Journal of Neurology & Experimental Neuroscience

https://doi.org/10.17756/jnen.2018-032

Research Article

Open Access

Acute Cocaine Exposure and Cerebrovascular Diseases: A Retrospective Clinical Study and Literature Review

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Received: November 13, 2017
Accepted: January 31, 2018
Published: February 02, 2018

Citation: Si X, Luo JJ. 2018. Acute Cocaine Exposure and Cerebrovascular Diseases: A Retrospective Clinical Study and Literature Review. *J Neurol Exp Neurosci* 4(1): 1-6.

Published by United Scientific Group

Abstract

Objective: To evaluate cocaine as a risk factor for Cerebrovascular Diseases (CVD).

Introduction: Illicit substance consumption is an independent risk factor for CVD, however studies on such substances, particularly cocaine, and their relationship to the occurrence of CVD in gender, age, and race are sparse.

Methods: A retrospective chart review of the patients with International Classification of Diseases, 9th revision (ICD-9) diagnostic code of 430-437 between January 1, 2003 to December 31, 2005 was performed. Three major CVD including Subarachnoid Hemorrhage (SAH, ICD-9 code: 430), Intracerebral Hemorrhage (ICH, 431), and cerebral artery occlusion with infarction (Infarct, 434.91) were included. Urine Drug Screen (UDS) was performed on admission. Patients who did not receive UDS were excluded. Patients were divided into Cocaine-Positive (CP) and Cocaine-Negative (CN) groups and further sub-groups based on the gender, age, race, and comorbidities.

Results: 562 CVD patients who had UDS were included. They were grouped into SAH (17.1%), ICH (31.3%) and infarct (51.6%) and then further sub-grouped as follows: SAH-CP: (15.6% = 15/96, patients/total numbers of the group patients; Male/Female = 7/8, age: 46.4 ± 9.4 years, mean ± SD) and SAH-CN (84.3% = 81/96, M/F = 48/33, 45.1 ± 14.2); ICH-CP (14.8% = 26/176, M/F = 8/18, 48.5 ± 7.4) and ICH-CN (85.2% = 150/176, M/F = 58/92, 54.7 ± 14.5); and infarcts-CP (10.3% = 30/290, M/F = 12/18, 45.3 ± 6.5) and infarcts-CN (89.7% = 260/290, M/F = 110/150, 53.4 ± 15.5). Our findings confirmed that cocaine: 1) facilitates the occurrence of ICH and infarcts, particularly in patients younger than 50 years ($p < 0.05$); 2) promotes ICH in the African American than non-African American ethnicity ($p < 0.05$); 3) displays no significant difference in genders and in subjects with or without cardiomegaly in promoting CVD.

Discussion/Conclusion: Cocaine may play discrete roles in promoting the onset of CVD in gender, age, race and comorbidities.

Keywords

Age, Cerebrovascular disease, Cocaine, Ethnicity, Gender, Hemorrhagic stroke, Ischemic stroke

Introduction

Human consumption of cocaine can be traced back to South American Indians for more than 2000 years ago, but there was no understanding of its risk

for CVD until much later [1].The risk of cocaine for stroke has generally been underestimated, preventing it from receiving much needed attention. Currently, strokes have become more prevalent in younger people. The first report of cocaine-associated stroke was in 1977 describing a male case using intramuscular injection followed one hour later by aphasia and right sided hemiparesis [1]. Subsequently, abundant evidence supports the relationship between substance abuse and stroke. Cocaine is one of the most commonly abused drugs in the USA and has been recognized as an independent risk factor for CVD [2-4]. The probability of stroke increases significantly in drug users to 4–14 times greater than that in non-drug users [5]. Approximately 5% to 8.5% of strokes occur in young adults [6] and approximately 5% of young people die of stroke. The average cost associated with hospital stays was $34,886 for ischemic CVD, $146,307 for SAH, and $94,482 for ICH [7].

Cocaine causes serious medical complications among drug abusers [8], which can become a devastating medical problem. Cocaine has been recognized as a significant risk factor for ICH and ischemic stroke (infarct) [9] in general populations. However, there is discrepancy in studies on cocaine related to CVD in gender, age, and race. This study was to evaluate the possible causal relationship between cocaine consumption and the onset of different types of CVD in subpopulations of age, gender, ethnicity and comorbidities.

Methods

This retrospective study was conducted in the entire adult CVD-patient population, aged at 18 years and above, admitted to University of Mississippi Medical Center (UMC) between January 1, 2003 to December 31, 2005 to evaluate whether there are increased risks for CVD in cocaine use. The UMC is located in Jackson, the capital city of Mississippi, and is the only state hospital in Mississippi. Charts were initially reviewed and CVD cases were collected by the discharge diagnostic codes (International Classification of Diseases, 9th revision, ICD-9 codes 430 to 437).

Ischemic stroke includes occlusion and stenosis of precerebral arteries (ICD-9:433), occlusion of cerebral artery with infarction (ICD-9:434.91), transient cerebral ischemia (ICD-9:435), acute but ill-defined CVD (ICD-9:436), and other and ill-defined CVD (ICD-9:437). Hemorrhagic stroke included subarachnoid hemorrhage (SAH, ICD-9:430), intracerebral hemorrhage (ICH, ICD-9:431), and unspecified intracranial hemorrhage (NS-ICH, ICD-9:432). ICH included intraparenchymal hemorrhage such as in the cerebral hemisphere, cortex, basal ganglion, thalamus, brainstem, and cerebellum. Subdural hemorrhage and non-traumatic extracranial hemorrhage are listed in the non-specific cranial hemorrhage group and were not included in this study. The term "hemorrhagic stroke" refers to the combination of ICH and SAH.

Among the above described diagnoses, the majority of patients fell into three categories: SAH, ICH, and Infarct. The diagnoses of infarct, SAH and ICH were made based on the diagnostic criteria of the National Institute of Neurological Disorders and Stroke [10].

All CVD patients who had a UDS at admission were included in the study. Patients who did not receive UDS were excluded. They were divided into two groups: CP and CN according to the UDS results regardless of which route or species of the cocaine was consumed. The two groups of subjects were further divided into subgroups by the diagnostic codes, gender, race, and age such as (younger or older than 50 years). All patients had a chest radiograph. They were divided into two subgroups based on either presence or absence of cardiomegaly as evaluated by the chest radiograph. Patients with cardiomegaly may suggest presence of a cardiac decompensation from a long-standing period of hypertension or cardiopulmonary complications. Brain image studies including computerized tomography (CT), CT angiogram (CTA), magnetic resonance imaging (MRI), MR angiogram (MRA) or conventional angiogram were employed to evaluate whether there was a presence of infract, ICH, SAH or intracranial vascular malformations, including aneurysm and arteriovenous malformation, which have been recognized as the common causes of spontaneous SAH.

The data of those groups and subgroups (such as CVD types, age, gender, and race) were analyzed using two-tailed *Chi-square* tests. A p value less than 0.05 was considered statistically significant.

Results

A total number of 1,473 charts of stroke patients were initially reviewed. Among them 562 CVD subjects who had a UDS test were included (Table 1). They were grouped into SAH (96 or 17.1%), ICH (176 or 31.3%) and infarct (290 or 51.6%) and then further sub-grouped into SAH-CP (UDS-positive: 15 or 15.6%; male/female = 7/8; age = 46.4 ± 9.4 years, mean ± SD) and SAH-CN (UDS-negative: 81 or 84.3%; M/F = 48/33; age = 45.1 ± 14.2); ICH-CP (26 or 14.8%; M/F = 8/18; age = 48.5 ± 7.4) and ICH-CN (150 or 85.2%; M/F = 58/92; age = 54.7 ± 14.5); and infarcts-CP (30 or 10.3%; M/F = 12/18; age = 45.3 ± 6.5) and infarcts-CN (260 or 89.7%; M/F = 110/150; age = 53.4 ± 15.5).

Table 1: Clinical data of participants.

CVD	Numbers	UDS	[% of UDS. CVD]	[% of total UDS]	UDS(+)	[% of UDS]	UDS (-)	[% of UDS]
SAH	342	96	28.1	17.1	15	15.6	81	84.3
ICH	413	176	42.6	31.3	26	14.8	150	85.2
Infarct	718	290	40.4	51.6	30	10.3	260	89.7
Sum	1473	562	38.1	100	71	12.6	491	87.4

Note: CVD: cerebrovascular diseases, **SAH:** subarachnoid hemorrhage, **ICH:** intracerebral hemorrhage, **UDS:** urine drug screen, **UDS(+):** UDS test positive, **UDS(-):** UDS test negative.

Subsequently, whether cocaine consumption plays a discrete role on subjects of younger or older than 50 years in

facilitating development of CVD was evaluated. Significantly increased frequency of strokes was observed in the younger subjects than the older ones in the CP subgroups, such as ICH (p = 0.04) and infarct (p = 0.0001) but not SAH (p = 0.71) (Table 2), indicating cocaine may facilitate the occurrence of CVD more in younger than older individuals.

Table 2: Age in strokes with cocaine positives and cocaine negatives.

	Age	CN	%	CP	%	P	Subtotal
SAH	<50	50	83.3	10	16.7		60
	>50	31	86.1	5	13.9	0.71	36
ICH	<50	60	78.9	16	21.1		76
	>50	90	90	10	10	0.04	100
Infarct	<50	101	80.2	25	19.8		126
	>50	159	97	5	3	0.001	164

Note: SAH: subarachnoid hemorrhage, **ICH:** intracerebral hemorrhage, **CN:** cocaine negative, **CP:** cocaine positive.

To evaluate if ethnicity plays a role regarding the onset of CVD, the frequency of CVD was compared in CP with CN in African-Americans (AA) and non-AA subgroups. Table 3 showed that AA were more prone to having ICH (p = 0.01) than infarct (p = 0.4). An increased trend in SAH was observed in AA but did not reach a statistically significant level (p = 0.08), which might be due to the small samples.

Table 3: Race in stroke with cocaine positives and cocaine negatives.

		CN	CN %	CP	CP %	P	Subtotal
SAH	Non-AA	29	93.5	2	6.5		31
	AA	50	79.4	13	20.6	0.08	63
ICH	Non-AA	49	96.1	2	3.9		51
	AA	101	79.5	26	20.5	0.01	127
Infarct	Non-AA	62	92.5	5	7.5		67
	AA	198	88.8	25	11.5	0.4	223

Note: SAH: subarachnoid hemorrhage, **ICH:** intracerebral hemorrhage, **AA:** African Americans, **CN:** cocaine negative, **CP:** cocaine positive.

Gender seemed not to be an amenable factor in cocaine-related CVD when comparing CP and CN subgroups, such as SAH (p = 0.4), ICH (p = 0.4) and infarct (p = 0.8) (Table 4). Additional analyses on cardiomegaly as a comorbidity failed to show a significant difference in the occurrence of hemorrhagic (p = 0.8) or ischemic strokes (p = 0.6) in our patients (Table 5).

Discussion

In this retrospective clinical study, we observed and confirmed that cocaine exposure increases the occurrence of ICH and infarcts in patients younger than 50 years and, particularly, ICH in the African American ethnicity (Table 2-3). However, cocaine exposure may have no significantly different effects on promoting CVD in genders and in subjects with or without cardiomegaly (Table 4-5).

Table 4: Gender in strokes with cocaine positives and cocaine negatives.

		CN	CN %	CP	CP %	P	Subtotal
SAH	Male	33	80.5	8	19.5		41
	Female	48	87.3	7	12.7	0.4	55
ICH	Male	92	83.6	18	16.4		110
	Female	58	87.9	8	12.4	0.4	66
Infarct	Male	150	89.3	18	10.7		168
	Female	110	90.2	12	9.8	0.8	122

Note: SAH: subarachnoid hemorrhage, **ICH:** intracerebral hemorrhage, **CN:** cocaine negative, **CP:** cocaine positive.

Table 5: Cardiomegaly in strokes of cocaine positives and cocaine negatives.

		Cardiomegaly (-)	(-)%	Cardiomegaly (+)	(+)%	Subtotal	p
ICH	CN	107	82.3	23	17.7	130	
	CP	16	66.7	8	33.3	24	0.8
Infarct	CN	174	79.8	44	20.2	218	
	CP	16	84.2	3	15.8	19	0.6

Note: ICH: intracerebral hemorrhage, **CN:** cocaine negative, **CP:** cocaine positive.

Cocaine, the alkaloid benzoylmethylecgonine, is highly lipophilic and traverses the blood-brain barrier rapidly. Cocaine blocks monoamine reuptake, particularly those related to dopamine [11], and induces changes in dopamine level mostly prominently in mesocorticolimbic neurons [12]. Augmentation of mesocorticolimbic dopamine function may be associated with cerebral ischemia since dopamine may control local blood flow by inducing vasospasm of smooth muscles lining the cerebral vessels [13], particularly those of the middle cerebral artery [11, 13].

The vasoconstriction effect of cocaine is due to its sympathomimetic action, inhibiting the reuptake of noradrenaline, serotonin and dopamine at pre-synaptic nerve terminals. Cocaine induced cerebral vasospasm is relatively specific to dopamine rich brain areas and dopamine pathways play a central role in controlling cerebral blood flow (CBF) [6], and the effect is dose-dependent [6]. About 80% of the infarcts occur in the territory of the middle cerebral artery [11, 13], typically in young adults without preexisting vascular malformations [14]. Deep cortical brain regions may be more susceptible to dopamine's vasospastic effects while norepinephrine may facilitate constriction of large cranial arteries [15].

Chronic cocaine use increases platelet levels, enhances adenosine diphosphate platelet activation, and augments sporadic release of platelet-bound α granules, which may facilitate thrombus formation [16]. Laboratory studies show that cocaine causes an enhanced response of platelets to arachidonic acid, leading to increased thromboxane production and platelet aggregation and pathological changes in the cerebral vasculature [17]. Additionally, cocaine promotes platelet response to arachidonic acid, thereby stimulating

thromboxane production and platelet aggregation [18]. Chronic cocaine use, causing fluctuations between vasospasm and reperfusion, may result in vessel damage [17].

Cocaine's vasospastic effects can persist beyond its half-life [19] because its major metabolites (benzoylecgonine and norcocaine) are also potent vasoconstrictors [16] and bradykinin-mediated endothelium-dependent relaxation is impaired in chronic cocaine users [20]. Cocaine and its metabolites can be detected in the body for up to 3 days – or longer in the chronic cocaine users. Importantly brain perfusion deficits can occur in the absence of clinically detectable symptoms [21] and may persist in abstinent cocaine addicts for 6 months [22] or longer [23]. Interestingly, while cocaine abuse was associated with an increased risk, methylphetamine abuse was not associated with increased risk of ischemia [24] although both amphetamine and cocaine use have been reported to be associated with cerebral vasculitis [25]. Cocaine causes cardiac arrhythmias and cardiomyopathy [26] which could produce brain infarction due to cardiac embolism.

The use of cocaine is associated with both ischemic and hemorrhagic CVD, with the incidence of hemorrhagic prevailing over ischemic [3]. Rapid reperfusion of the previously ischemic areas may conversely result in hemorrhage [27]. Crack cocaine seems to be associated with both ischemic and hemorrhagic CVD, whereas cocaine hydrochloride causes mainly ICH and SAH [28]. A high risk of stroke occurs shortly after use of cocaine as the onset of stroke symptoms was usually found immediately or within 3 hours after cocaine use [1, 11]. Cocaine-induced hemodynamic changes may be related to ICH [29], particularly in active cocaine users [30], with higher risk of aneurysm rupture causing subarachnoid hemorrhage [30], worse functional outcomes and higher mortality when compared to non-cocaine-users [31]. Autopsy studies demonstrated a higher incidence of hypertensive cardiovascular disease in cocaine-induced hemorrhagic stroke [32]. Cocaine has been recognized as an independent risk factor for cerebral vasospasm after aneurysmal SAH.

Our study confirmed the previous claims that cocaine exposure facilitates the onset of hemorrhagic and ischemic strokes, particularly in individuals younger than 50 years, supporting the notion that cocaine is an independent risk factor for CVD [4]. In agreement with the previous study [30], our findings also confirmed that cocaine exposure promotes more ICH, but not ischemic stroke, in AA when compared to non-AA, supporting the claim that the AA ethnicity has a higher incidence of illicit drug-related CVD [30].

Our current findings failed to show a significant gender difference of CVD after cocaine exposure which suggested that cocaine may exert relatively equal effects on provoking CVD in men and in women although previous studies showed that cocaine exposure increases CVD more in men than in women [3].

Treatment in chronic cocaine users improves CBF. A calcium antagonist dihydropyridine (isradipine) is a potent cerebral vasodilator, particularly in dopamine-innervated brain regions. Protective effects of isradipine have been documented on cerebral neuronal cells from ischemic [33] insults by counteracting cocaine-induced vasospasm [34], improving CBF, reversing cerebral ischemia and preventing the consequent neuronal cell injury [33] in dopamine-rich brain areas such as the inferior parietal, putamen, and superior temporal lobe [34], but no effect on striatal blood flow and glutamate levels [35].

Modification of N-methyl-D-aspartate (NMDA) receptors and glutamate functions may be therapeutic targets for cocaine users. The non-competitive NMDA receptor antagonists, i.e. amantadine and memantine, the partial NMDA receptor agonist D-cycloserine, and the anticonvulsants topiramate and perampanel [36] may have therapeutic effects in cocaine dependence [36]. Kappa opiate receptor agonists may also modulate glutamate transmission and prevent ischemic damage [3]. For example, the kappa opiate antagonist buprenorphine decreases cocaine-induced perfusion abnormalities in chronic cocaine polydrug users [37].

Prostaglandin synthesis is enhanced by cocaine. Aspirin blocks this process by irreversibly inhibiting the action of cyclo-oxygenase in platelets by which aspirin reduces cocaine-induced thrombogenesis. Clinical observation showed that aspirin (325 mg/day for 4 weeks) improved CBF in chronic cocaine users [38] but is unlikely to recover acute cerebral ischemia. Intravenous tissue plasminogen activator (tPA) in patients with cocaine-associated acute ischemic stroke showed comparable outcomes with those of tPA-treated non-cocaine patients with acute ischemic stroke [39].

The potassium-sparing diuretic amiloride may potentially be useful in treating ischemia in cocaine addicts [38]. *In vitro* and *in vivo* studies showed antiplatelet aggregation actions of 5-HT_2-receptor antagonists [40], however, their use in cocaine addicts remains uncertain.

Although much effort has been applied in experimenting and treating the cocaine-induced CVD in laboratories, the above discussed agents have yet to be evaluated in humans and need clinical trials to validate their therapeutic actions.

Our study has limitations as it was a retrospective observational study with small numbers. Only the patients with CVDs after acute cocaine exposure were sampled where those with chronic cocaine use were not addressed. Additionally, the type of cocaine, timing and the route of cocaine exposure were not specified.

In summary, our pilot study confirmed that cocaine users are more susceptible, or predisposed, to suffer hemorrhagic stroke, particularly in the young population. Our findings also suggested that cocaine may play discrete roles in promoting CVD in patients depending on age, gender, ethnicity and comorbidities.

Acknowledgements

The authors would like to thank Dr. Robert Herndon and Dr. Lianbin Xiang from University of Mississippi Medical Center for technical support with data collection and analysis.

Author Disclosure

Dr. Si and Dr. Luo report no disclosures.

Reference

1. Brust JC, Richter RW. 1977. Stroke associated with cocaine abuse--? *N Y State J Med* 77(9): 1473-1475.
2. Degenhardt L, Whiteford HA, Ferrari AJ, Baxter AJ, Charlson FJ, et al. 2013. Global burden of disease attributable to illicit drug use and dependence: findings from the Global Burden of Disease Study 2010. *Lancet* 382(9904): 1564-1574. https://doi.org/10.1016/S0140-6736(13)61530-5
3. Johnson BA, Devous MD Sr., Ruiz P, Ait-Daoud N. 2001. Treatment advances for cocaine-induced ischemic stroke: focus on dihydropyridine-class calcium channel antagonists. *Am J Psychiatry* 158(8): 1191-1198. https://doi.org/10.1176/appi.ajp.158.8.1191
4. Conway JE, Tamargo RJ. 2001. Cocaine use is an independent risk factor for cerebral vasospasm after aneurysmal subarachnoid hemorrhage. *Stroke* 32(10): 2338-2343. https://doi.org/10.1161/hs1001.097041
5. Degenhardt L, Singleton J, Calabria B, McLaren J, Kerr T, et al. 2011. Mortality among cocaine users: a systematic review of cohort studies. *Drug Alcohol Depend* 113(2-3): 88-95. https://doi.org/10.1016/j.drugalcdep.2010.07.026
6. Johnson B, Lamki L, Fang B, Barron B, Wagner L, et al. 1998. Demonstration of dose-dependent global and regional cocaine-induced reductions in brain blood flow using a novel approach to quantitative single photon emission computerized tomography. *Neuropsychopharmacology* 18(5): 377-384. https://doi.org/10.1016/S0893-133X(97)00168-1
7. Ellis C. 2010. Stroke in young adults. *Disabil Health J* 3(3): 222-224. https://doi.org/10.1016/j.dhjo.2010.01.001
8. O'Connor RJ, Cassidy EM, Delargy MA. 2005. Late multidisciplinary rehabilitation in young people after stroke. *Disabil Rehabil* 27(3): 111-116. https://doi.org/10.1080/09638280400007414
9. Neiman J, Haapaniemi HM, Hillbom M. 2000. Neurological complications of drug abuse: pathophysiological mechanisms. *Eur J Neurol* 7(6): 595-606. https://doi.org/10.1046/j.1468-1331.2000.00045.x
10. Kunitz SC, Gross CR, Heyman A, Kase CS, Mohr JP, et al. 1984. The pilot Stroke Data Bank: definition, design, and data. *Stroke* 15(4): 740-746. https://doi.org/10.1161/01.STR.15.4.740
11. Fessler RD, Esshaki CM, Stankewitz RC, Johnson RR, Diaz FG. 1997. The neurovascular complications of cocaine. *Surg Neurol* 47(4): 339-345. https://doi.org/10.1016/S0090-3019(96)00431-4
12. Kuhar MJ, Ritz MC, Boja JW. 1991. The dopamine hypothesis of the reinforcing properties of cocaine. *Trends Neurosci* 14(7): 299-302. https://doi.org/10.1016/0166-2236(91)90141-G
13. He GQ, Zhang A, Altura BT, Altura BM. 1994. Cocaine-induced cerebrovasospasm and its possible mechanism of action. *J Pharmacol Exp Ther* 268(3): 1532-1539.
14. Bartzokis G, Beckson M, Hance DB, Lu PH, Foster JA, et al. 1999. Magnetic resonance imaging evidence of "silent" cerebrovascular toxicity in cocaine dependence. *Biol Psychiatry* 45(9): 1203-1211. https://doi.org/10.1016/S0006-3223(98)00228-5
15. Langner RO, Bement CL, Perry LE. 1988. Arteriosclerotic toxicity of cocaine. *NIDA Res Monogr* 88: 325-336.
16. Konzen JP, Levine SR, Garcia JH. 1995. Vasospasm and thrombus formation as possible mechanisms of stroke related to alkaloidal cocaine. *Stroke* 26(6): 1114-1118. https://doi.org/10.1161/01.STR.26.6.1114
17. Martinez N, Diez-Tejedor E, Frank A. 1996. Vasospasm/thrombus in cerebral ischemia related to cocaine abuse. *Stroke* 27(1): 147-148.
18. Zurbano MJ, Heras M, Rigol M, Roig E, Epelde F, et al. 1997. Cocaine administration enhances platelet reactivity to subendothelial components: studies in a pig model. *Eur J Clin Invest* 27(2): 116-120. https://doi.org/10.1046/j.1365-2362.1997.680633.x
19. Madden JA, Powers RH. 1990. Effect of cocaine and cocaine metabolites on cerebral arteries *in vitro*. *Life Sci* 47(13): 1109-1114. https://doi.org/10.1016/0024-3205(90)90169-R
20. Copeland JR, Willoughby KA, Police RJ, Ellis EF. 1996. Repeated cocaine administration reduces bradykinin-induced dilation of pial arterioles. *Am J Physiol* 271(4 Pt 2): H1576-1583. https://doi.org/10.1152/ajpheart.1996.271.4.H1576
21. Volkow ND, Mullani N, Gould KL, Adler S, Krajewski K. 1988. Cerebral blood flow in chronic cocaine users: a study with positron emission tomography. *Br J Psychiatry* 152: 641-648. https://doi.org/10.1192/bjp.152.5.641
22. Strickland TL, Mena I, Villanueva-Meyer J, Miller BL, Cummings J, et al. 1993. Cerebral perfusion and neuropsychological consequences of chronic cocaine use. *J Neuropsychiatry Clin Neurosci* 5(4): 419-427. https://doi.org/10.1176/jnp.5.4.419
23. Bell KM, Milne N, Lyons KP. 1994. Regional cerebral blood flow and cocaine abuse. *West J Med* 161(4): 412-413.
24. Westover AN, McBride S, Haley RW. 2007. Stroke in young adults who abuse amphetamines or cocaine: a population-based study of hospitalized patients. *Arch Gen Psychiatry* 64(4): 495-502. https://doi.org/10.1001/archpsyc.64.4.495
25. Morrow PL, McQuillen JB. 1993, Cerebral vasculitis associated with cocaine abuse. *J Forensic Sci* 38(3): 732-738.
26. Willens HJ, Chakko SC, Kessler KM. 1994. Cardiovascular manifestations of cocaine abuse. A case of recurrent dilated cardiomyopathy. *Chest* 106(2): 594-600. https://doi.org/10.1378/chest.106.2.594
27. Caplan L. 1988. Intracerebral hemorrhage revisited. *Neurology* 38(4): 624-627.
28. Chiriboga CA, Bateman DA, Brust JC, Hauser WA. 1993. Neurologic findings in neonates with intrauterine cocaine exposure. *Pediatr Neurol* 9(2): 115-119. https://doi.org/10.1016/0887-8994(93)90045-E
29. Chang TR, Kowalski RG, Caserta F, Carhuapoma JR, Tamargo RJ, et al. 2013. Impact of acute cocaine use on aneurysmal subarachnoid hemorrhage. *Stroke* 44(7): 1825-1829. https://doi.org/10.1161/STROKEAHA.111.000749
30. Silver B, Miller D, Jankowski M, et al. 2013. Urine toxicology screening in an urban stroke and TIA population. *Neurology* 80(18): 1702-1709. https://doi.org/10.1212/WNL.0b013e318293e2fe
31. Martin-Schild S, Albright KC, Hallevi H, Barreto AD, Philip M, et al. 2010. Intracerebral hemorrhage in cocaine users. *Stroke* 41(4): 680-684. https://doi.org/10.1161/STROKEAHA.109.573147
32. Nolte KB, Brass LM, Fletterick CF. 1996. Intracranial hemorrhage associated with cocaine abuse: a prospective autopsy study. *Neurology* 46(5): 1291-1296. https://doi.org/10.1212/WNL.46.5.1291
33. Sauter A, Rudin M, Wiederhold KH. 1988. Reduction of neural damage in irreversible cerebral ischemia by calcium antagonists. *Neurochem Pathol* 9(1-3): 211-236. https://doi.org/10.1007/BF03160363
34. Johnson B, Barron B, Fang B, Lamki L, Wagner L, et al. 1998. Isradipine prevents global and regional cocaine-induced changes in brain blood flow: a preliminary study. *Psychopharmacology (Berl)* 136(4): 335-341. https://doi.org/10.1007/s002130050575
35. Ooboshi H, Sadoshima S, Ibayashi S, Yao H, Uchimura H, et al. 1993. Isradipine attenuates the ischemia-induced release of dopamine in the striatum of the rat. *Eur J Pharmacol* 233(1): 165-168. https://doi.org/10.1016/0014-2999(93)90363-M
36. Vazquez-Sanroman D, Leto K, Cerezo-Garcia M, Carbo-Gas M, Sanchis-Segura C, et al. 2015. The cerebellum on cocaine: plasticity and metaplasticity. *Addict Biol* 20(5): 941-955. https://doi.org/10.1111/adb.12223

37. Holman BL, Mendelson J, Garada B, Teoh SK, Hallgring E, et al. 1993. Regional cerebral blood flow improves with treatment in chronic cocaine polydrug users. *J Nucl Med* 34(5): 723-727.

38. Kosten TR. 1998. Pharmacotherapy of cerebral ischemia in cocaine dependence. *Drug Alcohol Depend* 49(2): 133-144. https://doi.org/10.1016/S0376-8716(97)00158-0

39. Martin-Schild S, Hallevi H, Shaltoni H, Barreto AD, Gonzales NR, et al. 2009. Combined neuroprotective modalities coupled with thrombolysis in acute ischemic stroke: a pilot study of caffeinol and mild hypothermia. *J Stroke Cerebrovasc Dis* 18(2): 86-96. https://doi.org/10.1016/j.jstrokecerebrovasdis.2008.09.015

40. Wagner B, Schneider B, Blöchl-Daum B, Speiser W, Brenner B, et al. 1990. Effect of ritanserin, a 5-hydroxytryptamine2-receptor antagonist, on platelet function and thrombin generation at the site of plug formation *in vivo*. *Clin Pharmacol Ther* 48(4): 419-423. https://doi.org/10.1038/clpt.1990.170