Cognitive Performance Following Caffeinated Chewing Gum in night-shift Emergency Physicians: A Double-blind Randomized Crossover Controlled Trial

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Project summary

This study aimed to examine the impact of caffeinated chewing gum on the cognitive performance of night-shift emergency physicians in a partially sleep-deprived state. A randomized, double-blind crossover controlled experimental design was employed in which fourteen (Age: 29.9 ± 1.44; height: 176.5±5.3; weight: 78.1±13.4) emergency physicians consumed either caffeinated chewing gum (CAF) containing 200 mg caffeine or a caffeine-free placebo gum (PLA) for 10 minutes at 03:30 am during their first 8-hour night shift after at least one day off, and completed cognitive performance tests before shift, mid-shift (10 minutes after gum chewing), and after shift, including included Corsi block test, Task-switching paradigm, Stroop Test, Visual search, and Wisconsin Card Sorting Task. Sleep quality was assessed subjectively by a single question score, and objectively by ActiGraph for one night on the off day and the last sleep before the first night shift, to evaluate the effect of sleep quality on cognitive

performance.

Keywords: Reaction time, cognitive function, Stoop test, Visual search, Patient safety

Introduction

A substantial body of research has demonstrated that the cognitive function of night shift doctors declines significantly before work [1-4], particularly in the context of the first consecutive night shift [5]; This raises concerns about the potential impact on patient safety. Consequently, there has been a significant focus on night shift scheduling and working hours [6], to identify the most appropriate rotation method and working hours for emergency physicians to ensure patient safety [7].

Caffeine is a psychoactive substance found in many drinks and certain foods. The most widely known and consumed source of caffeine is coffee, but caffeine is also found in tea, energy drinks, carbonated soft drinks, fruit, and foods containing cocoa [8, 9]. It is a recognized stimulant with psychomotor activation and alertness effects [10] and is often consumed by night shift workers, drivers, or the general public. Recent studies have also found that caffeine may reduce the risk of dementia and cognitive decline in the elderly and improve cognitive decline in people with cognitive impairment [11]. Low-dose caffeine's primary mechanism of action as a psychostimulant is based on central antagonism at A1 and A2A adenosine receptors at doses typically consumed orally with caffeinated foods and beverages. Caffeine's ability to bind to adenosine receptors helps to inhibit the brakes exerted by endogenous adenosine on the ascending dopamine and arousal systems, thereby enhancing cholinergic and dopaminergic transmission [12, 13]. Thus, caffeine intake helps to improve self-reported energy, mood, and cognitive functions such as attention; it may also improve simple reaction time, choice reaction time, memory, or fatigue [11, 14].

The ability of caffeine supplementation to improve cognitive function has been studied in several areas. For example, caffeine supplementation was found to be

effective in improving visual search and engagement speed in an alert state one hour before a test in e-sports athletes [15], as well as increasing the speed of keyboard tapping [16], increasing reaction time, and improving shot precision in e-sports shooting events [17, 18], and decreasing reaction time in a Stroop task [17, 19]. In addition, players in such video games must utilize different control strategies to respond quickly to fast-paced, high-stress visual and auditory stimuli, and they must have autonomy to adapt to changing environments [20]. This is similar to emergency physicians, who must respond quickly to changes in patient conditions in a high-pressure work environment. Zabelina et al., Crawford et al. and Marsden et al. have also shown that caffeine significantly improves problem-solving abilities [21-23]. Therefore, emergency physicians, who may be exposed to fast-paced, high-stress visual and auditory stimuli, may be able to find strategies to overcome these challenges by improving their problem-solving abilities through caffeine.

Graham Marsden and John Leach also found that caffeine improved visual search performance in experienced navigators [21], which may also be related to emergency physicians' ability to search for lesions on diagnostic clues and medical images. In addition, caffeine has been shown to improve performance and cognitive functioning in shift workers in a review of the literature [24]. In recent years, caffeine chewing gum has been marketed to facilitate and accelerate caffeine intake [25], and studies have

70 examined the effects of caffeine gum on cognitive performance in e-sports players [17].
71 However, no studies have been conducted on the effects of caffeine supplementation on
72 cognitive functioning in night-shift emergency physicians with caffeinated chewing
73 gum.

74 This study aims to investigate whether caffeine supplementation with caffeinated
75 chewing gum can be used by emergency physicians during night shifts to maintain
76 proper cognitive functioning and thus patient safety. At the same time, sleep monitoring
77 was performed to observe whether caffeine supplementation affected subsequent sleep.
78 This is to provide emergency physicians with a reference for caffeine supplementation
79 with caffeine gum during night shift work.

80

81 **2. Methods**

82 **2.1. Design**

83 This experiment was a double-blind, repeated-measures, crossover design
84 according to the guidelines of CONSORT 2010[26] and was divided into either a
85 caffeine trial (CAF) or a placebo trial (PL). To eliminate the impact of individual
86 physical differences, a crossover trial was conducted with the same group of subjects.
87 Randomized groups were created using Microsoft 365-Excel (Microsoft, Redmond,
88 Washington, United States), and allocation was randomized and unpredictable. Each

89 trial was separated by at least four weeks to avoid interactive effects. This study
90 compared CAF and PL trial to determine the effects of caffeinated chewing gum on
91 cognitive performance in emergency physicians engaged in night shift work., and
92 subjective, objective sleep quality. Caffeinated chewing gum and placebo chewing gum
93 are very similar in appearance, color, size, shape, and flavor and are difficult to
94 distinguish. The randomization was carried out by a research assistant, with another
95 resident performing the experiment, and neither the subjects themselves nor the resident
96 experimenting knew which group the subjects were assigned to or what type of gum
97 they were assigned. Once the data has been collected, it will be forwarded to the group's
98 statistical analyst for statistical analysis, who was also unaware of the group
99 assignments. At least one week before the formal experiment, all subjects participated
100 in three to five familiarization tests for the cognitive function tests. Sleep quality was
101 also assessed subjectively by a single question score, and objectively by ActiGraph for
102 one night on the off day and the last sleep before the first night shift. The primary
103 outcome was the results of cognitive function tests, and the secondary outcome was the
104 sleep quality.
105
106 **2.2. Participants**
107 Fourteen healthy male emergency physicians were recruited in this study and

based on previous research on caffeine in e-sport athletes [17, 18], we used the G*power 3.1 software 24 to achieve an alpha value of 5% and a power of 0.8, which was sufficient for the study with only six subjects. However, due to the lack of relevant studies on the effects of caffeine and caffeinated chewing gum on cognitive functioning in night-shift healthcare workers, reference was made to a recent study that examined the cognitive performance of emergency physicians after 24 consecutive hours of on-call duty, which included 13 subjects [3]. Therefore, it should be adequate to interpret the data derived and statistics from the study.

All participants had experience working regular rotating shifts on the emergency clinical front line and regularly accepted night shift assignments each month. The inclusion criteria were: (i) healthy male adults, those individuals who are free of pain, insomnia, or other injuries recently, without any medication used in recent 2 months, (ii) underwent rotating shifts on the emergency clinical front line with regularly accepted night shift more than two years. The exclusion criteria were: (i) allergy to caffeine, (ii) experience of adverse effects of caffeine, (iii) with cardiovascular diseases or any disease that made subjects feel ill. Two weeks before the main trial, all the participants were asked to avoid ingestion of more than 80 mg of caffeine a day. Before the experiment, all participants were fully informed of the experimental procedures and risks and provided informed consent. This study received approval from the

Institutional Review Board of China Medical University Hospital (CMUH111-REC2-169). This study was conducted following the Declaration of Helsinki.

2.3. Protocol

2.3.1. Experimental procedure

The entire study was conducted in the office of the emergency department of China Medical University Hospital, and the indoor ambient temperature was set at 22°C. Participants' diet and mealtimes were recorded for the 3 days before the first formal experiment, and the participants were required to follow the same diet 3 days before the next formal experiment. They were also required to avoid food and beverages with caffeine (e.g., coffee, energy drinks, chocolate, chocolate drink, and tea) 3 days before the formal experiment.

On the day of the formal experiment, participants had breakfast and lunch at 08:00 and 12:00, respectively. The participants arrived at the office at approximately 23:20 for the experiment. A brief explanation was given and the cognitive test was administered at 23:30, which took about 20 minutes to complete, after which the subjects were ready to go to work. At 03:30, according to the randomized results, the subjects were given two pieces of caffeinated chewing gum at an absolute dose of 200 mg (Military Energy Gum®, Ford Gum and Machine Go, Akron, NY, USA) (CAF trial)

146 or two pieces of similar looking and tasting placebo gum that did not contain caffeine
147 (xylitol, lime mint, green; Lotte, Saitama, Japan) (PLA trial). After 10 minutes of
148 chewing, cognitive function tests were administered. Finally, the last cognitive function
149 tests were performed after duty at 08:20. All subjects used a dedicated computer with a
150 screen frame rate of at least 240 Hz and a mouse response rate of 1ms.

151 To explore the validity of the blinding method, we asked the participants (before
152 and after the test) to identify the supplements they ingested. To do this, the question
153 was as follows: “Which supplement do you think you ingested?” There are three
154 possible answers to this question: (a) caffeine; (b) placebo; and (c) don't know.
155 Furthermore, the occurrence of side effects or complications was recorded during the
156 trial.

157 **2.3.2. Outcome measure**

158 **2.3.2.1. Cognitive function tests**

159 Subjects were sequentially given five tests: Corsi block test, Task-switching
160 paradigm, Stroop Test, Visual search, and Wisconsin Card Sorting Task. All the above
161 cognitive function tests were conducted using Psych/Lab for Windows. Measures used
162 in the literature have satisfactory reliability and validity[27].

163 **2.3.2.1.1. Corsi block test**

164 There will be 9 purple squares in the screen, when the test starts, it will flash a

number of them randomly in yellow color (the more the number increases), then you will hear “Go”, then you have to click the order of the flashing ones, and then press “DONE” in the lower right corner. The smiley face means correct, the crying face means wrong. The maximum number of correct answers will be displayed at the end of the test, which is mainly to test the ability of situational awareness and working memory. The whole process takes about 2 minutes[28-30].

2.3.2.1.2. Task-switching paradigm

There are two shapes (circle, square) and two colors (yellow, blue), four combinations in total. At the beginning of the test, you will see “SHAPE” or “COLOR” (which means that the answer to the question will be based on the shape or color), and then a colorful pattern (e.g., yellow square or blue circle) will appear, then answer the question according to the answer you have just seen (shape or color) as soon as possible. Press B for circles, N for squares, B for yellow, N for blue, and finally the average reaction speed is displayed, which is a test of cognitive structure, flexibility, and plasticity in task processing. The whole test takes about 4 minutes[31, 32].

2.3.2.1.3. Stroop Test

In this quiz, you will see different colors for different words, but all the answers are based on the colors (no matter what the words are). Press R for red, G for green, B for blue, and Y for yellow; for example, if you see “green in red color”, you have to

press R. The test results comprised a congruent condition, in which the key pressed corresponded correctly to the color on the screen, and an incongruent condition, in which the key pressed corresponded incorrectly to the color name on the screen. At the end of the test, the reaction time will be displayed, which is mainly a test of the ability to inhibit cognitive interference. The whole test takes about 5 minutes[33, 34].

2.3.2.1.4. Visual search

In the visual search test, participants identified orange “T” s on the screen from upside-down orange “T” s, blue “T” s, and upside-down blue “T” s. When an orange “T” would appear, the participants were required to press the spacebar as quickly as possible. If no orange “T” appeared, the participants were required to not react. The test contains 80 search displays, each containing 5, 10, 15 and 20 items, mainly to test the search ability of dynamic vision. Reaction speed was displayed at the end of the test, and the whole test took about 4 minutes[15, 21, 35].

2.3.2.1.5. Wisconsin Card Sorting Task

There is a trial-and-error component to this test. You have to answer the questions first and then determine what the question is based on what is right or wrong. The test is presented in a matching mode, where a pattern on the left is matched with one of the four patterns on the right, and the matching criteria are color, shape, and number. During the test, the questions will be changed from time to time, so if you find out the rules

and then suddenly get a question wrong, it means that the question has been changed. The number of errors is displayed at the end of the test to help measure a person's ability to reason abstractly and to change problem-solving strategies when necessary. The entire test lasted about 4 minutes[36-38].

2.3.2.2. Measure Of Sleep

Participants wore a wrist ActiGraph (wActiSleep, Pensacola, Florida, United States) on the nondominant hand for 2 sleep periods, including the sleep on off day and the sleep before the first third night duty. The sleep data were obtained from ActiGraph monitors and analyzed by ActiLife software version 6 using the Cole-Kripke algorithm, including eight sleep indices (sleep latency, total counts, sleep efficiency, total sleep time [TST], wake after sleep onset [WASO], number of awakenings, length of awakenings, time in bed)[39, 40]. Participants also recorded the time they went to bed and woke up to enable coordinate checks with the actigraphic data. Daily sleep quality was measured using a question that was chosen because it was easy to conceptualize, simple to understand, and less burdensome for participants. The question asked was: On a scale of 0-10, with 0 being the worst sleep and 10 being the best, rate the quality of the previous sleep[41].

Participants self-reported age, marital status, exercise habits, smoking, caffeine and alcohol consumption, and chronic diseases. Height and weight were measured from which body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m2).

Statistical analysis

All data are presented as averages ± standard deviations. The Shapiro–Wilk test was used to examine the normality of the data. Cognitive performance, accuracy, and hit reaction time were analyzed through a paired sample t test. Effect sizes were calculated using Cohen's D. Tests were performed (t tests or $\chi 2$ tests) to test for differences at baseline between the two groups. A 2 × 2 mixed-design analysis of variance with repeated measures was used to examine the effects of the intervention. The Bang's Blinding Index (BBI) was used to explore the effectiveness of the blinding whereas the McNemar test was used in the comparison of the incidence of side-effects between the placebo and caffeine conditions. All data were calculated using SPSS (version 20, Chicago, IL, USA), and the significance level was $\alpha < 0.05$.

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