Carotid surgery affects plasma kynurenic acid concentration: A pilot study

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, PI). 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 anaesthesia just before induction of anaesthesia. The choice of anaesthesia depended on the type of surgery: regional anaesthesia was performed in patients scheduled for CEA, and local anaesthesia was performed in CAS patients. For regional anaesthesia, the deep and superficial cervical plexus were blocked using 0.5% bupivacaine hydrochloride (Bupivcaine, Polfa, PI) at the dose of 5 mg and 2% lidocaine hydrochloride (Xylocaine, Polfa, PI) at the dose of 10 mg. The local anaesthesia 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 neutrophil/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, C18 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 χ² 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 – β).

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 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).
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 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 spondyloarthopathies 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.
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.

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 | Before surgery | 1 h after surgery | 6 h after surgery | 24 h after surgery | 48 h after surgery |
|----------|-------|----------------|-------------------|-------------------|-------------------|-------------------|
| Group A  | Median | 399.75         | 392.63            | 468.05*           | 625.5**          | 515.63           |
| (n=32)   | [quartile 1 and 3] | [193.5, 556.58] | [225, 671.64]     | [267, 642.11]     | [252, 704.72]    | [218, 682.91]    |
| Group B  | Median | 558.71         | 789.91            | 831.6**           | 1245.13*         | 945.5*           |
| (n=8)    | [quartile 1 and 3] | [391.16, 889.5] | [549.75, 951.38]  | [720, 907.13]     | [1146.75, 1421.78] | [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           | 8.87*          | 9.46*         |
|          |           | [5.65, 8.27]   | [7.42, 10.84]  | [7.48, 11.2]  |
|          | NLR       | 3.51‡‡          | 7.02**         | 6.94*         |
|          |           | [2.35, 4.59]   | [6.35, 10.01]  | [5.73, 8.84]  |
| SCP-CEA  | WBC (K/µL) | 6.83           | 9.24**         | 8.12, 10.7    |
|          |           | [5.45, 7.34]   | [8.03, 10.87]  | [8.12, 10.7]  |
|          | NLR       | 1.99           | 5.82**         | 6.36*         |
|          |           | [1.33, 3.17]   | [4.74, 7.24]   | [4.18, 7.49]  |
| CAS      | WBC (K/µL) | 6.38           | 9.03***        | 7.83*         |
|          |           | [5.05, 6.92]   | [8.55, 10.59]  | [7.06, 9.21]  |
|          | NLR       | 2.08           | 6.67***        | 5.99**        |
|          |           | [1.31, 2.45]   | [4.81, 7.58]   | [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.
Significantly higher plasma KYNA concentrations were noted in surgery patients with postoperative neurologic disorders. Therefore, we propose plasma KYNA concentration and NLR during the early postoperative period as a marker of inflammation 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 that 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 neurological outcome in patients undergoing CS.

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Conflict of interest

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

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