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Research Paper: Citicoline Improves Human Vigilance and Visual Working Memory: The Role of Neuronal Activation and Oxidative Stress

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ABSTRACT

Introduction: Psychomotor performance task is used to assess the arousal and cognitive functions of the central nervous system. Alternatively, human visual working memory reflects the capability of the individual's short-term memory. Psycho-mental stimuli are linked to the stimulation of Malondialdehyde (MDA) formations. Citicoline is a nootropic nucleotide agent with a favorable effect on the augmentation of human memory and cognitive function. Thus, the purpose of this study was to determine the effect of citicoline on human vigilance, visual working memory, and oxidative stress using healthy volunteers.

Methods: 40 healthy volunteers were enrolled and divided into two groups: group A: 20 volunteers received 500mg/day starch capsule for two weeks and group B: 20 volunteers received 500mg/day citicoline capsule for two weeks. Human vigilance, visual working memory, and oxidative stress markers of each volunteer were assessed before and after citicoline and placebo intake. The obtained data were analyzed by SPSS regarding $P<0.05$ as statistically significant.

Results: Placebo had no significant effect on human vigilance and visual working memory after two weeks of therapy ($P>0.05$), whereas citicoline improved most variables of psychomotor performances and working memory ($P<0.01$). Placebo significantly increased serum MDA levels from 19.44±2.11 to 29.66±3.28 nmol/mL ($P=0.0001$), while citicoline significantly decreased MDA serum levels from 19.11±2.66 to 15.63±1.33 nmol/mL ($P=0.0001$).

Conclusion: Citicoline improves human psychomotor vigilance, arousal, and visual working memory with significant amelioration of oxidative stress compared with placebo.

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Highlights

- Citicoline improves human psychomotor performances and working memory accuracy.
- Citicoline attenuates high vigilance induced-oxidative stress.
- Citicoline provokes cognitive functions in normal healthy volunteers.

Plain Language Summary

Citicoline is a nootropic nucleotide agent with a positive effect on the conservation of the neurons and augmentation of human memory and cognitive functions. We examined the effect of citicoline on psychomotor performances and working memory accuracy in relation to the oxidative stress in healthy volunteers. Our results demonstrated that citicoline advances psychomotor performances and working memory precision with the noteworthy lessening of oxidative stress compared with controls in both genders.

1. Introduction

A psychomotor performance task is used to assess the arousal and cognitive functions of the central nervous system through the necessary information from the sensory organs that are provoked in response to different stimuli (Kim et al., 2013). Motor-sensory perception is one of the most important mental processes of psychomotor performances, which plays a role in the integration between the sensory and motor organs during the psychomotor performance (Manita et al., 2015). Psychomotor performance plays an important and vital role in the process of synergy between the motor and sensory integration that is reliant on the awareness of the individual (Elsworthy, Burke & Dascombe 2016). Besides, human visual working memory reflects the capability of an individual's short-term memory that requires encoding, loading, and interpretation of sensory neuronal information (Schwarb, Nail & Schumacher 2016). Many drugs may improve psychomotor performance and working memory by the modulations of different neurotransmitters through antioxidant effect and free radical scavenger activity (Al-Kuraishy, 2016). Citicoline is a cytidine 5′-diphosphocholine composed of ribose, cytosine, pyrophosphate, and choline (Figure 1).

Citicoline is a nootropic nucleotide agent with a favorable effect on the conservation of the neurons and augmentation of human memory and cognitive functions. It acts as choline donors, which stimulates acetylcholine biosynthesis and activates tyrosine hydroxylase activity leading to activation of dopamine release (Roohi-Azizi et al., 2017).

Different clinical trials have shown that citicoline has a potential effect on human cognition, whereas other studies failed to confirm and prove this positive effect (Agarwal & Patel, 2017). Despite its positive effect on the reduction of the rate of disability and death after the ischemic stroke, a meta-analysis found no advantage of citicoline therapy (Bustamante et al., 2012).

Citicoline has a neuroprotective effect through the preservation of neuronal sphingomyelin, cardiolipin, and arachidonic content, as well as phosphatidylethanolamine and phosphatidylcholine. Citicoline also improves glutathione reductase activity and choline availability for acetylcholine synthesis (Trimmel et al., 2018). Moreover, citicoline prevents phospholipase A2 stimulation during ischemic stroke; thus, it attenuates free radical generations from cardiolipin catabolism. It preserves and restores mitochondrial cardiolipin at the inner membrane (Topuz et al., 2014). Citicoline also decreases neuronal glutamate concentration via intensification of glutamate uptake by astrocytes through increasing the expression of glutamate transporters. When the accessibility of choline is low and the requirement for acetylcholine is high, choline from neuronal cell membrane phosphatidylcholine will be the pool for acetylcholine synthesis (Kim et al., 2018).

Psychological and mental stress due to psycho-mental stimuli is associated with the stimulation of Malondialdehyde (MDA) because of the production of oxidative free radicals. It has been reported that psychological stress in medical students during examinations contributes to the initiation of oxidative stress and a rise in MDA serum levels; therefore, irresistible psychosomatic stimuli trigger neuronal oxidative and extreme lipid peroxidation (Srivastava & Batra, 2014).

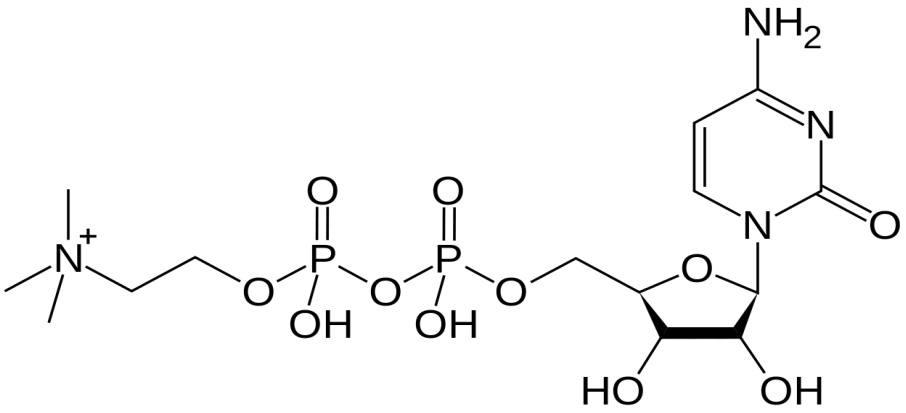

Figure 1. Chemical structure of the citicoline

Furthermore, psychomotor retardation is linked to oxidative stresses, indicating the possible connection between oxidative stress and psycho-mental capacity (Pomara et al., 2015). Thus, the purpose of this study was to determine the effect of citicoline on human vigilance, visual working memory, and oxidative stress in healthy volunteers.

2. Materials & Methods

This study was conducted in the Department of Clinical Pharmacology, College of Medicine, Al-Mustansiriya University and approved by the Scientific Adjudicators and Ethical Committee of Student Research Center at Medical Board, College of Medicine, Al-Mustansiriya according to the revised Helsinki Declaration 2013. All of the enrolled participants provided written informed consent permission for their contributions. In this double-blind study, 40 healthy volunteers (22 males and 18 females) were recruited from the College of Medicine with the age range of 21-22 years and divided into two groups: Group A: 20 volunteers (10 males +10 females) receiving 500mg/day starch capsule for two consecutive weeks and group B: 20 volunteers (12 males+8 females) receiving 500mg/day citicoline capsule (Pittsburgh, PA, healthy origin) for two consecutive weeks.

Starch capsules were prepared by putting 500 mg of starch in each non-gelatin soft-gel capsule and each volunteer received an adequate amount of these capsules to ensure a daily intake of one capsule per day in the morning. This research was a single-blind study; thus, the examiner was aware but the volunteer was unaware of this agent.

In this study, vigilance, visual working memory, and oxidative stress markers of each volunteer were assessed before and after citicoline or placebo intake; i.e. before the intake of the pharmaceutical agents and two weeks after the therapy.

Human vigilance was estimated by the Leeds psychomotor tester, through which Total Reaction Time (TRT), Processing Time (PT), Recognition Reaction Time (RRT), and Movement Reaction Time (MRT) were evaluated.

2.1. Measurement of human psychomotor performances and vigilance

Each participant was asked to press the central button of the device when saw the red light as soon as possible, and the mean of five readings was displayed on the digital screen. TRT (ms) represents the time from the onset of stimuli to the end of the reaction. RRT (ms) presents the time from the onset of stimuli to commencement of motor reaction. MRT (ms) represents the time from the recognition of the stimulus to the end of motor action (MRT=TRT-RRT) and finally, PT (ms) provides the latency time between RRT and MRT (PT=RRT-MRT).

2.2 Measurement of Critical Flicker Fusion Frequency (CFFF)

After the training period, each participant was asked to focus on the four red-emitting diodes located on the black panel of the psychomotor tester device. The participant was asked to press a specific mobile key as soon as possible when he or she detects flicking or fusion of emitting red light. Critical Fusion Frequency (CFF) or ascending frequency (CFFA) represents the time needed in minutes for the red light to be perceived from flickering to be steady. Critical Flicker Frequency or Descending Frequency (CFFD) represents the time needed in minutes for the red light to be perceived from steady to be flickered. Both CFFA and CFFD reflect cortical arousal activity. The range of fusion-flicker frequency was from zero to 60 Hz. Good values for CFFA should be more than 30 Hz and less than 30Hz for CFFD (CFFF= CFFA+CFFD/2) (Alkuraishy & Al-Gareeb, 2017; Angeli, Veres, Nagy & Schneider 2016).

2.3. Measurement of the Short-Term Working Memory Accuracy test (Computerized N-Back test)

This test was carried out on the laptop screen; the eight squares at dissimilar sites were accessible repeatedly on laptop monitor at a tempo of three seconds, a response is demanded each time, and then the single site reverses in sequence. In a one-back test, the participant detects and seeks squares site in relation to the preceding square. In a two-back test, the participant tries to find the site of a square in relation to two reverse trails of the preceding square. In the three-back test, the participant detects and seeks a square site in relation to three reverse trails of the preceding square. One-back (I-back), two-back (II-back), and three back (III-back) represent a low, moderate, and high level of memory accuracy, respectively (Al-kuraishy, Al-Gareeb, Albuhadilly & ALmgoter 2014). The total time needed for the measurement of vigilance, working memory, and CFFF was 10-20 min for each volunteer. Also, 5ml of the blood sample from all volunteers was taken before and after this study for the estimation of MDA, which was assessed by a specific ELISA kit (Shanghai Yuhua Biological Technology Co., Ltd. China).

2.4. Statistical analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) software version 20 (IBM, Statics for Window, Version 20.00; Armonk, NY, USA, IBM Corp.) and expressed as Mean±SD and percentage. The paired t-test and unpaired t-test were used to detect the significance of differences regarding a P-value of less than 0.05 as significant.

3. Results

3.1. Effects ofciticoline on psychomotor performances and working memory accuracy

Placebo illustrated an insignificant effect on the working memory and human vigilance after two weeks of therapy (P>0.05). Placebo shortened the values of TRT, RRT, and MRT but not to the significant levels compared with the baseline values. Besides, it improved working memory accuracy insignificantly (P>0.05). Citicoline therapy for two weeks illustrated a significant improvement in TRT, RRT, MRT, and working memory accuracy (P<0.01) compared with the baseline value; however, it showed no significant effect on CFFD (P=0.30) (Table 1).

Regarding PT, placebo caused an insignificant reduction in the PT (209.11±15.97 ms) compared with the baseline value (210.12±15.56 ms) (P=0.84), whereas citicoline significantly reduced PT from 223.5±12.82 ms to 208.25±18.88 ms (P=0.004) (Figure 2)

Citicoline and placebo caused significant differences after treatment in all vigilance parameters and working memory and citicoline-treated subjects were more affected. TRT, RRT, MRT, and CFFD reduced (getting better and showing a fast reaction) mainly in the citicoline group. On the other hand, CFFA and working memory accuracy significantly increased in the citicoline group. The changes in vigilance, arousal, and working memory accuracy were significant in the citicoline group (P<0.05) (Table 2).

3.2. Effects of citicoline on the biomarker of oxidative stress

Concerning the biomarker of oxidative stress, placebo significantly increased MDA serum levels from 19.44±2.11 to 29.66±3.28 nmol/mL (P=0.001), while citicoline significantly decreased MDA serum levels from 19.11±2.66 15.63±1.33 nmol/mL (P=0.001) (Figure 3).

3.3. Effect of Gender on the citicoline or placebo effects on psychomotor performances and working memory accuracy

In the present study, 22 males (55%) and 18 females (45%) were enrolled, of whom 10 males (50%) compared with 10 female (50%) received citicoline, whereas 12 males (60%) compared with 8 females (40%) received the placebo. The results showed that gender had no significant effect on human psychomotor performances (TRT, RRT, MRT, and CFFF) and working memory parameters (working memory-one back (WM-1), WM-2, and WM-3) in both citicoline- and placebo-treated groups (P>0.05) (Figures 4 & 5).

4. Discussion

Placebo in the present study caused no significant effect on psychomotor performance, attention, and working memory parameters. These results are in harmony with a study, in which a placebo did not cause a significant effect on the psychomotor performance and working memory, concerning TRT, CFF, and working capacity that were not changed after two hours of placebo intake (Adibhatla, Hatcher, & Dempsey, 2002). Our results are not consistent with a previous study that showed the effectiveness of placebo on choice reaction time and working memory tasks through increasing dopamine levels in the frontal lobe and striatum (Hindmarch, Trick, & Ridout, 2005). Thus, a placebo may cause upgrading

Table 1. Effect of citicoline on the vigilance parameters and working memory compared with placebo (n=20)

Vigilance Parameters	Mean±SD		P	Mean±SD		P
	Placebo			Citicoline		
	Before	After		Before	After	
TRT (ms)	655.11±22.62	650.44±21.62	NS	666.18±24.62	493.53±12.58	0.0001*
RRT(ms)	432.55±31.82	429.77±28.83	NS	453.37±22.59	400.31±/ 401.47±19.56	0.001*
MRT(ms)	222.55±20.51	220.66±20.66	NS	229.87±17.49	193.22±11.97	0.0001*
CFFA(Hz)	30.11±11.84	30.88±11.31	NS	30.44±6.44	35.45±4.67	0.0001*
CFFA(Hz)	28.99±9.88	27.55±9.64	NS	29.63±5.83	27.98±4.11	0.30
WM-1(%)	90.54±18.64	95.44±18.42	NS	90.66±17.61	100.65±11.63	0.04
WM-2 (%)	59.66±9.41	61.66±9.39	NS	55.32±8.55	77.63±7.65	0.001*
WM-3 (%)	37.88±9.55	40.45±9.6331	NS	40.29±8.93	49.84±7.56	0.008*

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*P<0.01; TRT: Total Reaction Time; RRT: Recognition Reaction Time ; MRT: Movement Reaction Time; CFFA: Critical Fusion Frequency; CFFD: Critical Flicker Frequency; WM-1: Working Memory-one back; WM-2: Working Memory-two back; WM-3: Working Memory-three back, NS: Not Significant

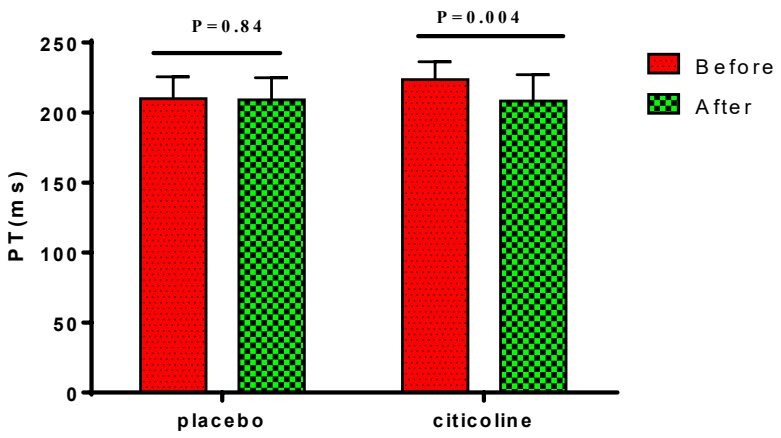

Figure 2. Effect of citicoline and placebo on human Processing Time (PT)

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Table 2. Percent of changes and differences between the effect of citicoline and placebo on the vigilance parameters and working memory accuracy (n=20)

Vigilance Parameters	%		P
	Placebo	Citicoline	
TRT (ms)	0.712↓	25.91↓	0.001*
RRT (ms)	0.642↓	11.44↓	0.001*
MRT (ms)	0.849↓	59.44↓	0.001*
CFFA (Hz)	2.55↑	16.45↑	0.001*
CFFD (Hz)	4.96↓	5.56↓	0.04¶
WM-1 (%)	5.411↑	10.30↑	0.02¶
WM-2 (%)	3.352↑	40.32↑	0.001*
WM-3 (%)	6.785↑	23.70↑	0.001*

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* P<0.01; ¶ P<0.05; ↑ Increase; ↓ Decrease; TRT: Total Reaction Time; RRT: Recognition Reaction Time; MRT: Movement Reaction Time; CFFA: Critical Fusion Frequency; CFFD: Critical Flicker Frequency; WM-1: Working Memory-one Back; WM-2: Working Memory-two back; WM-3: Working Memory-three back

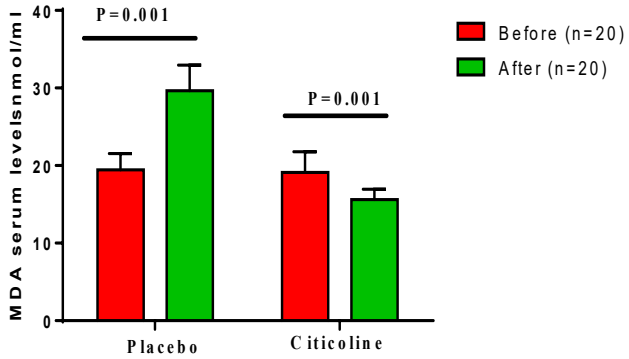

Figure 3. Effect of citicoline on malondialdehyde serum levels compared with the placebo

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* P<0.05

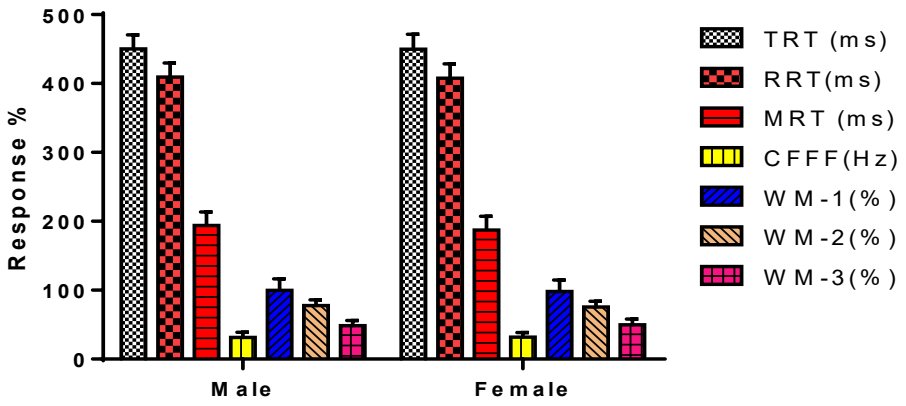

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Figure 4. Gender differences following citicoline therapy on psychomotor performances, vigilance, and working memory accuracy

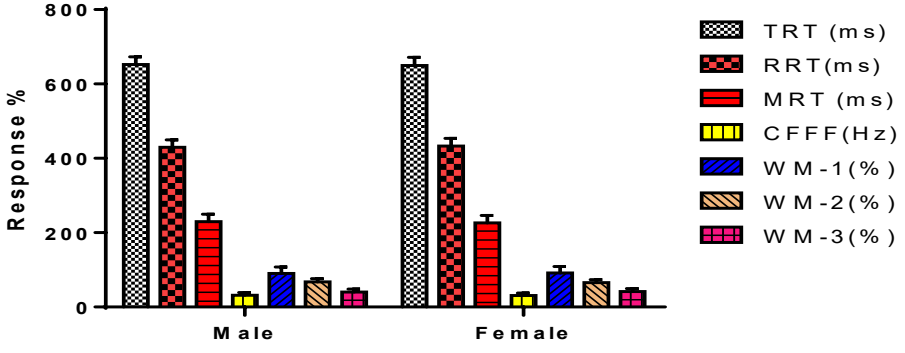

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Figure 5. Gender differences following placebo therapy on psychomotor performances, vigilance, and working memory accuracy

or deterioration of human cognitive function depending on specific expectations. Therefore, the effect of placebo may be revealed on human cognitive functions and reaction time during psychomotor performance, vigilance, and working memory testing depending on stereotype stimulations (Al-Kuraishy, Al-Gareeb, & Ashor, 2012).

The present study also showed that citicoline led to the significant augmentation of psychomotor performance variables. It improved attention and vigilance through upgrading CFFA. Furthermore, citicoline improved Working Memory-one back (WM-1), WM-2, and WM-3 significantly as supported by a study that dealt with the enhancement effect of citicoline on neurological and cognitive impairment, indicating that citicoline plays a precious role in the neuroprotection, neuromodulatory, and neuroregeneration (Secades et al., 2016). Recently, Hutchinson showed a significant effect of citicoline on the acceleration of memory and psychomotor performance in patients with multiple sclerosis through neuronal remyelination and neuroprotection (Hutchinson, 2014). Moreover, Hurtado et al. demonstrated that citicoline therapy for stroke patients led to significant amelioration of cognitive functions due to activation and up-regulation of sirtuin 1 (silent information regulator-1) protein in the brain, which is a deacetylated histone protein that preserves neuronal metabolic homeostasis. Thus, it has a potential therapeutic effect on the amelioration of cognitive function in different neurodegenerative diseases (Hurtado et al., 2013). Additionally, Knott et al. revealed that citicoline improved cognitive function due to the activation of the alpha-7-nicotinic receptor that increasing the sensory gate and executive functions on normal healthy volunteers compared with the placebo group (Knott et al., 2014).

Regarding the arousal and the vigilance effect of citicoline, McGlade et al. showed that 28 days of treatment of citicoline led to significant improvement of attention and arousal state compared to the placebo effect (McGlade et al., 2019).

Different molecular mechanisms of citicoline are involved in the improvement of working memory and psychomotor performances; it improves neuroplasticity because it is a precursor of the membrane phosphatidylcholine and choline, which plays a crucial role in the activation of cerebral metabolism (Secades, 2019). Citicoline restored injured neurons through the acceleration of membrane phospholipid synthesis, stabilization of neuronal Na 2+/K 2+ ATPase, attenuation of free radical generations, and free fatty acids release (Knott et al., 2014). Additionally, the central effect of citicoline may be mediated through the regulation of immunological response following cerebral injury and activation of the repair process. Citicoline significantly modulates the expression and activity of neuronal protein kinases (extracellular signal-regulated kinase and mitochondrial activated protein kinase) that are involved in cerebral neuronal death (Gareri et al., 2015).

Therefore, citicoline has been shown to be effective in the management of Alzheimer disease and vascular dementia because long-term citicoline therapy may prevent memory-cognitive decline through the acceleration of executive functions, temporal orientation, and attention. Besides, citicoline advances verbal memory, short- and long-term memory, and also it improves motor-perceptual ability and emotional-behavioral problems (Gareri et al., 2017).

It has been reported that MDA serum levels are positively correlated with the eustress during psychomotor performances (Al-kuraishy & Al-Gareeb, 2017), which may explain the elevation of MDA during psychomotor activations following the placebo effect. In our study, citicoline illustrated a significant reduction in the level of MDA; thus, it prevents lipid peroxidation and free radical formations as supported by Anthonymuthus et al. study that showed the significant effect of citicoline on the reduction of lipid peroxidation in traumatic brain injury and cerebral ischemia (Anthonymuthu, Kenny, & Bayır, 2016). Moreover, citicoline activates glutathione reductase activity, which plays an important role in the attenuation of free radical effects and lipid peroxidation. Citicoline administration leads to an elevation in glutathione reductase levels within one day, which may be due to the stimulation of glutathione synthesis (Adibhatla, Hatcher, & Dempsey, 2002), but unfortunately, the level of glutathione reductase activity was not estimated in the present study.

Therefore, citicoline improves human cognitive function and working memory through the reduction of oxidative stress and potentiating of endogenous antioxidant capacity as revealed by McGlade et al. and Menku et al. studies that subjected adolescent males to citicoline for 28 days, resulting in a significant improvement in psychomotor performances and cognitive-attention activity, as well as a reduction in impulsivity (McGlade et al., 2019).

Our study showed insignificant differences following citicoline administration in both males and females because there are minimal gender differences in the neuro-cognitive recognition, working memory, and psychomotor speed (Iverson, Brooks, & Ashton Rennison, 2014). On the contrary, Guarraci and Bolton study illustrated significant differences

between males and females in the behavior and cognition after stimulation by nootropic or stimulant agents in conjugation with sex stimulants (Guarraci & Bolton, 2014).

In addition, citicoline caused no significant effect on both males and females regarding the activation of psychomotor speed and cognitive functions following ischemic stroke (Alvarez-Sabín et al., 2016; Mashin, Belova, Bakhtogarimov, Bergelson, & Sharafutdinova, 2017). This insignificant effect of citicoline on both genders might be related to the insignificant differences in male and female cognitive functions. Hyde 2016 study illustrated that males outperform females in spatial tests and mathematics, while females are better than males in verbal tests. The gender distinction in verbal skills is variable according to the stressful factors and skill types (Hyde, 2016). Moreover, Gruber et al. reported that citicoline therapy for 4 weeks improved memory and cognitive functions in subjects with poor logic memory and inefficient mental performances in both sexes equally (Gruber et al., 2015). These findings give a clue that citicoline improved psychomotor performances and working memory of the studied subjects in the present study regardless of gender difference.

It can be concluded that citicoline significantly improved psychomotor vigilance, arousal, and visual working memory with a significant amelioration of oxidative stress compared with placebo on normal healthy volunteers.

Limitations of the present study were its small sample size and also the learning level of the medical student groups was found to influence watchfulness and temporary working memory; however, this marker was not incorporated or evaluated amid additional learning echelons. Antioxidant capacity was not determined and the short duration of the study was also another limitation. But in spite of these limitations, this study can be regarded as a preliminary large-scale study for the evaluation the cognitive improvement by citicoline in healthy subjects.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Scientific Adjudicators and Ethical Committee of Student Research Center at Medical Board, College of Medicine, Al-Mustansiriya according to the revised Helsinki Declaration 2013 (Ethics Code: 421RT; 11/9/2016).

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Authors' contributions

Both authors contributed equally in data collection, data acquisition, and analysis, data interpretations, manuscript writing. Both authors approved the final version of the manuscript for publication.

Conflict of interest

The authors declared no conflict of interest.

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