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Subarachnoid and intracerebral hemorrhage in cocaine abusers

Subarahnoidalno i intracerebralno krvarenje kod korisnika kokaina

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Abstract

Background/Aim. Cocaine is an alkaloid extracted from the leaves of the plants *Erythroxylum coca* and *Erythroxylum novogranatense*. It can be taken orally, intranasally, intravenously, by inhalation, or intragenitally. Cocaine abuse can cause subarachnoid and intracerebral hemorrhage. The aim of this study was to determine cocaine and benzoylecgonine (BZ) concentrations in various body fluids and organs, the frequency of subarachnoid and intracerebral hemorrhage, and the relationship of concentration of cocaine and BZ in different body fluids with subarachnoid and intracerebral hemorrhage. **Methods.** The study analyzed a total of 26 autopsies reports from 2005 to 2018 with detected cocaine and/or BZ in the bodies during a forensic autopsy at the Institute of Pathology and Forensic Medicine, Military Medical Academy in Belgrade, Serbia. Brain tissue was taken for histopathological analysis and blood from the femoral vein, while urine, gastric content, brain, kidney, and liver with gallbladder samples were taken for toxicological analyses. **Results.** There were 26 autopsied patients aged 23 to 56 years (mean age 33.77±8.52); 20 (75.92%) were men and 6 (23.08%) were women. Cocaine was found in the blood of 12 (46.15%), in the urine of 15 (57.69%), and in the brain of 8 (30.77%) autopsied patients. BZ was found in the blood of 20 (76.92%), in the urine of 21 (80.77%), and in the brain of 10 (38.46%) autopsied patients. Subarachnoid hemorrhage was found in 10 (38.46%), intracerebral hemorrhage in 18 (69.23%), and both subarachnoid and intracerebral hemorrhage in 6 (23.07%) autopsied patients. Intracerebral (focal and perivascular) hemorrhage was more frequent. There were statistically significantly higher concentrations of both cocaine and BZ in most of the body fluids and organs of examinees with intracranial hemorrhage compared to examinees without hemorrhage. **Conclusion.** Subarachnoid and intracerebral hemorrhage were frequent findings in autopsied cocaine abusers. The correlation between subarachnoid and intracerebral hemorrhage and cocaine concentrations in blood was moderate. There were strong correlation between subarachnoid and intracerebral hemorrhage and BZ concentrations in almost all the samples.

Key words:
brain; cocaine; autopsy; blood; cerebral hemorrhage; cocaine-related disorders; subarachnoid hemorrhage.

Apstrakt

Uvod/Cilj. Kokain je alkaloid iz lišća biljki *Erythroxylum coca* i *Erythroxylum novogranatense*. Kokain se u organizam može uneti oralno, intranazalno, intravenski, inhalatorno i intragenitalno. Njegovom zloupotrebom mogu nastati subarahnoidalno i intracerebralno krvarenje. Cilj rada bio je da se prikažu koncentracije kokaina i benzoilekgonina (BZ) u telesnim tečnostima i organima, učestalost subarahnoidalnog i intracerebralnog krvarenja i povezanost tih krvarenja sa koncentracijama kokaina/BZ kod obdukovanih korisnika kokaina. **Metode.** Ispitivanje je obuhvatilo analizu 26 obdukcionih nalaza sa ustanovljenim prisustvom kokaina i/ili BZ iz baze podataka Instituta za patologiju i forenzičku medicinu Vojnomedicinske akademije u Beogradu, Srbija, za period 2005−2018. godine. Analizirane su vrednosti koncentracija kokaina i BZ u krvi, urinu, želudačnom sadržaju, mozgu, bubrezima i jetri sa žučnom kesom, kao i patohistološki nalaz mozga. **Rezultati.** Istraživanjem je obuhvaćeno 26 obdukovanih pacijenata starih od 23 do 56 godina (srednja vrednost 33,77 ± 8,52), 20 (75,92%) muškaraca i 6 (23,08%) žena. Toksikološko-hemijskom analizom nađen je kokain u krvi kod 12 (46,15%), u urinu kod 15 (57,69%) i u mozgu kod 8 (30,77%) obdukovanih pacijenata. U krvi je nađen BZ kod 20 (76,92%), u urinu kod 21 (80,77%) i u mozgu kod 10 (38,46%) obdukovanih pacijenata. Subarahnoidalno krvarenje ustanovljeno je kod 10 (38,46%), intracerebralno

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krvarenje kod 18 (69,23%), a subarahnoidalno i intracerebralno krvarenje zajedno kod 6 (23,07%) obdukovanih pacijenata. Intracerebralno (fokalno i perivaskularno) krvarenje bilo je češće. Koncentracije kokaina i BZ u telesnim tečnostima i organima kod obdukovanih pacijenata kod kojih je ustanovljeno intracerebralno i subarahnoidalno krvarenje bile su statistički značajno više nego kod onih koji nisu imali krvarenja. **Zaključak.** Subarahnoidalno i intracrebralno krvarenje su bili često zastupljeni kod obdukovanih pacijenata koji su koristili kokain. Korelacija između subarahnoidnog i intracerebralnog krvarenja i koncentracije kokaina u krvi bila je umerene jačine. Utvrđena je jaka korelacija između subarahnoidalnog i intracerebralnog krvarenja i koncentracija BZ u skoro svim analiziranim uzorcima.

Ključne reči:
mozak; kokain; autopsija krv; krvarenje, moždano; poremećaji izazvani kokainom; krvarenje, subarahnoidno.

Introduction

Cocaine is an alkaloid extracted from the leaves of the plants *Erythroxylum coca* and *Erythroxylum novogranatense*. There are two chemical forms of cocaine: hydrochloride salt and alkaloid, the so-called "freebase". It is usually taken orally, intranasally, intravenously, by inhalation, or intragenitally [1]. Cocaine is well absorbed, rapidly metabolized, and excreted. It is detected within 30 min in the blood or plasma. Maximal concentration of cocaine in plasma is reached between 50 and 90 min [2]. The elimination half-life of cocaine is between 30 min and 4 h, and it depends on the chronicity of abuse [3]. Most of cocaine is metabolized in the liver, except the amount of 1–9% that is excreted unchanged through the urine [4]. The two most important metabolites of cocaine are benzoylecgonine (BZ) and ecgonine methyl ester (EME) [5]. The effects of cocaine are dose-dependent and intake-dependent, and they depend on individual organism sensitivity of an user and other simultaneously used drugs. Low doses of cocaine lead to euphoria, increased motor activity, increased satisfaction, logorrhea, and rarely hallucinations. A high dose of cocaine causes hyperthermia, tachycardia, ventricular arrhythmia, elevated blood pressure, hallucinations, nausea, vomiting, anorexia, and suicidal ideas [6]. It is the second most commonly abused drug in Europe in the last twenty years with an increasing tendency. It is estimated that over 12,000,000 people in Europe aged 15 to 64 have tried cocaine at least once [7]. Cocaine abuse can frequently cause subarachnoid hemorrhage [8] and intracerebral hemorrhage [9].

The aim of this study was to analyze cocaine and BZ concentrations in the blood, urine, gastric content, liver with gallbladder, brain, and kidneys, as well as the frequency of subarachnoid and intracerebral hemorrhage, and the relationship of cocaine and BZ concentration in different body fluids with subarachnoid and intracerebral hemorrhage in cocaine abusers.

Methods

This retrospective study was conducted on archival material at the Institute of Pathology and Forensic Medicine, Military Medical Academy in Belgrade, Serbia. A total of 26 autopsy reports from 2005 to 2018 with detected cocaine and/or BZ in the organisms of autopsied patients during the forensic autopsy were analyzed. During the autopsies, brain tissue was taken to histopathological analysis and blood samples from the femoral artery, while urine, gastric content, brain, kidney, liver, and gallbladder tissue were taken for toxicological analyses.

Brain tissue samples were standardly processed. They were fixed in buffered 4% neutral formalin solution, dehydrated in increasing ethanol concentration, cleared by chloroform, infiltrated by wax in automatic tissue processing machine Leica ASP300S, (Germany) and paraffin-embedded by machine Thermo Scientific™ HistoStar™ (USA). Paraffin-embedded tissue blocks were clamped into a microtome Leica® RM2135 (Germany) for section cutting down to 4 µm thick, floated out on a water bath Leica HI1210 (Germany), picked up and placed on microscopic slides. The slides were then dried on a hot plate Leica HI1220 (Germany) for one h, dewaxed by xylene, hydrated by decreasing ethanol concentrations and water, and stained by hematoxylin and eosin (HE) staining.

Multistainer Leica ST5020 (Germany) did HE staining. When a stain was completed, the section was covered with a coverglass by DPX by automated glass coverslipper machine Leica® CV5030 (Germany). Microscopic slides were analyzed by microscope Olympus BX43 (Germany) with camera Olympus SC 50 (Germany) and software for digital photo analysis CellSense.

Brain, kidney, and liver with gallbladder tissues were prepared for toxicological analysis according to Stas-Otto-Ogier-Kohn-Abrest. Minced tissue was treated with 95% ethanol, previously acidified with tartaric acid. The proportion of the tissue sample to ethanol was 1 : 2. Alcoholic extract was filtered and evaporated into a syrup. It was distilled off under a vacuum, and the result was aqueous residue that was treated with petroleum-ether at the temperature of 60 °C to remove the fatty components. Each step of the procedure was repeated twice. The residue was treated with sodium hydrogen carbonate and taken to dryness by ether. The dry extract was mixed with 5% methanol and internal standards. The mixture was analyzed using High-Performance Liquid Chromatography (HPLC) with UV detection (Bio-Rad Diagnostics Group, Hercules, USA) and compared to the toxicological UV spectra library.

Blood, urine, and gastric content samples were prepared for toxicological analysis through the following steps: addition of 100 mL of ammonia solution (Merck, Germany) and 5 mL of chloroform (Merck, Germany), 20 min of mixing, centrifugation for 10 min at 3,000 rotations per min and evaporated to dry extract. The dry extract was analyzed using (HPLC) with UV

detection (Bio-Rad Diagnostics Group, Hercules, USA) and compared to the toxicological UV spectra library.

Data were statistically analyzed using the software package IBM SPSS Statistics Version 24. Descriptive statistical methods (minimal and maximal values, mean value ± standard deviation, frequencies) were used. Relation between variables was measured using nonparametric Mann-Whitney test and nonparametric correlation using Spearman's correlation test. The level of statistical significance was $p < 0.05$.

Results

There were 26 autopsied patients included in this study, aged 23 to 56 (33.77 ± 8,520) years, 20 (75.92%) men and 6 (23.08 %) women. BZ was detected in more blood, urine, and gastric content samples than cocaine; as well, BZ was detected in more tissue samples of the brain, kidney, and liver with the gallbladder. Cocaine was found in the blood in 12 (46.15%) autopsied patients, in the urine in 15 (57.69%), in the gastric content in 12 (46.15%), in the liver with gallbladder in 8 (30.77%), in the brain of 8 (30.77%), and in the kidneys in 8 (30.77%) of post-mortem examined patients. BZ was detected in the blood of 20 (76.92%) autopsied patients, in the urine of 21 (80.77%), in the gastric content of 16 (61.54%), in the liver with gallbladder of 14 (53.85%), in the brain of 10 (38.46%), and in the kidneys of 13 (50%) autopsied patients.

Cocaine and BZ concentrations in various samples were presented in Table 1.

The leading cause of death in all the autopsied patients was acute cocaine intoxication.

Intracranial (subarachnoid and intracerebral) hemorrhage was revealed during gross examination during autopsy and histopathologically confirmed by microscopic analysis of brain tissue in all samples. Subarachnoid hemorrhage was found in 10 (38.46%) autopsied patients. Intracerebral hemorrhage was found in 18 (69.23%) autopsied patients, including focal intracerebral hemorrhage in 4 (15.38%) (Figure 1), perivascular intracerebral hemorrhage in 6 (23.08%) (Figure 2), and both focal end perivascular intracerebral hemorrhage in 8 (30.77%) autopsied patients. Subarachnoid and intracerebral hemorrhage both were found in 6 (23.07%) autopsied patients.

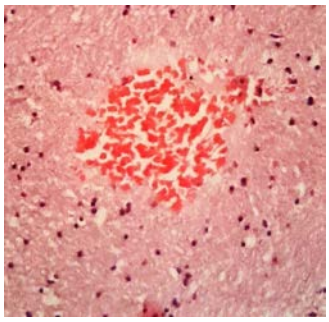

Fig. 1 – Acute focal intracerebral hemorrhage (hematoxylin eosin staining, 100×).

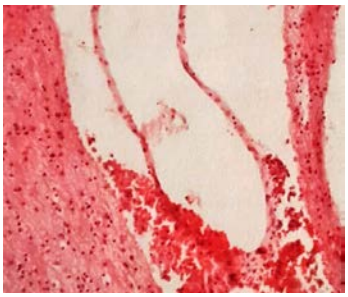

Fig. 2 – Acute perivascular intracerebral hemorrhage (hematoxylin eosin staining, 40×).

Frequencies of currently detected cocaine and BZ in various samples with subarachnoid and intracerebral hemorrhage are presented in Table 2.

Table 1

Cocaine and benzoylecgonine (BZ) concentrations in body fluids and organs

Sample	Cocaine			BZ		
	min	max	MV ± SD	min	max	MV ± SD
Blood (mg/L)	0.040	20.380	2.481 ± 5.766	0.009	10.420	1.278 ± 2.398
Urine (mg/L)	0.040	71.880	15.459 ± 25.279	0.350	684.720	63.984 ± 151.060
Gastric content (mg/L)	0.172	825.560	76.900 ± 236.008	0.003	26.190	3.441 ± 6.577
Brain (mg/g)	0.008	36.370	7.025 ± 13.562	0.0003	1154.520	118.652 ± 365.021
Kidneys (mg/g)	0.066	37.290	8.045 ± 14.620	0.005	539.550	43.022 ± 149.252
Liver with gallbladder (mg/g)	0.007	250.310	34.040 ± 87.697	0.0004	1309.750	98.933 ± 349.469

Min – minimum; Max – maximum; MV – mean values; SD – standard deviation.

Table 2

Frequencies of currently detected both cocaine and benzoylecgonine (BZ) in various samples of examinees with subarachnoid and intracerebral hemorrhage

Sample	Subarachnoid hemorrhage n (%)	Intracerebral hemorrhage n (%)	Subarachnoid and intracerebral hemorrhage, n (%)
Blood	9/10 (90)	7/18 (38.88)	5/6 (83.33)
Urine	10/10 (100)	11/18 (61.11)	6/6 (100)
Gastric content	8/10 (80)	10/18 (55.55)	6/6 (100)
Brain	5/10 (50)	8/18 (44.44)	5/6 (83.33)
Kidneys	6/10 (60)	8/18 (44.44)	6/6 (100)
Liver with gallbladder	5/10 (50)	8/18 (44.44)	5/6 (83.33)

The ratio between cocaine and BZ concentrations in samples of post-mortem examined patients with subarachnoid and intracerebral hemorrhage is shown in Table 3.

Vasculitis (infiltration of neutrophils in vessel's wall) was found histopathologically in one autopsied patient. In addition, blood vessel spasm was found in one autopsied patient, too. There was histologically revealed atherosclerosis in two cases, of which additionally thrombus was found in one, and microaneurism in the other.

Statistical analyses have shown statistically significant difference in the concentration of cocaine in the blood (p = 0.0088), gastric content (p = 0.244), liver with gallbladder (p = 0.0366), and brain (p = 0.03) between autopsied patients with and without subarachnoid hemorrhage.

There was no statistically significant difference in cocaine concentrations in the urine (p = 0.1141) and kidneys (p = 0.9296) between cases with and without subarachnoid hemorrhage.

Statistically significant difference was found in concentrations of cocaine in the blood (p = 0.034), urine (p = 0.0434), gastric content (p = 0.006), liver with gallbladder (p = 0.36), and brain (p = 0.0367) between autopsied patients with and without intracerebral hemorrhage.

There was no statistically significant difference in cocaine concentration in the kidneys (p = 0.1739) between cases with and without intracerebral hemorrhage.

Statistically significant difference was found in BZ concentrations in the blood (p = 0.027), urine (p = 0.0011), kidneys (p = 0.0041), liver with gallbladder (p = 0.0002), and brain (p = 0.0096) between cases with and without subarachnoid hemorrhage.

There was no statistically significant difference between BZ concentrations in the gastric content between cases with and without subarachnoid hemorrhage (p = 0.2187).

Statistically significant difference was found in BZ concentrations in the blood (p = 0.008), urine (p = 0.0006), kidneys (p = 0.0164), liver with gallbladder (p = 0.0002), and brain (p = 0.0025) between cases with and without intracerebral hemorrhage.

There was no statistically significant difference in BZ concentrations in the gastric fluid between cases with and without intracerebral hemorrhage (p = 0.5419).

Subarachnoid hemorrhage was statistically significantly often found in men (p = 0.0178). There was no statistically significant difference between genders in intracerebral hemorrhage presence (p = 0.63).

Correlation between cocaine and BZ concentrations in different body samples and subarachnoid and intracerebral hemorrhage presence was presented in Table 4.

Discussion

Most of the post-mortem examined patients in our study were men, which is similar to the data of the European Poison Control Centre [7]. The estimated cocaine concentrations in the blood of the autopsied patients in this study were between 0.040 mg/L and 20.380 mg/L, and those of BZ between 0.009 mg/L and 10.420 mg/L. A wide range difference of concentrations of cocaine and BZ could be attributable to cocaine pharmacokinetics, as it was confirmed in the study of Pilgrim et al. [10] in which concentrations of cocaine and BZ in the blood were found in the range between 0.01 and 3.0 mg/L in 49 autopsies of the cases with sudden death.

Having in mind the fact that blood fluctuation and metabolism stop at the moment of death, the ratio between cocaine and BZ concentration could lead to a conclusion

Table 3

Ratio between cocaine and benzoylecgonine (BZ) concentrations in samples of examinees with subarachnoid and intracerebral hemorrhage

Subarachnoid hemorrhage		Intracerebral hemorrhage	
cocaine/BZ in blood	cocaine/BZ in brain	cocaine/BZ in blood	cocaine/BZ in brain
0.320/0.170 (1.88)	18.950/1.590 (9.72)	4.060/10.420 (0.39)	18.950/1.590 (9.72)
4.060/10.420 (0.39)	36.370/0.020 (1.82)	0.070/0.610 (0.11)	36.370/0.020 (1.82)
0.410/1.490 (0.28)	0.064/0.238 (0.27)	0.410/1.490 (0.28)	0.064/0.238 (0.27)
20.380/4.120 (4.95)	0.071/0.125 (0.57)	20.380/4.120 (4.95)	0.071/0.125 (0.57)
0.040/0.040 (1.00)	0.070/0.005 (14.00)	1.235/0.204 (6.05)	0.008/0.003 (25.33)
0.120/0.260 (0.46)		1.870/2.070 (0.90)	0.123/0.016 (7.60)
0.1235/0.2043 (0.60)		0.130/1.830 (0.07)	0.070/0.005 (14.00)
0.280/0.400 (0.07)			

Note: concentrations in blood are expressed in mg/L and those in brain in mg/g.

Table 4

Correlation coefficient (r) as measure of the relationship between subarachnoid and intracerebral hemorrhage and concentrations of cocaine and benzoylecgonine (BZ)

Sample	Subarachnoid hemorrhage		Intracerebral hemorrhage	
	cocaine	BZ	cocaine	BZ
Blood	0.688	0.397	0.581	0.526
Urine		0.006	0.026	0.945
Gastric content	0.422		0.108	
Brain	0.356	0.635	0.071	0.711
Liver with gallbladder	0.101	0.775	0.052	0.971
Kidneys		0.770		0.365

r > 0.7 – strong correlation; 0.5 < r < 0.7 – moderate correlation; r < 0.5 – weak correlation.

about the duration of cocaine abuse. High cocaine and low BZ concentration or BZ absence indicate acute cocaine intoxication. BZ presence and cocaine absence in brain tissue indicates chronic cocaine abuse [11].

The ratio between cocaine and BZ concentrations can approximately indicate the time of cocaine intake of autopsied patients. Cocaine has a very short elimination half-life, thus it can be absent in samples while BZ is present. In a situation when the concentration of BZ in the brain is lower than in the blood, cocaine intake is estimated to be two hours or less before death. In our study, this was the case in seven autopsied patients, among which both subarachnoid and intracerebral hemorrhage were found in three cases and intracerebral hemorrhage in two cases. In the case of cocaine concentrations being a few times higher than BZ concentrations, the intake of cocaine was just before the death, as it was in two cases with subarachnoid hemorrhage and five cases with intracerebral hemorrhage in our study. BZ concentration in the brain higher than in the blood indicates chronic cocaine abuse, as it was in two autopsied patients in our study, one with subarachnoid and another with intracerebral hemorrhage [3]. According to the correlation coefficient, a moderate relationship was found between subarachnoid hemorrhage and cocaine concentrations in the blood, as well as between intracerebral hemorrhage and cocaine concentrations in the blood. A weak relationship was found between subarachnoid hemorrhage and cocaine concentration in gastric content and brain.

According to the correlation coefficient, a strong correlation between subarachnoid hemorrhage and BZ concentrations in the kidneys and liver with gallbladder was found. The correlation was also strong between intracerebral hemorrhage and BZ concentration in the brain, urine, and liver with gallbladder. A moderate correlation was found between subarachnoid hemorrhage and BZ concentrations in the brain and between intracerebral hemorrhage and BZ concentrations in the blood. A weak correlation was found between subarachnoid hemorrhage and BZ concentrations in the blood and intracerebral hemorrhage and BZ concentrations in the kidneys.

Both concentrations of cocaine and BZ in the blood had a moderate correlation with subarachnoid and intracerebral hemorrhage. The study on seven examinees has shown that the concentration of cocaine in the blood leads to an increase in systolic and diastolic blood pressure, which can cause blood vessel rupture and intracranial hemorrhage [12].

In a study on newborn pigs, the impact of cocaine and its metabolites on cerebral arterioles was studied. It was found that a greater amount of cocaine and BZ and higher concentrations in body fluids cause vasoconstriction of cerebral arterioles. Vasospasm was in a strong correlation with the dosage of cocaine intake and concentrations of cocaine and BZ in body fluids [13].

Stroke is more common in people that have used cocaine in alkaloid form than in the form of hydrochloride salt [14]. The relationship between cocaine and stroke leads to the risk of early onset of stroke. Some authors recommend toxicological analysis of urine and blood in stroke in young adults because of suspicious connection of cocaine and stroke [15]. The young age for stroke onset is between the 20s and 50s, as it was in our study with examinees aged between 23 and 56 years [16]. According to the literature data, arterial hypertension is the main reason for hemorrhagic stroke [17]. The indirect sympathomimetic effect of cocaine temporarily increases systolic arterial blood pressure, which can cause spontaneous bleeding from existing arteriovenous malformations, aneurysms, parts of the brain previously affected by stroke, or can cause new aneurysm [18]. Cocaine also causes an increase in blood pressure in people with hypertensive cerebral vasculopathy in subcortical brain regions, which leads to intracerebral hemorrhage, especially in those regions of the brain [19]. The results of this cohort study have shown that patients with toxicologically detected cocaine had higher arterial blood pressure values, increased risk of intraventricular cerebral hemorrhage, and greater mortality than the patients who had negative drug screens for cocaine. The most frequent localization of intracerebral hemorrhage in that study was in subcortical regions [20]. Cocaine usually leads to intracerebral hemorrhage in the basal ganglia and thalamus [3]. The way cocaine affects the intracranial hemorrhage development in autopsy cases of cocaine-related cerebrovascular disease, without histopathological changes on brain blood vessels, is still unknown [21].

Subarachnoid hemorrhage due to cocaine abuse is usually caused by arterial aneurysm rupture [22]. Aneurism rupture in cocaine abusers is more often localized in anterior and medial cerebral artery blood supply, unlike in other people where it is localized in posterior cerebral artery supply [23].

During a gross examination of autopsied patients with subarachnoid hemorrhage in our study, no arterial aneurysm was found. In spite of that, during the histopathological examination, wall thinning and dilatation of blood vessels were present in one case, which points to microaneurysm. Cocaine causes vasospasm in blood vessels, thrombosis, hypertensive vasculitis, necrotizing arteritis, thicking of the *tunica intima* of blood vessels, and atherosclerosis [24]. Vasospasm, which was detected in one case in our study, is considered a complication of subarachnoid hemorrhage, even though in cocaine abusers chronic vasospasm is caused by changes in *tunica media* and elastic lamina of blood vessels in the brain. Vasospasm leads to intimal hyperplasia by thrombocytes aggregation and activation. The wall of blood vessels becomes thicker and the obstruction occurs. Long-term cocaine abuse can cause atherosclerosis, intimal thinning, and periadventitial fibrosis of blood vessels [25]. In our study, atherosclerosis was found in two autopsied patients with BZ concentrations higher in the brain than in the blood. It can be concluded that the abuse of cocaine was chronic in those patients. Cocaine leads to an increase in plasma lipid concentrations, direct and indirect cholesterol concentrations, endothelial permeability, and more frequent inflammatory cells infiltration in atherosclerotic plaques [4]. Radiological studies using angiography examination during autopsy show vascular lesions in 78% of cocaine abusers with subarachnoid hemorrhage and 48% of cocaine abusers with intracerebral

hemorrhage. The most common vascular lesions in people with subarachnoid hemorrhages are saccular aneurysms of the anterior communicating artery, in spite of people with intracerebral hemorrhages who had arteriovenous malformations [26]. According to the study of Kibayushi et al. [27] on the evaluation of chronic changes of blood vessels in the brain, 36.84% of autopsied patients did not have vasculopathy. In our study based on histopathological examination of brain tissue, there were no morphological changes in blood vessels in the brain in 66.66% of cases. Therefore, vasculopathy is not the only cause of intracerebral hemorrhage in cocaine abusers.

In our study, mean values of cocaine and BZ concentrations in the blood and organs of post-mortem examined patients with intracranial hemorrhage were higher than in cases without hemorrhage. It can be concluded that a greater amount of cocaine intake can cause intracranial hemorrhage, regardless of the blood vessels' damage.

Histopathological analysis showed inflammatory infiltrate in the wall of blood vessels in one case. Cocaine-induced vasculitis is a rare complication of abuse and it consists of perivascular inflammatory infiltrate, partial damage of blood vessels' wall, and vascular thrombosis [28, 29]. Besides cocaine, adulterant levamisole can cause vasculitis [30]. In our study, levamisole was toxicologically detected in one case, in the so-called "body packer" [31].

Conclusion

Subarachnoid and intracerebral hemorrhage in autopsied patients, cocaine abusers, was frequent. Intracerebral (focal and perivascular) hemorrhage was more frequent. There were statistically significant higher concentrations of both cocaine and BZ in most of the body fluids and organs of autopsied patients with intracranial hemorrhage compared to the cases without hemorrhage. The correlation between subarachnoid and intracerebral hemorrhage and cocaine concentrations in the blood was moderate. There were strong correlation between subarachnoid and intracerebral hemorrhage and BZ concentrations in almost all samples.

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