Patients	Parameter	Before surgery	After 24 hours	After 48 hours
UCP-CEA	WBC (K/μL)	6.95 [5.65, 8.27]	8.87* [7.42, 10.84]	9.46* [7.48, 11.2]
	NLR	3.51‡‡ [2.35, 4.59]	7.02** [6.35, 10.01]	6.94* [5.73, 8.84]
SCP-CEA	WBC (K/μL)	6.83 [5.45, 7.34]	9.24** [8.03, 10.87]	9.35** [8.12, 10.7]
	NLR	1.99 [1.33, 3.17]	5.82** [4.74, 7.24]	6.36* [4.18, 7.49]
CAS	WBC (K/μL)	6.38 [5.05, 6.92]	9.03*** [8.55, 10.59]	7.83* [7.06, 9.21]
	NLR	2.08 [1.31, 2.45]	6.67*** [4.81, 7.58]	5.99** [3.14, 7.24]

UCP-CEA – patients with unstable carotid plaque undergoing carotid endarterectomy (CEA) under regional anaesthesia, SCP-CEA – patients with stable carotid plaque undergoing CEA under regional anaesthesia, CAS – patients undergoing carotid angioplasty stenting under local anaesthesia (CAS). * p<0.05; ** p<0.01; *** p<0.001 – significant differences in comparison with value measured before surgery (Wilcoxon test). The WBC and NEU/LYM ratio were similar in all analysed groups (Mann-Whitney U test). ‡‡ p<0.01 significant differences in NLR between UCP-CEA and CAS groups.

It is possible that perioperative changes in plasma KYNA concentration may result from anesthesia (*per se*) in addition to surgery. Patients undergoing elective carotid surgery were anesthetized with lidocaine or/and bupivacaine. Thus, this is the first study documenting the changes in plasma KYNA concentration in patients undergoing elective carotid surgery under local anesthesia. It is known that both anesthetics used in this study block sodium/potassium pumps and inhibit neuronal membrane permeability to sodium. Previous experimental studies demonstrated that a decrease in the concentration of sodium significantly increased KYNA production, whereas high potassium inhibited this process in brain slices, but not in liver and kidney tissues [27–29]. Our results showed that KYNA

changes did not differ in patients undergoing local or regional anesthesia. The lack of changes in KYNA content at 1 and 6 h after surgery suggests that local anesthetics did not significantly affect plasma levels of this compound.

Based on our results, an increased level of KYNA resulting from a surgery-related inflammatory response should be considered. The effect of surgery on plasma KYNA concentration has been poorly documented, but it can be assumed that a significant increase in plasma proinflammatory cytokines following the surgical procedures implemented may increase the activity of IDO and enhance production of kynurenine metabolites. This hypothesis is in accordance with our previous study,

which demonstrated a significant increase in plasma KYNA concentration following cardiac surgery [30]. Likewise, Forrest et al. presented an increase in plasma KYNA concentration after major surgery [31]. In the present study, increases in WBC and NLR were observed in all studied groups during the postoperative period. This result supports the possibility that increased KYNA levels are partially related to the surgery-related inflammatory response.

A postoperative increase in KYNA may also result from perioperative cerebral microembolization. Intra-operative cerebral microembolisms occur frequently during CEA and CAS [32–34]. Manipulation of the carotid artery during revascularization may result in gaseous and/or atheroembolization, leading to silent or symptomatic cerebral embolization [35,36]. Cerebral microembolization was observed in 100% of patients undergoing CAS and in 99% in patients undergoing CEA [33]. Importantly, most of these embolisms were gaseous. The new ischemic events were detected in up to 17% of patients undergoing CEA and in 15–54% of patients undergoing CAS [34,36]. Hyper-acute brain ischemia causes an increase in plasma KYNA concentration [4,6,37]. A persistent increase in plasma KYNA concentration may result from stroke-related inflammation [37]. However, an increase in the plasma KYNA concentration corresponds with neither stroke volume and final outcome nor stroke-related neuroinflammation [6,37]. Neuroinflammation is one of the key factors in the pathogenesis of ischemic stroke [38]. Circulating neutrophils adhere to vessel walls and migrate into injured tissues within 6 to 24 h after ischemia onset, and the number of cells corresponds to the severity of stroke and poor neurologic outcome [39,40]. Lymphocytes subsequently increase after the first day following ischemia. However, the number of lymphocytes is negatively correlated with stroke severity and mortality. Based on these observations, NLR has been proposed as a sensitive marker of inflammation following cerebral ischemia [37,41,42]. Interestingly, Brouns et al. [37] showed that an increase in NLR was associated with an increase in plasma KYNA concentration. In their stroke study, plasma KYNA concentration and NLR increased 24 h after admission to the hospital. They observed an elevated KYNA concentration at day 7, whereas NLR decreased after 72 h of treatment. Our findings demonstrating that changes in plasma KYNA concentrations are related to neurologic outcome are consistent with the study by Brouns et al. [37]. We also observed an increased KYNA concentration and NLR during the early postoperative period. Moreover, we found a strong correlation between NLR and plasma KYNA concentration in patients with different postoperative neurological disorders. Therefore, we propose plasma KYNA concentration as a marker of inflammation in carotid surgery patients with postoperative neurologic disorders.

Significantly higher plasma KYNA concentrations were noted in patients with postoperative neurological disorders. Accumulated

data suggest that increased KYNA concentration in the brain plays a crucial role in development of different psychiatric or neurologic diseases such as schizophrenia, bipolar disorders, or HIV encephalopathy [43–46]. The cerebrospinal KYNA concentration is associated with the occurrence of maniac episodes [44]. Moreover, increased KYNA concentrations are an unfavorable factor activating glial cells in patients with multiple sclerosis [46]. Conversely, diminished KYNA synthesis may improve cognition and memory [47]. The analysis of postoperative neurological disorders has highlighted impairment in neuropsychological outcome in patients after carotid surgery [48].

KYNA is a broad-spectrum antagonist of the ionotropic glutamate receptor and α7 nicotinic receptor and provides neuroprotective activity. Inhibition of N-methyl-D-aspartate (NMDA) receptors decreases the over-excitation of glutamatergic transmission, which can affect many physiological and pathological processes [3,49–51]. An increase in plasma KYNA concentration is associated with oxidative stress and corresponds to stroke volume [6]. Moreover, prolonged increases in the KYNA concentration can predict a fatal outcome after brain ischemia [2,6,15]. Our findings are consistent with previous data. A significant postoperative increase in plasma KYNA concentration may result from perioperative symptomatic brain ischemia, and the highest plasma KYNA concentration was observed in a stroke patient who died on postoperative day 10 (data not shown).

Despite the promise of the novel findings of our study, a few limitations should be discussed. First, our studied population was small. Second, we did not analyze the changes in plasma KYNA concentration according to preoperative metabolic diseases. Several authors presented a significant impact of metabolic disorders on KYNA production [52–54]. Changes in perioperative plasma KYNA concentration might have resulted from degree of carotid stenosis and general atherosclerosis. Higher carotid stenosis causes greater disorders in cerebral circulation and severe general atherosclerosis increases risk of postoperative cerebral ischemia [55]. Hence, a multitude of factors that may affect plasma KYNA concentration in the perioperative period indicate than our research on this topic should be continued.

Conclusions

In conclusion, we demonstrated for the first time that in patients with an unstable carotid plaque, the plasma KYNA concentration was higher than in patients with stable carotid plaque. This finding suggests an involvement of plaque inflammation in KYNA content regulation. Moreover, this observation suggests that determination of KYNA levels may be considered as a marker of inflammation in atherosclerosis.

We found that in all studied groups an increase in plasma KYNA content was observed after surgery and this effect did not depend on anesthesia. The KYNA concentration was significantly higher after CS in patients with postoperative neurological disorders. Thus, our results suggest that monitoring changes in plasma KYNA concentration can indicate neurologic outcome in patients undergoing CS.

Acknowledgements

Conflict of interest

All authors declare that there is no conflict of interests regarding the publication of this article.

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