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Detrimental Effects of Mosquito Coil Smoke Exposure on Memory and Hippocampal Morphology

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ABSTRACT

Mosquito coil smoke is widely used to repel mosquitoes and prevent malaria in many malaria-endemic regions. While there is considerable awareness of the toxicity of carbon monoxide (CO), exposure to CO from less obvious sources like MC smoke is often overlooked. This study investigates the neurotoxic effects of mosquito coil smoke in mice. In this study, sixteen adult male mice were randomly divided into two groups: an experimental group and a control group, each comprising 8 mice. The experimental group was exposed to MC smoke (Wavetide, China) for 15 minutes daily over a period of 14 days, inside a gas chamber (length 75x breadth 50x height 50cm). A digital CO meter (PCMM05 Pyle) was employed to measure CO gas levels within the chamber. Our findings indicate that burning an MC for 15 minutes produces an average of 312 parts-per-million (ppm) of CO, significantly elevating blood carboxyhemoglobin (COHb) levels by 15.8%. These levels greatly exceed the World Health Organization's recommended limits of CO exposure (<100 mg/m³ or 87 ppm for 15 minutes) and COHb levels (<2%). Furthermore, MC smoke exposure was linked to impaired learning and memory and extensive apoptosis of brain cells. However, body weight was unaffected. Despite the widespread use of MCs for malaria prevention, they could represent a significant source of CO and other neurotoxins, posing a potential threat to human health. The health risks associated with their use are frequently underestimated, even by public health professionals.

Keywords: Mosquito coil, carbon monoxide, neurotoxicity, learning and memory, hippocampus

INTRODUCTION

Mosquito coil smoke is a prevalent mosquito repellent in many parts of Asia and Africa, designed to burn slowly and release smoke containing active ingredients that repel or kill mosquitoes [1]. While effective in reducing mosquito bites and lowering the risk of diseases such as malaria and dengue fever, the use of mosquito coils raises significant health concerns due to the toxic substances released during combustion [2].

Despite a global reduction in malaria incidence and mortality, regions like Nigeria continue to experience disproportionately high rates, contributing to 25% of global malaria cases and 30% of deaths [2]. To address this, the WHO recommends vector control as a key strategy [3]. In many regions of Nigeria, mosquito coils are the second most popular malaria control method, used by 15.4% of the population [3].

Mosquito coils are effective in repelling mosquitoes and reducing mosquito-borne diseases. Studies show that these coils, which often contain synthetic pyrethroids like allethrin, significantly lower mosquito bites indoors and outdoors [4]. Despite their efficacy, mosquito coils pose health risks due to toxic by-products released during combustion.

Common ingredients in mosquito coils include pyrethrins, organic fillers, binders, and synergists like piperonyl butoxide [5]. These coils are effective against mosquitoes such as Aedes, Anopheles, and Mansonia [6]. However, burning them releases sub-micrometer particles and gaseous irritants like aldehydes, sulfates, and polycyclic aromatic hydrocarbons, which can prevent mosquitoes from entering rooms [7].

Mosquito coils are mainly used at night in bedrooms, where people may burn them in enclosed spaces. This can expose vulnerable groups like pregnant women, children, and the elderly to toxic smoke for several hours, especially in poorly ventilated rooms. Although mosquito coils are more effective in enclosed or poorly ventilated areas, maintaining good ventilation is advised to reduce toxicity [8].

The smoke generated by burning mosquito coils contains a variety of potentially harmful substances, including particulate matter (PM), carbon monoxide, polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds (VOCs), and other toxic chemicals [9]. The inhalation of these substances poses a range of health risks to several systems [10]. The respiratory system is one of the primary targets of mosquito coil smoke toxicity. Inhaling the smoke can lead to the deposition of fine particulate matter in the lungs, causing respiratory problems such as asthma, bronchitis, chronic obstructive pulmonary diseases (COPD), and lung cancer [11]. Studies have shown that burning one mosquito coil can release the same amount of PM as burning 75-137 cigarettes [12].

The chemicals released in mosquito coil smoke can also affect cardiovascular health. Long-term exposure to fine particulate matter and PAHs has been linked to an increased risk of hypertension, heart diseases, and atherosclerosis [13]. The oxidative stress and inflammation caused by these toxicants can contribute to the development of cardiovascular conditions. The reproductive system is not immune to the harmful effects of mosquito coil smoke. The toxic substances can have detrimental impacts on both male and female reproductive health, including, reduced fertility and several adverse pregnancy outcomes [14]. The immune system can be compromised by the toxic components of mosquito coil smoke. Prolonged exposure can lead to immunosuppression and chronic inflammation [15].

Mosquito coil smoke poses significant neurotoxic risks due to its content of polycyclic aromatic hydrocarbons (PAHs) and heavy metals. Chronic exposure to these compounds can cause cognitive impairments and neurodegenerative diseases through oxidative stress and inflammation [16,17]. Also, carbon monoxide (CO), produced when burning carbon-containing substances, is highly toxic to the body by reducing oxygen supply to tissues and generating reactive oxygen species (ROS) [18,19]. The brain and heart are particularly affected due to their high energy demands. The brain's sensitivity to oxygen deprivation can lead to tissue damage within minutes, resulting in acute symptoms like headaches, dizziness, and nausea, or chronic symptoms such as fatigue, memory deficits, and emotional distress.

Vulnerable populations, including children and pregnant women, are especially at risk, with potential long-term impacts on cognitive and behavioral development [20]. Therefore, mitigating exposure to mosquito coil smoke is crucial to protecting brain health. Additionally, some studies have indicated that children and pregnant women are particularly susceptible to the neurotoxic effects of these chemicals. Exposure during critical periods of brain development can result in long-term deficits in cognitive and behavioral functions [20]. This underscores the importance of mitigating exposure, especially in vulnerable populations.

The study aims to assess the effects of exposure to mosquito coil smoke on the brain. While various toxicities have already been documented for several organs of the body, brain toxicity has received the least attention. Additionally, although the toxicities of prominent constituents such as allethrin have been thoroughly evaluated, the toxicity of less obvious gaseous toxins like carbon monoxide has often been overlooked. These factors, among others, prompted the need for this research.

MATERIALS AND METHODS

Sixteen, adult (6-8 weeks old), male mice were used for the study. They were housed in the animal room for about a week prior to the start of the study for acclimatization. Animals were maintained under natural day and light atmospheric conditions (24 - 30^0C). They were fed with laboratory animal feed and tap water ad libitum. They were also handled in accordance with the Ahmadu Bello University animal use and care guidelines. The animals were randomly categorized into either the experimental or control groups, each containing 8 mice. The experimental group was exposed to MC smoke (Wavetide, Xiaoshan Yunshi, China) that was made to burn inside the partially ventilated gas chamber (75 cm x 50 cm x 50 cm) for 15 minutes, daily, for 14 days. The control group was however maintained in ambient room air. The exposure was in the mornings (8-9 am daily). A digital CO meter (PCMM05, Pyle) was used to measure the amount of CO produced when the MC was burning inside the gas chamber. The peak daily dose of CO attained within the period of exposure was recorded. Environmental temperature and that inside the gas chamber were measured during each exposure session.

Screening for Motor Coordination Deficits

There is a general requirement for motor strength and coordination before a reliable assessment of cognitive behavior can be made; therefore, all the animals were screened for motor coordination deficits before recruitment into the study [21]. The balance beam test

(Beam Walk), which was used here, is a useful measure of motor coordination and balance deficits that can be used to show gross or subtle motor coordination and balance deficits. It consists of 100 cm long 12 mm and 6 mm flat beams resting on two poles which are 50 cm above the surface of a table. A black escape box is attached to one end of the beam at the finish point. The mouse was forced to move away from the aversive stimulus (60-watt light bulb) at the starting point of the beam towards the escape box; during which the latency and hind-feet slips were recorded as a measure of motor coordination and balance [22].

Assessment of Learning Memory

The elevated plus maze (EPM) protocol as described by Itoh et al., (1990) was used to assess Long-term learning and memory deficits [23]. It was made of plywood and consisted of two open arms (25 x 5 cm) and two closed arms (25 x 5 x 15 cm) which extended from a central 5 x 5 cm platform. It was elevated 50 cm above the floor and the whole apparatus was painted black. On the first day (learning task), a mouse was placed at the end of one of the open arms, facing away from the central platform. Latency (time taken for the mouse to enter one of the closed arms) was recorded in seconds. Following entry into an arm, the animal was allowed to explore the apparatus for 30 seconds; and 24 hours later, the second trial (retention test) was performed. Mice appear unwilling to venture into the open arms of the maze because of a general aversion to open spaces and height; this induced learning responses in the animal [23]. Behavior was timed using a stopwatch, and events were recorded by a video camera. The transfer latencies (TLs) on day 1 (acquisition) were compared with that of day 2 (recall) to assess learning and memory respectively. A significant decrease in the TL on day 2 when compared to TL on day 1 indicates enhanced learning and memory abilities.

Histology of Brain Tissue

On the final day of the study, animals were euthanized through inhalation of chloroform vapor in an airtight container. The head was decapitated and the brains were carefully harvested, weighed, and kept in Bouin's fluid before analysis. Brain slices containing the cerebellum and hippocampus were obtained and fixed with 10% formal saline. They were dehydrated by passing them through ascending grades of alcohol. Tissues were then cleared with toluene, infiltrated with molten paraffin wax and sectioned at 5 microns on a rotator microtome. The sections were later stained with hematoxylin and eosin stain, Toluidine blue, and Bielschowsky's/ silver staining techniques [24]. Slides were examined with a Leica icc50 HD microscope.

Assessment of Plasma Carbon Monoxide Level

About 2.5 ml of blood was collected via cardiac puncture in test tubes containing ethylene diamine tetra acetic acid (EDTA, potassium salt), 1.5 mg/mL of blood. Measurement of plasma carboxy-hemoglobin (COHb) is a principal biomarker for assessing exposure to CO by spectrophotometric method [25].[12]

Statistical Analysis

Data obtained from the study were expressed as means ± standard error of the mean (SEM). Depending on the normality test, parametric or nonparametric tests were employed to analyze the results. For all evaluations, values of $p \leq 0.05$ were considered to imply statistical significance. Microsoft Office Excel version 2013 and Statistical Package for Social Sciences (SPSS) version 22.0 software were used in analyzing the data.

RESULTS

Animals in both groups gained weight throughout the period of the study. There was no significant difference ($p=0.4$) in the changes in the body weight (final body weight – initial body weight) when compared between the control and MC smoke group (Table 1). There was no significant difference between the temperature inside the gas chamber and that of the environment (Table 2). In terms of temperature, all the groups were maintained under similar conditions throughout the study period. The mean daily CO exposure was 312 ppm for the MC group and 2 ppm for the control group (Figure 1). The COHb was 15.4% and 1.8% for the MC and control groups respectively (Figure 2). All animals were screened for possible motor coordination deficits prior to the start of the study. There were no statistically significant differences in terms of the left foot slip (LFS) ($p=0.52$), right foot slip (RFS) ($p=0.44$), and Latencies ($p=0.92$) between the two groups (MC and control) (Table 3). They were all free from any gross motor coordination and balance deficit that might have affected their performance in the EPM tasks.

Table 1: Effects of mosquito coil smoke exposure on body weight.

Variable	Control	Mosquito coil smoke	P value
Change in body weight (FBW-IBW)	6.6	6.5	0.4

Independent-Samples T-Test, n=8, p≤0.05, FBW= final body weight, IBW= initial body weight.

Table 2: Temperature variation between the inside of the gas chamber and the environment

Location	**Gas Chamber**	**Environment**	**p-value**
Temperature (Mean ^{0}C ± SEM)	27.8 ± 0.4	28.0 ± 0.4	0.7

Independent-Samples T-Test, *n*=8, p≤0.05.

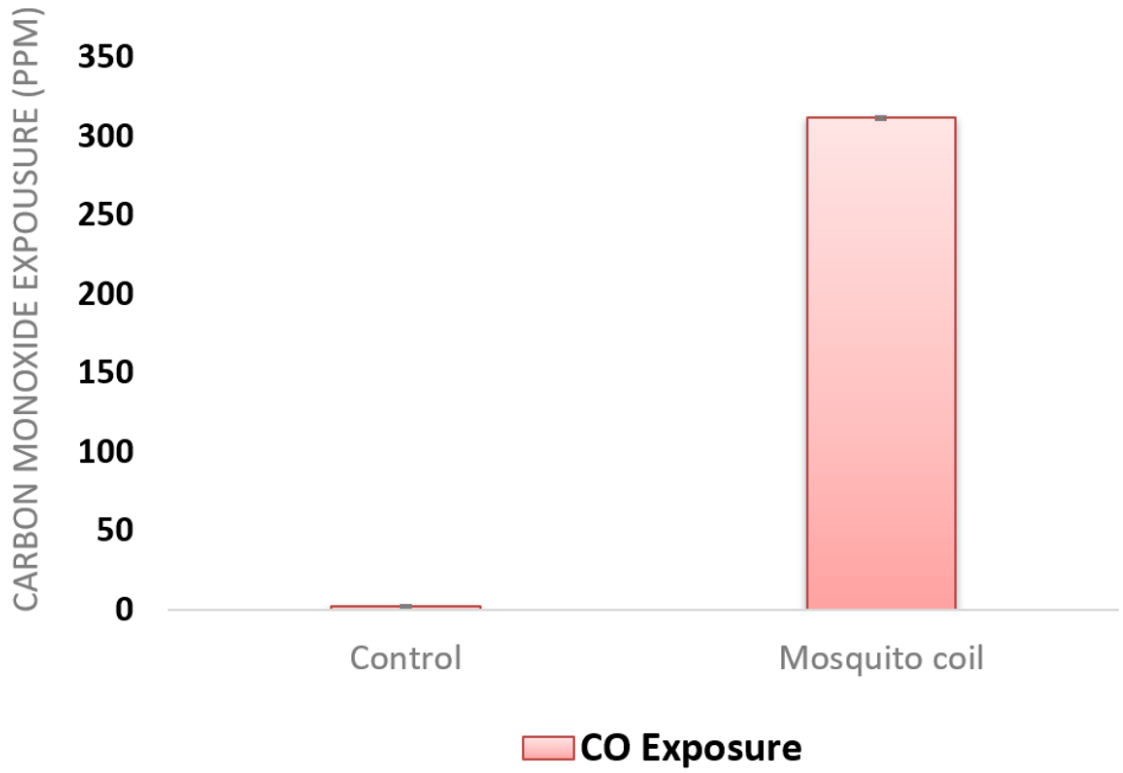

Figure 1: Comparison of the carbon monoxide exposure between the groups

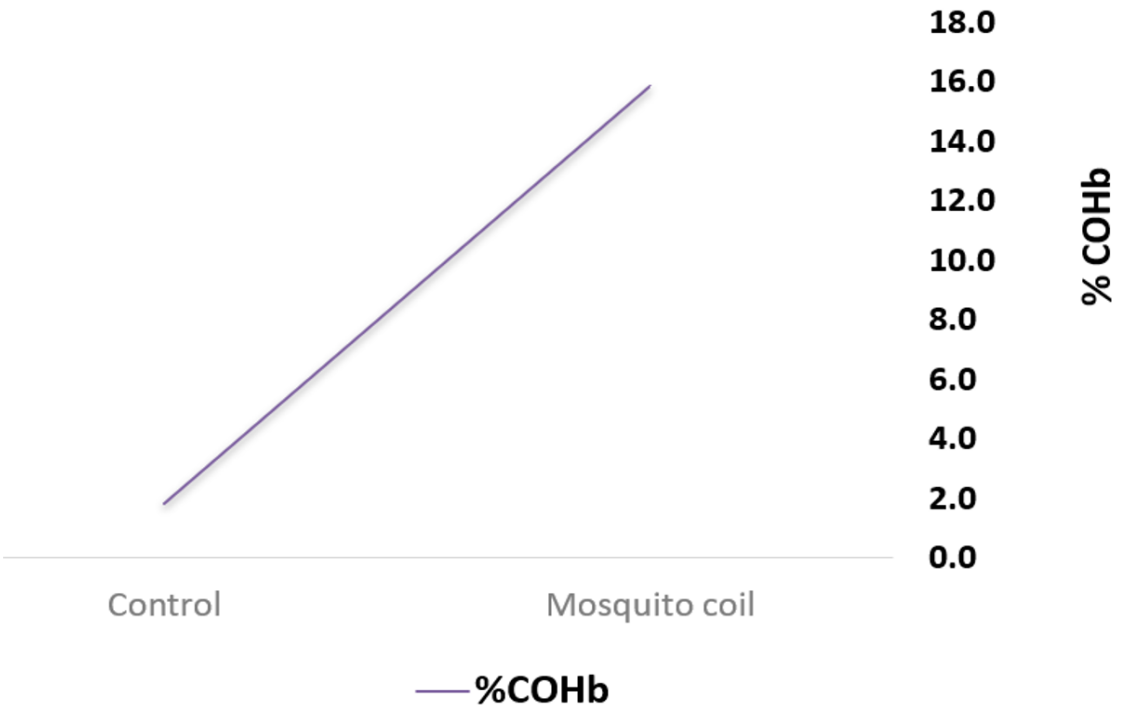

Figure 2: Comparison of the percentage carboxyhemoglobin between the groups

Table 3: Screening for motor coordination deficit in the animals

Groups	Control	Mosquito coil smoke	P value
Left Foot Slip (LFS)	1.50	1.88	0.52
Right Foot Slip (RFS)	0.50	0.94	0.44
Latency (Sec)	57.06	455.31	0.92

Mann-Whitney U-test, n=8, $p \leq 0.05$.

There was a significant difference between the transfer latency (TL) on day 1 (acquisition) and day 2 (recall) in the control group. There was, however, no significant difference in the MC group (Figure 3). Fewer pyramidal and Purkinje cells were observed in the hippocampus and cerebellum respectively; most of which were devoid of their nuclei in the MC smoke-exposed group when compared to the control (Figure 4). There was also a disappearance of the nucleoli in the hippocampal pyramidal cells (Figure 4) in the MC group. The Nissl substance of Purkinje cells in the cerebellum has disappeared from the center to the periphery of the cell (Figure 4) in the MC group.

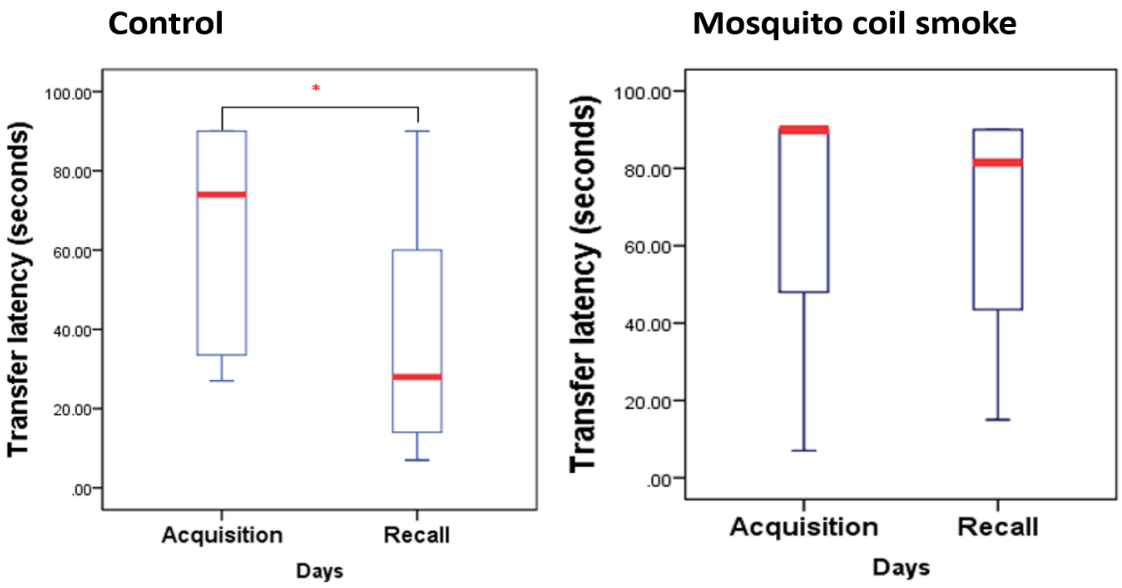

Figure 3: Effect of exposure to mosquito coil smoke on learning and memory. * indicates statistical significance

Wilcoxon signed-rank test indicates a significant difference between the acquisition (D1) and recall (D2) in the control (Z= -1.99, p=0.046) group as opposed to the mosquito coil smoke exposed group (Z= -0.00, p=1.00), n=*8*, p≤0.05.

Mosquito coil smoke **Control**

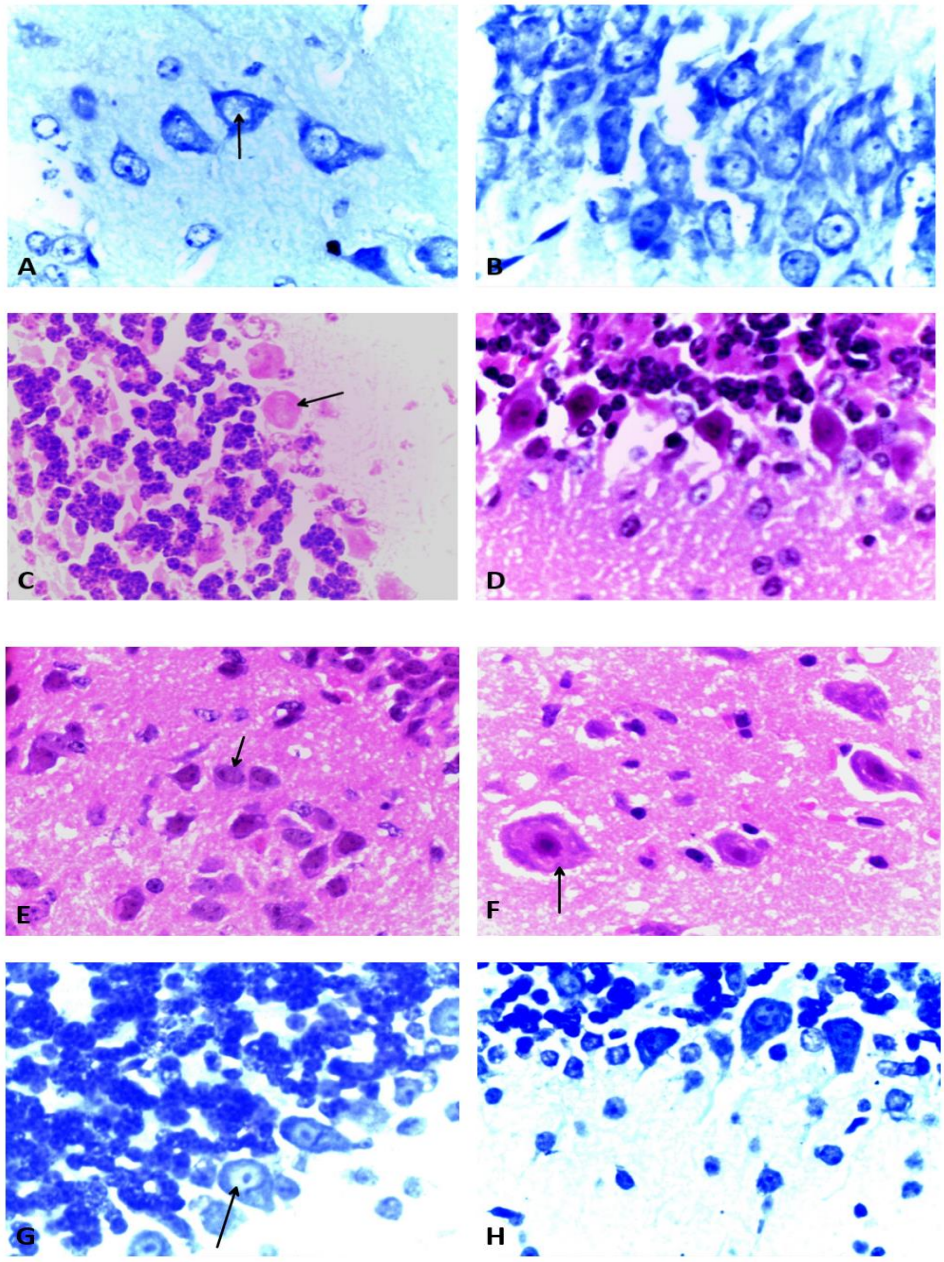

Figure 4: Effects of exposure to mosquito coil smoke on the Brains of the experimental group when compared to the control group.

A: Fewer pyramidal cells in the hippocampus, devoid of nuclei (Arrow) in the MC group. B: Numerous pyramidal cells with intact nuclei in the control mice. C: Absence of nuclei in the Purkinje cells of the cerebellum (Arrow) in the MC group. D: Numerous Purkinje cells with their preserved nuclei in the control mice. E: Disappearance of the nucleoli in the pyramidal cells of the hippocampus (arrow). F: Intact nucleoli in the pyramidal cells of the control mice (arrow). G: the Nissl substance of Purkinje cells disappearing from the center to the periphery of the cell (Arrow). H: Uniformly distributed Nissl substance in the Purkinje cells of the control mice. [Mag.X100, H&E (C, D, E & F), Toluidine Blue (A, B, G & H)].

DISCUSSION

Body growth is a major marker of health, and growth can be objectively assessed through the measurement of organs and body weights. Our result indicated a normal growth of the animals in both groups with no

significant difference between the control and MC smoke groups. However, several studies of CO poisoning, especially during pregnancy were found to be associated with increased risk of fetal death, developmental disorders, and chronic cerebral lesions [26]. Salam and colleagues also found perinatal exposure to CO as a major risk factor for low birth weight, and intrauterine growth retardation [27]. The normal weight gain observed in our result could be explained by the short duration of exposure (15 min.), small CO dose (312 ppm), and age of mice used. To buttress our point, exposure to a higher dose of CO (up to 1000 ppm) equally led to 25% mortality and poor growth in those animals that survived (data not shown).

To maintain both the control and experimental groups under similar conditions aside from the difference in the treatment; the environmental temperature of the two groups was monitored throughout the period of the study. Our results showed that the temperature inside the gas chamber during the exposure did not differ significantly from the temperature outside the gas chamber, nor was it different from that of the control groups' environment, throughout the study period. Therefore, based on our result, we can conclude that both groups were maintained under similar conditions of temperature throughout the period of the study, and any observed behavior could not have been caused by the variations in the temperature.

The CO exposure observed in the control group was within the World Health Organization (WHO) recommended ambient levels (<2.5 ppm); however it was beyond the WHO recommended limit in the MC smoke exposed group (<100 mg/m^3 or 87.1 ppm for 15 min) [28]. The %COHb was significantly lower and fell within the non-smoker, ambient range (<2%) in the control group. However, that of the MC smoke-exposed group was much higher than the WHO recommended limit; it falls within the chronic smoker range (> 9 ppm). From the literature, patients who were mildly exposed to CO (<1 %COHb) usually had intact memory functions equivalent to that of the control group and were even better in some areas like learning, word recall, and quality of learning by Buschke's verbal memory testing. Attention was also found to be better in the patients, in whom visual reaction time was shorter than in controls [29]. Although the mean of the %COHb recorded in our control was up to 1.8%, it was still within the non-smoker range and did not pose much toxicity risk. Such mild exposures were even found to enhance learning by the same author [17].

The significant decrease in the TL observed in the control group indicates the normal ability of mice to learn about the existence of the safe, enclosed arm of the EPM, and also to be able to recall and escape from the open arm 24 hours after the learning process. On the other hand, our result clearly shows impaired learning and memory in the mice exposed to MC smoke. This could probably be due to the exposure to the high CO gas (up to ≈ 312 ppm) from the MC smoke. Although CO is not the only constituent of MC smoke, and may not be the only toxin responsible for the impaired memory, however, the result is comparable to that of many cases of CO poisoning [30,31,32,33,34,35]. It is also worth noting that most CO poisoning doesn't involve CO gas in isolation; rather, together with many other toxic gases and substances as in the case of fire accidents.

It is common for households to burn mosquito coils throughout the night on daily basis, and sometimes for a lifetime [36,37]. Among the family members are pregnant women, neonates, infants with their poorly developed brain, and children that may equally have other hemolytic diseases that may further compromise their health status [38]. In most of our communities, cigarette smoking is considered antisocial behavior because it goes against most of our cultures, therefore seriously rejected; however, the use of MC is considered culturally normal [39,40]. Therefore the hazard posed by MC could be far more dangerous when compared to cigarette smoke; therefore, MC is a potential source of indoor air pollution. On average, we found that burning either cigarette (Aspen brand) or MC inside the chamber for 15 minutes produces similar concentrations of CO (cigarette ≈347 ppm and MC≈312 ppm). Therefore; based on the dose of CO produced, families that use MC in the night will be approximately 28 times more affected by the toxicity of CO (assuming they were exposed for 7 hours equivalent to the average duration of a night sleep), when compared to cigarette smoking which usually lasts no more than 15 minutes. It is also important to realize that cigarette smokers exhale most of the smoke after inhalation; some even use filters, and mostly smoke in an open space where there is enough ventilation. In contrast, most people use MC indoors to concentrate the smoke; with very poor ventilation, especially during the winter season. Liu *et al*., (2003) established that exposure to a single MC was equivalent to burning 75-137 cigarettes in terms of the particulate matter (PM, 2.5) and also equivalent to burning 51 cigarettes in terms of formaldehyde exposure [7].

The level of community awareness of the hazards of cigarette smoke is quite high; however, that of MC and other commonly ignored indoor air pollutants is quite low even among the high socioeconomic class [8]. Salvi and colleagues observed that simply opening the windows and door when MC burns in the night, decreases the CO and $PM_{2.5}$ levels by 50%; this shows the importance of health education in the fight against MC hazards in our community [41]. Nandasena and colleagues concluded that air quality and air pollution (especially indoors), may be considered a neglected

public health problem in Sri Lanka just like any other developing nation [42]. Animals exposed to MC similar to that of humans for just 60 days, had a lower body weight, histopathological lesions in the respiratory tract, and elevated levels of liver enzyme activities [10]. Nephrotoxicity [4], damage to other organs [11], and neurobehavioral changes [43] were all documented in MC smoke exposure. Significantly higher frequencies of chromosome aberrations were earlier identified in MC smoke-exposed animals by Vences-Mejía and colleagues [18].

Patients with CO poisoning usually exhibit impaired memory, attention and executive functions [44]. Carbon monoxide poisoning impaired memory and attention, and also causes severe white matter damage (WMD) which is associated with Parkinsonism-like features that abate after 13 months later [45]. Similarly, CO-poisoned subjects were found to have impaired ability to remember new temporal, linguistic, and spatial information while previous knowledge for temporal, linguistic, and spatial information was intact [30]. Significant atrophic changes in the fornix were associated with significant decline in verbal memory; however, visual memory, processing speed and attention, and or concentration did not decline [31]. Neuropsychological tests such as memory, new learning ability, attention and concentration, tracking skills, visuomotor skills, abstract thinking, and visuospatial planning and processing were all impaired after CO poisoning [32]. The recall and recognition memory was significantly impaired in patients who suffered bilateral hippocampal damage and temporal-parietal atrophy after CO poisoning [33].

There was widespread neuronal cell death in the studied parts of the brain. In contrast with the control groups, numerous healthy and large pyramidal and Purkinje cells were found in similar locations of the brain. Previous data suggested specific toxicity of CO on memory functions in animals and also delayed neuronal death in areas involved in memory process [46]. Equally, Gilmer *et al.* (2002) reported a damage to the CA1 layer of the hippocampus after severe CO poisoning [34]. Among the numerous accompanying morphological changes in tissues/ organs observed by Taiwo and colleagues (2008) were meningitis and demyelination of neuronal axons [11]. Temporo-parietal cortical atrophy was also observed after CO poisoning [33]. Acute CO poisoning was found to cause intravascular neutrophil activation which liberates myeloperoxidase (MPO) that mediates perivascular oxidative stress, which is linked to immune-mediated neurologic sequelae [47].

The features observed here were mainly those of apoptosis. However, several studies have confirmed the coexistence of both necrosis and apoptosis in CO poisoning and were proposed to contribute to CO poisoning-induced brain cell death [19]. Some of the features observed could be due to some specific constituents of MC other than CO. It is also important to note that most CO poisoning is associated with exposure to other chemicals and organic compounds; therefore, a clear picture of pure CO toxicity may not be understood except in a well-designed setting using pure CO gas. One of the significance of this study was to mimic a similar CO exposure scenario like that of MC; which although important, however, most often neglected in our society. Neuroimaging has revealed evidence of specific hippocampal, and generalized brain atrophy in CO-poisoned patients [48]. Delayed encephalopathy after acute CO intoxication was found to be associated with cerebral white matter lesions on MRI [49]. Subtle, but significant corpus callosum atrophy that was underestimated before, was surprisingly picked up by Quantitative MRI analysis after CO poisoning [35]. Cerebral white matter lesions were significant findings in many CO poisoning that might be associated with cognitive sequelae [50]. Chronic cerebral lesions were also documented by Raub and colleagues in 2000 [26].

Conclusion

Our study indicates that exposure to MC smoke is neurotoxic, with CO probably being a significant contributor to this toxicity. Given that CO gas from commonly overlooked sources like MC can impair learning and memory, minimizing exposure is crucial for health.

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