Original Article

Correlation between Urinary Cotinine, Exhaled Carbon Monoxide, and Nicotine Dependence among Indonesian individuals in the National Narcotics and Illicit Drug Rehabilitation Center

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Abstract

Background: Environmental tobacco smoking exposure increased the level of urine cotinine and exhaled carbon monoxide (COex). Evidence suggests that there is an association between nicotine dependence and COex. The purpose of this study is to elucidate the correlation between urinary cotinine, COex, and nicotine dependence among Indonesian individuals with a history of substance use undergoing rehabilitation program. **Materials and Methods:** This cross-sectional study recruited participants who undergone rehabilitation at rehabilitation unit in Lido, aged >18 years old, and current smokers. We investigated the cigarette and substance consumption, Fagerstrom test for nicotine dependence (FTND), Addiction Severity Index (ASI), level of urinary cotinine, and level of COex. The ASI was determined by a psychologist who was working for rehabilitation unit. **Results:** The 72 assessed participants were male and aged 18–44 years old (mean 29 ± 7.1). We found significant positive correlation between urinary cotinine and COex (Spearman r = 0.3473, P = 0.0028), age of smoking initiation and age of substance use initiation (Spearman r = 0.5660, P < 0.0001), FTND and ASI (Spearman r = 0.3107, P = 0.0079), COex and age (Spearman r = 0.3323 P = 0.0043), COex and years smoking (Spearman r = 0.3028, P = 0.0097), as well as negative significant correlation COex and ASI (Spearman r = −0.2743, P = 0.0197). **Conclusion:** There was a significant correlation between urinary cotinine and COex, age of smoking initiation and age of substance use initiation, FTND and ASI, COex and age, COex and years smoking, and between COex and ASI.

Keywords: Carbon monoxide, cotinine, nicotine dependence, substance

Introduction

In 2013, 64.9% of Indonesian males were smokers and the prevalence of tobacco smoking increased to 36.3%.[1,2] Nicotine and carbon monoxide (CO) are related to tobacco smoking and can be used as indicators of tobacco smoking.[3-7] Age of smoking initiation has been shown to be a predictor for substance use.[8] Illicit drug use may contribute additional health problems which constituted 200,000 deaths/year and 11.8 million moderate-or-severe disabilities.[9] About 2.1%–2.25% of Indonesians aged 10–59 years old were estimated to be illicit drug users in 2014.[10] Tobacco smoking in individuals with substance use was reported as highly prevalent, heavier and was more difficult to quit.[11] Furthermore, nicotine dependence rate in illicit drug users can reach 100%.[11,12]

Access this article online

Quick Response Code:

Website: www.jnsbm.org

DOI: 10.4103/jnsbm.JNSBM_39_18

Urinary cotinine is a major metabolite form of systemic nicotine and is sensitive and specific as a biomarker of tobacco smoke exposure.[3,5] In pathological level, CO has deleterious effects (e.g., hypoxia and fatal intoxication).[6] Exhaled CO (COex) is also associated with air pollution, tobacco smoke exposure, and smoking status.[7] Urinary cotinine and COex are correlated with Fagerstrom test for nicotine

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How to cite this article: Priyonugroho G, Zaini J, Samoedro E, Firmansyah I, Nurwidya F, Antariksa B, *et al*. Correlation between urinary cotinine, exhaled carbon monoxide, and nicotine dependence among indonesian individuals in the national narcotics and illicit drug rehabilitation center. J Nat Sc Biol Med 2018;9:268-72.

dependence (FTND) which is widely used to determine the level of nicotine dependence.[13,14] Among Indonesian nonsmokers aged 6–12 years old, median of urinary cotinine level was reported to be significantly higher in exposed group than unexposed group.[15] Median of urinary cotinine level was also significantly higher in exposed adult female group compared to unexposed group.[16] Furthermore, previous studies revealed that COex was correlated with the level of nicotine dependence.[17,18]

There has been no study in Indonesia that focused on urinary cotinine, COex, and nicotine dependence among individuals with substance use despite its potential benefit of smoking cessation program in rehabilitation center. This study aimed to determine the correlation between urinary cotinine level, COex level, and level of nicotine dependence among smokers undergoing rehabilitation program of substance use.

Materials and Methods

This cross-sectional study was conducted on March and April 2016 in the National Narcotics and Illicit Drug Rehabilitation Center (Lido, Indonesia) where substance users were treated. Inclusion criteria were individuals in residential substance use treatment, aged >18 years, and had ever smoked >100 cigarettes and still smoking every day or some days. Exclusion criteria were acutely ill individuals, history of asthma or cancer, the inability to urinate or perform COex measurement, no nicotine dependence, and last time smoking was >72 h before the measurement.

We collected data from medical history interview, questionnaire, medical record, physical examination, and measurement of urinary cotinine and COex level. This study was granted ethical clearance from the Institutional Review Board (IRB) of Faculty of Medicine Universitas Indonesia (Ethical Clearance No. 183/UN2.F1/ETIK/2016) and all participants signed a written consent. Informed consent was confirmed by the IRB. We administered FTND, a structured question-embedded self-report questionnaire. Addiction Severity Index (ASI) of patients was assessed based on medical status, employment and support, drug use, alcohol use, legal status, family/social status, and psychiatric status. Participants were asked to collect their urine samples >5 ml into sterile pot. Cotinine levels were assessed using cotinine enzyme-linked immunosorbent assay kit (Bio-Quant Inc., San Diego, CA, USA) according to manufacturer's instructions. The COex levels were measured using CO analyzer (Bedfont Scientific Ltd., Maidstone, UK). Participants were asked to inhale fully, to hold their breaths for 15 seconds, and then to exhale slowly into the analyzer until the analyzer informed to stop. The results were analyzed using GraphPad Prism version 6.07 (GraphPad Software, San Diego, CA, USA). Correlations were considered statistically significant when $P < 0.05$.

Results

We enrolled eighty participants. Two participants were excluded because FTND score was 0–2 (no nicotine dependence). Mean age of participants was 29.21 ± 7.061 (95% confidence interval: 27.55–30.87), ranging 18–46 years. The majority of participants were senior high school graduates (53 participants, 73.61%). Some comorbidities were found such as HIV, hypertension, hepatitis C, and pulmonary tuberculosis. The participant characteristics are described in Table 1.

As presented in Table 2, the median age of smoking initiation was 15, median years of smoking was 13.5, and the median

Table 1: Participants'' characteristics

Variable	*n*	Percentage
Gender		
Male	72	100
Age	Point	95% CI
Mean	29.21±7.061	27.55-30.87
Educational level		
Bachelor	4	5.56
Diploma (associate's degree)	4	6.94
Senior high school	53	73.61
Junior high school	8	11.11
Primary school	2	2.78
Comorbidity		
Human immunodeficiency virus infection	5	6.94
Hepatitis B infection	1	1.39
Hepatitis C infection	1	1.39
Pulmonary tuberculosis	1	1.39
Hypertension	3	4.16

CI: Confidence interval

Table 2: Description of smoking and substance use

Variable	*n*	Percentage
Age of smoking initiation (year old)	9-21	Median: 15
Years of smoking	4-31	Median: 13.5
<10	19	26.39
10-<20	35	48.61
20-<30	15	20.83
>30	3	4.17
Number of cigarettes/day	5-80	Median: 16
Brinkman index		
Light	23	32
Moderate	41	57
Heavy	8	11
Age of substance use initiation (year old)	9-39	Median: 18
Years of substance use	1-26	Median: 10
Type of substance		
Methamphetamine	69	95.83
MDMA	29	40.27
Cannabis	46	63.88
Heroin	9	12.5
Buprenorphine-naloxone	1	1.38
Diazepam	1	1.38
Cocaine	1	1.38
Addiction severity index score	3-9	Median: 1

MDMA: Methylenedioxymethamphetamine

number of cigarettes per day was 16. The majority of participants were in moderate Brinkmann index. Inhaled methamphetamine was the most common substance used, followed by inhaled cannabis and oral methylenedioxymethamphetamine. The most common administration route was inhalation, followed by per oral and injection.

Next, we analyzed the nicotine dependence, COex, and urinary cotinine level [Table 3]. The majority of participants were having mild nicotine dependence and the median FTND score was 4. Median COex level was 22 ppm. There was a very high COex level (146 ppm) in one participant. We also found the median urinary cotinine level was 223.5.

Finally, we analyzed the correlation between urinary cotinine level, COex level, and FTND score. As shown in Figure 1a, urinary cotinine level was correlated positively with COex level (Spearman r = 0.3473, P = 0.0028). We also found that age was correlated positively with COex level (Spearman r = 0.3323, P = 0.0043) and years of smoking was correlated positively with COex level (Spearman r = 0.3028, P = 0.0097) [Figure 1b and c, respectively]. In Figure 1d, there was a positive correlation between COex level and ASI score (Spearman r = −0.2743, P = 0.0197). Moreover, FTND score was positively correlated with ASI score as shown in Figure 1e (Spearman r = 0.3107, P = 0.0079). Finally, age of smoking initiation was also positively correlated age of substance use initiation [Spearman r = 0.5660, P < 0.0001, shown in Figure 1f].

We found no correlation between urinary cotinine level and FTND score, age, and a number of cigarettes/day (data not shown). There was also no correlation between COex level and FTND score, between level of COex and number of cigarettes/day, between FTND score and age, age of smoking initiation, years of smoking, number of cigarettes/day, years of substance use, and age of substance use initiation. Age of substance use initiation did not correlate with years of smoking and number of cigarettes/day.

Table 3: Nicotine dependence, exhaled carbon monoxide, and urinary cotinine

Variable	*n*	Percentage
FTND score category	Range: 3-8	Median: 4
Mild	39	54.17
Moderate	26	36.11
Severe	7	9.72
Exhaled CO level (ppm)	0-146	Median: 22
Urinary cotinine level (ng/ml)	15.8-235	223.5

FTND: Fagerstrom test for nicotine dependence, CO: Carbon monoxide

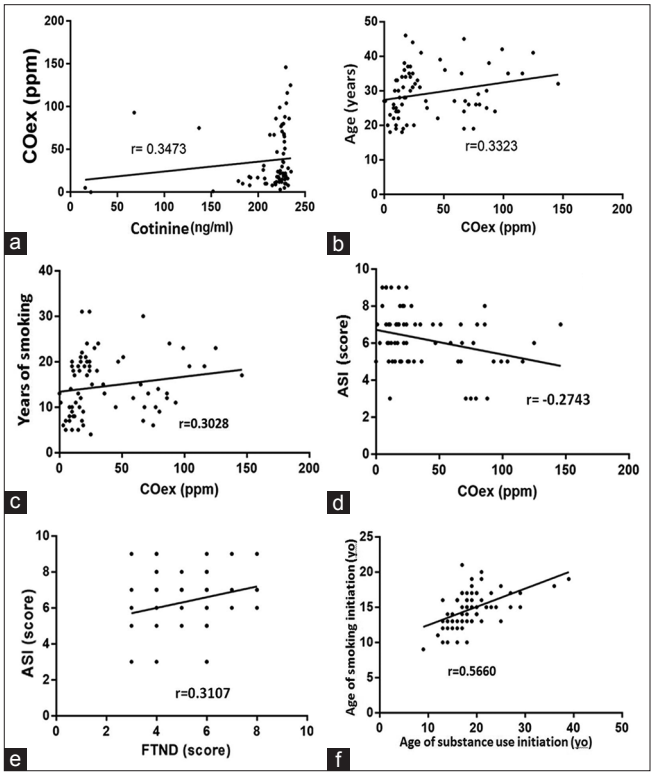

Figure 1: Correlation between some variables. Spearman rho test was used to analyze the correlation between variables. (a) Urinary cotinine and COex level. (b) COex level and age. (c) COex level and years of smoking. (d) COex level and ASI score. (e) FTND and ASI score. (f) Age of substance use initiation and age of smoking initiation. FTND: Fagerstrom test for nicotine dependence, COex: Exhaled carbon monoxide, ASI: Addiction Severity Index

Discussion

In this study, mean of age was 29.21 ± 7.061 years old. This is quite similar with data of Indonesian National Narcotics Bureau (BNN), 27 years old.[10] United Nations Office on Drug and Crime in 2012 reported that average age of people receiving treatment for illicit drug use was the late 20s to the early 30s.[9]

The most common level of education in this study is senior high school. Similarly, BNN found that 71.3% of illicit drug users were graduated from senior high school or higher.[10] Guan and Ann found that education level of 94.39% males with nicotine dependence was secondary school or higher.[14] Alessi *et al.* reported that mean years of education among residential substance abuse treatment patients were also 12 years old.[19]

Median age of smoking initiation was 15 years old with 44 participants (61.11%) started smoking at <15 years old, which is similar with Alessi *et al*.,[19] although Guan and Ann found higher mean age of smoking initiation of 19.61 ± 11.47 years old.[14] United States Department of Health and Human Service reported that 90% adult smokers started smoking before they were 18 years old.[20] Global Adult Tobacco Survey Indonesia Report in 2011 found that 39.9% smokers started smoking at 17–19 years old.[21] Study in 17 provinces in Indonesian revealed illicit drug users started smoking at 14 years old.[22] Charkazi *et al.* found that 25.5% participants with nicotine dependence started smoking before 16 years old.[23]

In this study, median FTND score was 4 and more than half of participants had mild nicotine dependence, which is different

with a study by Jhanjee *et al.*, who found that the most common moderate nicotine dependence.[12] The difference may be caused by the difference of years of smoking.

Median age of substance use initiation and median years of substance use were 18 years old and 10 years, which was quite similar to Indonesian BNN data.[10] Substance Abuse and Mental Health Services Administration found that 74% substance abuse treatment admissions had begun substance use at <17 years old. Moreover, 78.1% of substance abuse treatment admissions that began substance use at <11 years old reported abusing >2 substances.[24] We think that median years of substance use in our study (10 years) are important, as Lopez-Quintero *et al.* found that probability of transition to dependence 10 years after use onset was 14.8% among cocaine users and 5.9% among cannabis users.[25] Median age of substance use initiation in our study (18 years old) is also important as Merline *et al.* found that a history of substance use at 18 years old was strong predictor of cigarette use, heavy alcohol use, cannabis consumption, cocaine use, and prescription drugs' misuse at 35 years old.[26] Hser *et al.* found mean that age of heroin use initiation among narcotic-dependent criminal offenders in treatment program was 18 years old.[27]

In our study, urinary cotinine level was correlated with COex level. Suryatama *et al*. also found strong correlation between urinary cotinine level and COex among environmental tobacco smoking-exposed females. This study, however, showed no correlation between urinary cotinine level and FTND score, as well as between COex level and FTND score. These are different with a study by Jung *et al.,* who stated that urinary cotinine level was correlated with FTND score.[13] Previous study in Indonesia and Malaysia showed that COex level was correlated with FTND score.[14,18] The different findings might be caused by the difference of time elapsed between urine collection and last cigarette smoked, and also the cotinine level variability in every cigarette as revealed by Muscat *et al.*[28] Furthermore, no correlation between urinary cotinine level and FTND score as well as in this study might be due to relatively small number of participants. The other possibilities behind this no correlation are may be due to discrepancy between the allowed number of smoke per day, as regulated by the rehabilitation center, with the actual consumed smoker per day. Finally, other possibilities were that different types of substances were used in different doses. We suggest that this affected the dependence syndrome as nicotine and other psychoactive substances activate mesolimbic dopamine system.[29]

The use of combined cannabis was associated with greater likelihood of nicotine dependence.[30,31] Harrel *et al.* study found that regular/heavy smokers tended to use a greater number of other substances including injected substances.[32] These findings suggest that euphorigenic substances and nicotine are interacted one to another. Nicotine and euphorigenic effects of some substances result in stress reduction and rewarding sensation. Cannabis increases firing of dopamine neurons and increases dopamine activity projecting to the nucleus accumbens (ACB). Nicotine promotes dopamine synthesis in mesolimbic dopamine pathway and increases dopamine output in ACB. Dopamine and nucleus ACB are key substance and region in the development of substance dependence.[33]

Study limitation

There was a different number of cigarettes/day between participants-reported data and what the center reported. There are potential variable confounding factors because of different substance used, number of participants of each substance, drug dose, and months of residential treatment.

Conclusion

There was positive correlation between urinary cotinine level and COex level among residential substance use treatment participants with nicotine dependence. Age of smoking initiation positively correlated with age of substance use initiation. Amphetamine-type substances were the most common substance used by residential substance use treatment patients. Our findings support for intensified smoking education and prevention activities in school-age people. More studies are needed to determine the best evaluation instrument to assess nicotine dependence level among residential substance use treatment patients. We urge for future studies to identify profile of urinary cotinine and COex level and nicotine dependence in every substance used and route administered by users.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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