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Merenda, A., Muir, K. W., and Koch, S. (2016) Cracking the role of cocaine in stroke. *Stroke*, 47(4), pp. 909-910.

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Deposited on: 04 May 2016

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Cocaine in ischemic stroke...not all it's cracked up to be?

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Word count:

Cocaine, ischemic stroke, stroke in the young

Cocaine is widely assumed to be a risk factor for stroke, yet good scientific evidence for a causal association between the use of cocaine and ischemic stroke is not as clear as commonly held. Cocaine use is widespread. In 2013, an estimated 24.6 million Americans, approximately 9% of the population aged 12 or older, had used an illicit drug in the past month.¹ While the majority was using marijuana, past month cocaine intake was still reported by 1.5% of the US population.¹

A similarly high use of cocaine was also found in a population-based case-control study by Cheng et al., reporting, in the current issue of *Stroke*, on the association of cocaine exposure and risk of ischemic stroke, from "The Stroke Prevention in Young Adults Study".² In their study population, derived from the greater Baltimore/Washington DC area, a quarter of subjects with recent ischemic stroke (cases), between the ages 15-49, were found to have previously used cocaine. An equally high prevalence of having ever used cocaine was recorded in an age-, gender-, race- and geographically- matched control group of stroke-free subjects. Subjects with stroke, however, were more likely to have used cocaine more than once per week in the past year and the odds of having used cocaine in the 24h prior to stroke onset were approximately 6 times higher in cases, when compared to a reference date for controls. This led the authors to conclude that the risk of ischemic stroke is highest in the first few hours after cocaine consumption, the period most likely to be of biological relevance.

But how does one reconcile these findings? Even if the risk for ischemic stroke is restricted to the first few hours after cocaine exposure, why does this not translate into an increased risk for stroke in those having ever tried cocaine? Some of the answers may lie within the limitations of a case-control study. Overall, the risk of cocaine and ischemic stroke seems to be quite low, given the widespread exposure to the risk factor. The authors commendably acknowledge several limitations to their study, including the small sample size and the inadequate control for confounding factors such as amount of smoking and alcohol intake, which casts doubt on the isolated role of cocaine in promoting stroke and raises the question of other vascular risk factors to potentiate the risk of cocaine-related stroke.

The authors also point out that the selection of the reference day for cocaine use in the control group, was a limitation to their findings. In the stroke cases, the reference date is clearly defined as the date of stroke. In the control group, the reference date for cocaine use was, in the early study period, the date of the interview. The authors speculate that knowledge of the pending interview, scheduled in advance, could have affected any drug related behavior in the days preceding the interview. Along similar lines, the interview was likely scheduled during regular working days, and any increased cocaine use during holidays and weekends may have been also missed in this manner. All this could have led to an under-reporting of acute cocaine use in the control group.

While this does not refute the fact that fewer controls used cocaine acutely and were less likely to have stroke, influencing subject behavior in an observational study always raises the concern for introducing bias. The authors subsequently adjusted the reference date to match the weekday that the stroke occurred in a matched case. The subgroup analysis of this optimal data set did not find an effect of cocaine use in the acute setting, suggesting perhaps that the risk of stroke with cocaine use is more tenuous than previously accepted.

The authors raise the possibility that other factors might augment the risk of ischemic stroke with cocaine. A review of the characteristics of the 26 stroke patients who had used cocaine in the 24h prior to stroke, shows that all had at least one vascular risk factor and almost a quarter had pre-existing cardiac pathology. Unfortunately, due to sample size limitations this could not

be explored further. Also of note is that the subjects with stroke and cocaine were virtually all in their late thirties and forties, with the overall study inclusion criteria ranging between the ages of 15-49. The mean age, however does not appear to be much different than the stroke-case group as a whole (39.8 vs. 40.9 years). Interestingly, in 2013 the average age of first cocaine use among 12 to 49 years olds was 20 years.¹ The fact that none of the stroke patients with acute cocaine use was in their teens or twenties, and that all had vascular risk factors certainly suggests that acute use of cocaine entails a very low risk of cerebral infarction in a young otherwise healthy person. The issue gets further complicated by the frequent use of cocaine in the 26 patients who reported acute cocaine use and stroke. Over half were using cocaine daily and many several times daily, thus blurring perhaps the definition for acute use. The fact that the case group as a whole seemed to report more frequent consumption of cocaine also raises the possibility of a dose effect. Alternatively, it may have been difficult to find appropriate controls from a population of more active daily cocaine users, who may not have been as accessible for contact and consent to the study.

This may be a potential source of bias, and also warrants careful interpretation of the author's findings. The absence of graded exposure data for tobacco, alcohol, or other illicit drug use, hypertension or diabetes is another major caveat, since the cocaine exposure data alone indicate a pattern of poor cardiovascular risk across multiple major risk factors, and cocaine use may simply represent a surrogate for general neglect of health. Information on treatment for the risk factors that are documented is not given.

If cocaine is a significant risk factor for ischemic stroke then a more specific mechanistic relationship should perhaps be evident, yet the pattern of ischemic events is not different from younger adults in general, with a range of mechanisms and predominance of cardioembolism and "cryptogenic" stroke. It is possible that the cocaine history influenced the extent of investigation, but nonetheless it is notable that a clear mechanism is lacking. If hypertension consequent to sympathomimetic effects is the most relevant mechanism, then a relationship with intracerebral hemorrhage should also be found, and this was unfortunately not explored in the current study. CNS vasculitis, often attributed to cocaine use, is absent from the list of mechanisms.

The article by Cheng et al. contributes to the existing literature and advances our understanding of the role of cocaine in stroke. It is difficult to argue against their concluding recommendations to screen young stroke patients for cocaine use. This would allow timely interventions on drug counselling and rehabilitation. However some of their finding should make us question the commonly held belief of cocaine as a robust risk factor for ischemic stroke. Clearly there is more behind the story. The manner of cocaine ingestion, dose effect, and potential contaminants are likely additional factors of importance, but will probably never be known in most cases. How these interact with individual predispositions, particularly age and other vascular risk factors, will ultimately define the true risk of cocaine and stroke and the pathophysiological mechanisms involved.

Acknowledgements:

The authors have nothing to disclose

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