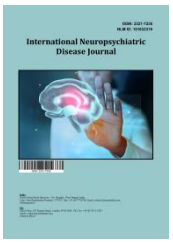

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Sub-Anesthetic Dose of Ketamine Improves Cognitive Function and Motor Responses in Wistar Rats

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Authors' contributions

This work was carried out in collaboration among all authors. Author POU conceived, designed and analyzed the data. Author VTI supervised and critically reviewed the manuscript. Authors POU and CEE performed the experiments and drafted the manuscript. Author OMA critically revised the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Background: The cognitive and motor effects of sub-anesthetic doses of ketamine remain controversial. The aim of this study was to investigate the effects of ketamine administration under anesthesia on cognitive function and motor responses in Wistar rats.
Methods: Twenty-five Wistar rats were randomized into five groups of five rats each (n=5): group 1

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(normal control), group 2 (1mg/kg ketamine), group 3 (2mg/kg ketamine), group 4 (3mg/kg ketamine) and group 5 (0.5ml/100g celecoxib). Treatment for each group lasted 3 weeks. Rats from each group were subjected to a total of nine (9) trials of cognitive-motor tests, including; the Barnes maze test (memory based on visual scenes), hand grip test (motor response to foreleg strength), rotarod test (coordination ability). The neurobehavioral ability displayed by the animals was recorded and analyzed using analysis of variance (ANOVA).

Results: Observations from the cognitive function study showed a significant improvement ($p<0.05$) from week 1 to week 3. The quality of motor task performance also improved from week 1 to week 3 compared to control and celecoxib-treated groups.

Conclusions: Sub-anesthetic doses of ketamine improved cognitive function and motor responses in Wistar rats.

Keywords: Ketamine; cognitive function; motor responses; chronic administration; sub-anesthetic.

ABBREVIATIONS

NMDAR : N-Methyl-D-aspartic Acid Receptor
NAc : Nucleus accumbens
PFC : Prefrontal Cortex
mPFC : Medial Prefrontal Cortex
DA : Dopamine Receptor
VTA : Ventral Tegmental Area
ANOVA : Analysis of Variance

1. INTRODUCTION

"Ketamine has been a complex medication with unusual properties, heterogeneous mechanisms, and diverse, sometimes contested, clinical uses since it was synthesized in a Detroit laboratory nearly six decades ago" [1].

"Anesthesia was revolutionized when scientists identified a new class of drugs in 1956 called cyclohexaylamines" [2]. Phencyclidine (PCP) was the first medication in this class [1]. An entirely new compound (CI-581) was discovered in 1962 that exhibited all the positive properties of PCP without causing severe excitation and severe psychosis [3]. According to the initial results from studies, some subjects experienced an undetected lack of arms or legs after they received ketamine. Others experienced vivid hallucinations and felt "dead" [4-6]. The term "dissociative anesthesia" was coined based on these descriptions [3,4,7].

Ketamine's effects on memory, sleep, and dissociation are primarily attributed to its antagonism of the NMDA receptor [8]. Rodent memory development has been demonstrated to be inhibited by NMDA receptor inhibition [9]. Due to the direct implication of spinal NMDA receptors in central sensitization, repeated agonism may generate hyperalgesia. Acetylcholine, GABA, and nitric oxide (NO) synthase activity may also play a role in the special and intricate activities and side effects of ketamine [10].

In order to treat pain, it can be given intramuscularly, intraperitoneally, or intravenously. Ketamine is not just an anesthetic; it also has the potential to be abused, which can raise the risk of experiencing a number of potentially undesirable outcomes, including both physical and psychological dependence [11-13]. Sometimes used illegally, ketamine has effects that are similar to PCP in terms of intoxication [5,13]. Ketamine occasionally causes users to feel detached from pain and their environments, causing altered visual and sound perceptions, along with a sense of detachment, relaxation, and amnesia [13]. As a result, ketamine is an increasingly popular recreational drug due to its hallucinogenic and dissociative properties [5,13].

Studies have revealed that ketamine is a promising and powerful antidepressant in therapeutic settings [14,15]. It has been demonstrated in neurochemical and neurophysiological investigations that it can generate symptoms resembling those of schizophrenia, such as decreased dopaminergic and GABAergic neurotransmission, which is brought on by NMDA receptor dysfunction [16].

The influence of ketamine on recognition memory is currently poorly supported by experimental data. Although a different study [17] refuted this conclusion, it has been claimed that ketamine interfered with rats' ability to recall familiar objects [18]. Additionally, it is still unclear if ketamine has an impact on the several phases of memory formation (information acquisition, storage, or retrieval).

With the aforementioned findings in consideration, the aim of our investigation was to determine the effect of sub-anesthetic dose of ketamine on cognitive function and motor responses in Wistar rats.

2. MATERIALS AND METHODS

2.1 Experimental Animals

Twenty-five (25) male Wistar rats weighing 180–200g were procured from the University of Port Harcourt's animal house. The rats were kept in clean, disinfected wooden cages with sawdust as beddings in the animal house with a 12-hour light/dark cycle, 50–60% humidity, and a temperature of roughly 30°C. They were given two weeks to acclimate while having free access to clean water and animal feed. Before the experiment began, the rats were weighed using an analytical weighing balance.

2.2 Drugs and Chemicals

Pfizer Corporation, an American multinational pharmaceutical and biotechnology firm with its headquarters in Manhattan, New York City, produced celecoxib (Celebrex) and ketamine (Ketalar) used for this study. They were purchased from Alpha Pharmacy and Stores along NTA Road, Port Harcourt, Rivers State.

2.3 Experimental Design

The experimental design as described by Olorunfemi et al. [19] was adopted. Twenty-five (25) Wistar rats were randomly assigned to five groups of five rats each, as stated below;

Table 1. Experimental design and grouping of the Wistar rats

Groups	No. of Animals	Treatment
Group 1	5	2ml of Distilled Water
Group 2	5	1mg/kg Ketamine
Group 3	5	2mg/kg Ketamine
Group 4	5	3mg/kg Ketamine
Group 5	5	0.5ml/100g Celecoxib

The animals in respective groups received treatment for 3 weeks upon which different cognitive and motor function assessments were done weekly with 3 trials. 1mg/kg of ketamine was administered intraperitoneally to group 2 experimental animals before the trial. Since ketamine is an anesthetic drug, the rat slept before the trial was started. The rats slept for 4 hours. The group administered 2mg/kg of ketamine intraperitoneally before the trial started, slept immediately and it lasted for 8 hours then after 2 hours the rats got their balance before the test trial commenced. The group of animals administered 3 mg/kg of ketamine intraperitoneally before the trial started, slept immediately and it lasted for 24 hours before they regained balance and then the test trial commenced. 0.5ml/100g of Celecoxib was administered orally to group 5 animals every day before the experiment.

2.4 Behavioural Tests

Following the administration of ketamine and celecoxib to the test groups respectively, cognitive evaluations were done on a weekly basis. For a total of three weeks, the test was done on three trials per week, and the results were recorded as such. Barnes Maze test was used to ascertain the sub-anesthetic effect of Ketamine in Wistar rats. Also, the motor effect of the administration of ketamine and Celecoxib was assessed weekly. The test was done on three trials per week, and the results were recorded as such. Handgrip and Rotarod tests were used to ascertain the sub-anesthetic effect of Ketamine on motor function in Wistar rats.

Barnes Maze test: It is a rat-specific visual-spatial learning and memory task. It consists of a raised circle with holes all the way around it. First created by Carol Barnes to examine rat spatial memory, it was later modified for use with mice [20,21]. The rats locate an escape hole that allows them to move from an area of open space and strong light into a dark box beneath the maze using extra-maze visual cues. It should be timed how long it takes to find the entrance to the hidden box beneath the maze.

Handgrip Test: The grip strength test is a simple and direct, non-invasive procedure created to assess mouse muscle force in vivo. It also measures the grip-strength (i.e., peak force and time resistance) of rats' forelimbs and hind limbs by taking advantage of the animal's propensity to grasp a horizontal metal bar or grid while suspended by its tail. The bar or grid is connected to a force transducer, allowing the force generated by pulling on the bar to be periodically recorded at regular intervals over the course of an experiment. For this study, Takeshita et al. modified method was applied [22]. By turning the apparatus vertically, the new forelimb grip strength test was altered from the traditional test. With this change, we anticipated that mice would be more strongly encouraged to continue grabbing the equipment's bar.

This test is designed to evaluate the animal's forelimb strength. The technique can be applied to mice models of neuromuscular disorders to evaluate the effects of particular therapeutic approaches as well as the course of the disease. The performance of the muscular system in conscious dystrophic mice and the impact of different experimental therapies can both be measured using the grip strength test.

Rotarod Test: As first reported by Dunham and Miya and updated by Crawley, the rotarod, commonly known as the rotarod test, is used as a fundamental evaluation tool for coordination, endurance, and balance in rodents and offers one measure of locomotor capacity [23,24]. Testing the effects of experimental drug/chemical agents or following traumatic brain injury, one of the test's functions is to assess the subjects' balance, grip strength, and motor coordination [25]. The rotarod's most basic design consists of a revolving cylinder on which a horizontally oriented animal is mounted. The animal must advance while the cylinder turns in order to prevent falling off. In order to lessen the possibility of hurting animals that fall, the cylinder is positioned above a cushioned landing area. Animals with balance or coordination issues tumble off the apparatus more quickly than those with typical motor skills. The cylinder is usually made of a solid material such as rubber. The rotation of the rod may be manual or, most usually today, motor driven. This period of time, or latency to fall, is the dependent variable of the test [24].

2.5 Method of Data Analysis

Statistical Package for Social Sciences (IBM SPSS) version 25 was used to analyze the study's data. Data were statistically examined using a one-way analysis of variance (ANOVA) followed by a Tukey post-hoc multiple comparison test, with results expressed as mean standard error of mean (SEM), (n=5). An interval of 95% confidence was used to determine statistical significance ($p \leq 0.05$). Histograms were plotted using GraphPad Prism Version 8.0.2.263

3. RESULTS

3.1 Effect of Ketamine and Celecoxib on Cognition and Perceptual Activities of Wistar Rats

Table 2 shows the effect of ketamine and celecoxib on the cognition and perceptual activities of experimental animals from different trials from week 1 to week 3 using Barnes Maze Task. In week 1, there was a significant ($p<0.05$) decrease in the time spent performing the visual-based memory task in the animals administered 1mg/kg ketamine when compared to the control in the first trial. In the second trial, there was a significant increase in the time spent when compared to the control. A slight decrease in the time spent performing the task was observed in the third trial of week 1. A similar trend was also observed in weeks 2 and 3. In the animals administered 2mg/kg and 3mg/kg ketamine, there was a significant ($p<0.05$) increase in the time spent performing the visual-based task in the three trials when compared to the control in week 1 to week 3. However, treatment with celecoxib caused a significant ($p<0.05$) decrease in the time spent performing the visual-based task when compared to control in week 1 and week 3. In week 2, a significant ($p<0.05$) decrease in the time spent performing the task was observed in trial 1, but there was an increase in the time spent in trial 2 and a significant increase in trial 3 in week 2 (see Fig. 1).

3.2 Effect of Ketamine and Celecoxib on Cognito-motor Activities of Wistar Rats

Table 3 shows the effect of ketamine and celecoxib on the cognito-motor activities of experimental animals from different trials from week 1 to week 3 using handgrip test. In week 1, there was a decrease in the grip strength of animals administered 1mg/kg ketamine when compared to the control in all trials. This decrease in grip strength was, however, not significant ($p>0.05$). In week 2, there was an insignificant ($p>0.05$) in the grip strength of the animals in the first trial when compared to control. However, there was an increase in the grip strength in the second and third trials when compared to the control. The increase in the grip strength in the third trial was statistically significant when compared to control. In week 3, there was a significant ($p<0.05$) increase in the grip strength of the animals in the three trials when compared to the control (see Fig. 2). There was a significant ($p<0.05$) increase in the grip strength of animals administered 2mg/kg ketamine when compared to control in the first trial in week 1. However, there was a decrease and increase in the grip strength in the second and third trials respectively. This decrease and increase in the grip strength in the second and third trials were not statistically significant

(p>0.05). In week 2, there was a significant (p<0.05) decrease in the grip strength of animals in the first trial. An increase in grip strength was observed in the second and third trial. However, only the increase in the second trial was significant (p<0.05) when compared to control. In week 3, there was increase in grip strength in the three trials. However, the grip strength in the second and third trials were significant (p<0.05) when compared to control. There was decrease in the grip strength of animals administered 3mg/kg ketamine when compared to control in the first trial in week 1. This decrease in grip strength was not significant (p>0.05) when compared to control. In the second and third trial, there was significant (p<0.05) increase in grip strength of the animals. In week 2 and week 3, there was significant (p<0.05) increase in the grip strength in the three trials when compared to control (see Fig. 2). However, treatment with celecoxib caused increase in the grip strength of the animals in the three trials. This increase in grip strength was significant (p<0.05) in the second and third trial when compared to control in week 1. In week 2 and week 3, there was significant (p<0.05) increase in grip strength of animals in the three trails when compared to control (see Fig. 2).

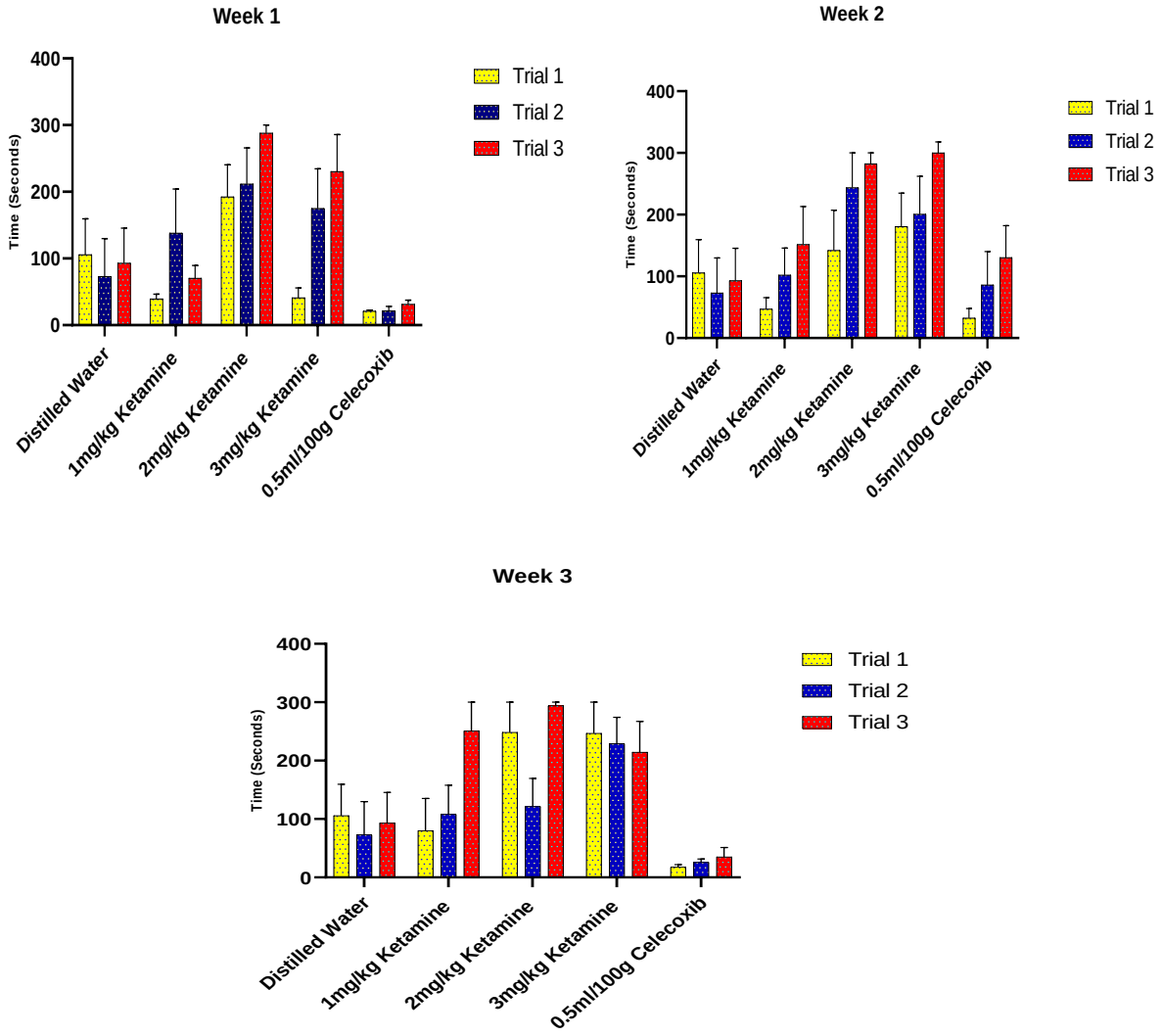


Fig. 1. Profile of Cognition and Perceptual Assessment Using Banes Maze Task in the Test and Control Groups week 1 to week 3. Values are presented in Mean ± SEM; n=5, *means values are statistically significant at p<0.05 when compared to the control values

Table 2. Assessment of cognition, perceptual activities using barnes maze task on ketamine, celecoxib treated rats and control groups

Groups	Treatments	Week 1			Week 2			Week 3		
		Time (S±SEM)			Time (S±SEM)			Time (S±SEM)		
		Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3
Group 1	Distilled Water	105.80±53.6	73.00±56.7	93.20±52.3	105.80±53.6	73.00±56.7	93.20±52.3	105.80±53.6	73.00±56.7	93.20±52.3
Group 2	1mg/kg Ketamine	39.60±7.0*	138.20±66.1*	70.60±18.9	47.00±18.6*	102.20±43.7*	151.80±61.4*	80.00±55.1	108.00±49.9*	250.80±49.2*
Group 3	2mg/kg Ketamine	192.40±48.1*	211.80±54.1*	288.20±11.8*	142.20±64.9*	243.80±56.2*	282.40±17.6*	248.60±51.48*	121.40±48.2*	294.00±6.0*
Group 4	3mg/kg Ketamine	41.00±14.8*	175.00±59.4*	230.40±55.4*	180.80±54.0*	200.80±61.3*	300.00±0.0*	246.80±53.2*	229.00±45.1*	214.60±52.5*
Group 5	0.5ml/100g Celecoxib	21.00±1.5*	21.40±6.7*	31.40±6.0*	32.40±15.4*	86.00±54.2	130.60±51.4*	17.80±4.1*	25.80±5.6*	35.00±16.3*

*Values are presented in Mean ± SEM; n=5, * means values are statistically significant at p<0.05 when compared to the control values.*

Table 3. Assessment of Cognito-Motor Activities Using Handgrip Test on Ketamine, Celecoxib Treated Rats and Control Groups

Group	Treatment	Week 1			Week 2			Week 3		
		Time (S±SEM)			Time (S±SEM)			Time (S±SEM)		
		Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3
Group 1	Distilled water	24.00 ± 4.4	10.20 ± 2.4	9.40 ± 2.2	24.00 ± 4.4	10.20 ± 2.4	9.40 ± 2.2	24.00 ± 4.4	10.20 ± 2.4	9.40 ± 2.2
Group 2	1mg/kg Ketamine	19.60 ± 6.0	14.40 ± 2.2	8.20 ± 1.5	20.60 ± 8.9	12.20 ± 3.4	27.40 ± 6.3*	36.20 ± 12.0*	42.40 ± 18.6*	59.80 ± 24.9*
Group 3	2mg/kg Ketamine	81.00 ± 55.4*	6.20 ± 2.1	13.60 ± 5.0	18.40 ± 7.7*	16.00 ± 7.1*	12.00 ± 6.1	26.60 ± 13.5	44.20 ± 21.0*	34.40 ± 10.9*
Group 4	3mg/kg Ketamine	20.80 ± 12.3	19.00 ± 7.5*	23.80 ± 11.3*	61.40 ± 28.0*	59.40 ± 18.9*	52.80 ± 19.4*	47.20 ± 11.6*	43.40 ± 16.2*	35.00 ± 12.8*
Group 5	0.5ml/100g Celecoxib	25.40 ± 11.4	22.00 ± 5.6*	22.40 ± 5.0*	40.80 ± 14.0	29.60 ± 7.0	28.80 ± 8.8	58.40 ± 25.5*	42.20 ± 24.4*	21.40 ± 5.0*

*Values are presented in Mean ± SEM, n=5, * means values are statistically significant at p<0.05 when compared to the control values*

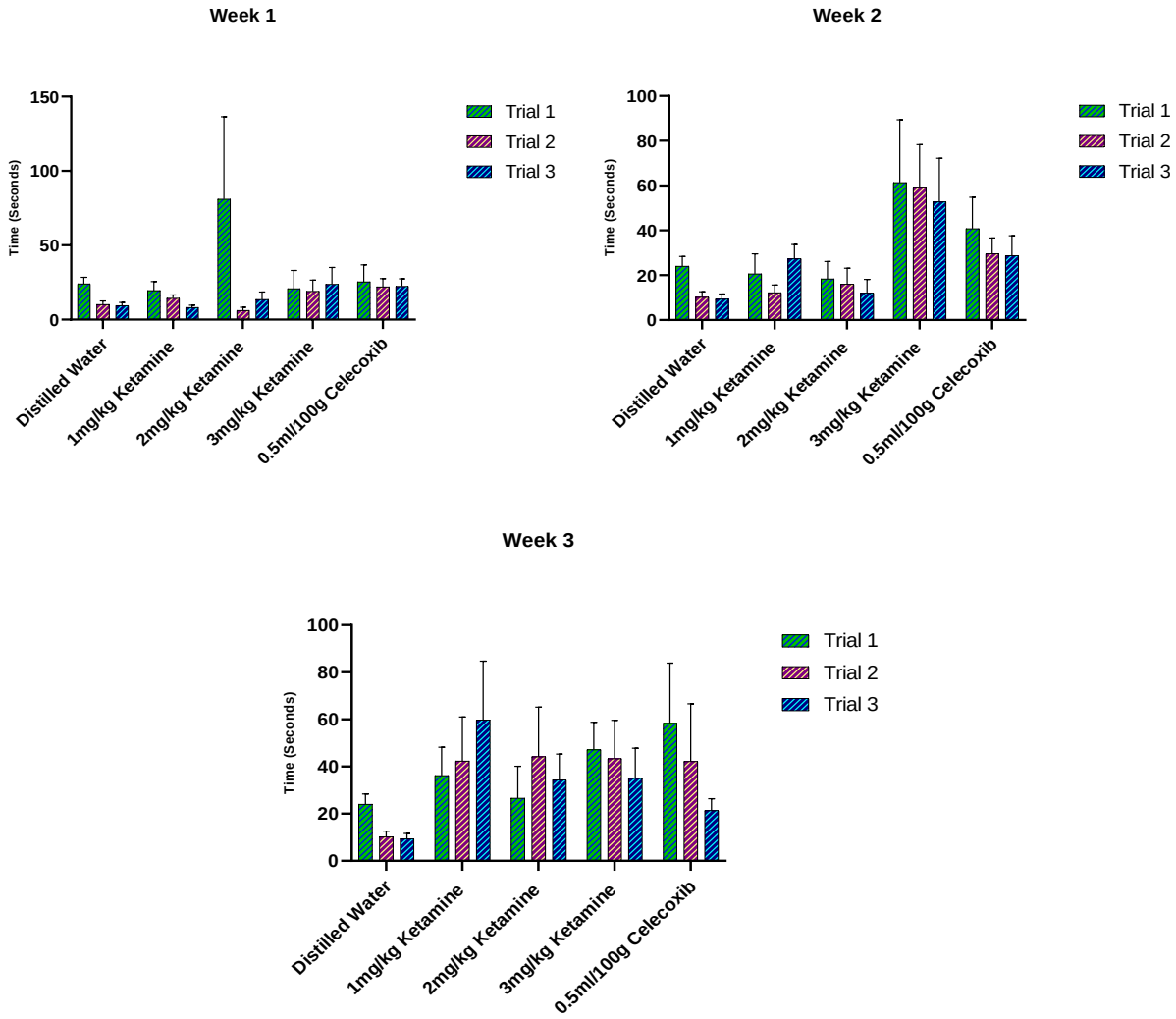


Fig. 2. Profile of Cognito-Motor Assessment Using Handgrip Test in the Test and Control Groups week 1 to week 3. Values are presented in Mean ± SEM; n=5, *means values are statistically significant at p<0.05 when compared to the control values

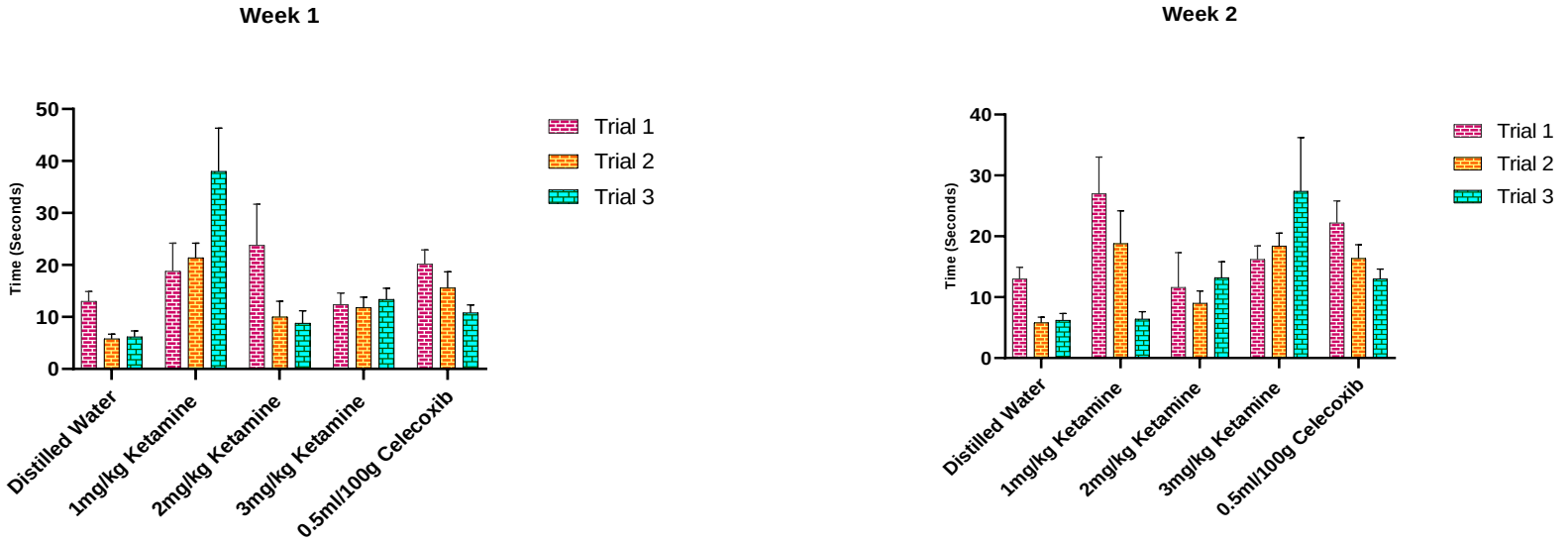
3.3 Effect of Ketamine and Celecoxib on Locomotive Activities of Wistar Rats

Table 4 shows the locomotive activities using rotarod test on ketamine, celecoxib treated rats and control group. There was increase in the time spent by the animals treated with 1mg/kg ketamine on the rotarod before falling off in the three trials in week 1 and week 2. This increase in time spent on the rortarod before falling off was significant ($p<0.05$) in the second and third trial in week 1 and in the first and second trial in week 2 when compared to control. In week 3, there was significant ($p<0.05$) increase in time spent on the rortarod before falling off in the three trials when compared to control. There was increase in the time spent by the animals treated with 2mg/kg ketamine on the rotarod before falling off in the three trials in week 1. This increase in time spent on the rortarod before falling off was significant ($p<0.05$) in the first and second trial when compared to control (see Fig. 3). Significant ($p<0.05$) increase in the time spent on the rotarod was observed in the second and third trial in week 2 and week 3. However, there was decrease in the time spent on the rotarod in the first trial. This decrease was not significant ($p>0.05$) when compared to control. There was increase in the time spent by the animals treated with 3mg/kg ketamine on the rotarod before falling off in the three trials in week 1. This increase in time spent on the rortarod before falling off was significant ($p<0.05$) in the first and second trial when compared to

Table 4. Assessment of locomotive Activities Using Rotarod Test on Ketamine, Celecoxib Treated Rats and Control Groups

Groups	Treatment	Week 1			Week 2			Week 3		
		Time (S±SEM)			Time (S±SEM)			Time (S±SEM)		
		Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3	Trial 1	Trial 2	Trial 3
Group 1	Distilled Water	13.00±1.9	5.80±0.9	6.20±1.1	13.00±1.9	5.80±0.9	6.20±1.1	13.00±1.9	5.80±0.9	6.20±1.1
Group 2	1mg/kg Ketamine	18.80±5.4	21.40±2.8*	38.00±8.3*	27.00±6.0*	18.80±5.38*	6.40±1.2	19.00±6.2*	15.60±3.3*	15.80±1.8*
Group 3	2mg/kg Ketamine	23.80±7.9*	10.00±3.0*	8.80±2.4	11.60±5.7	9.00±2.0	13.20±2.6*	11.40±4.2	17.2±6.3*	13.40±5.7*
Group 4	3mg/kg Ketamine	12.40±2.2	11.80±2.0*	13.40±2.1*	16.20±2.2	18.40±2.1*	27.40±8.8*	13.00±3.7	9.60±2.1	15.40±5.1*
Group 5	0.5ml/100g Celecoxib	20.20±2.7*	15.60±3.1*	10.80±1.5	22.20±3.6*	16.40±2.2*	13.00±1.6	9.20±0.9	17.60±5.0*	14.20±5.3*

*Values are presented in Mean ± SEM, n=5, * means values are statistically significant at p<0.05 when compared to the control values*



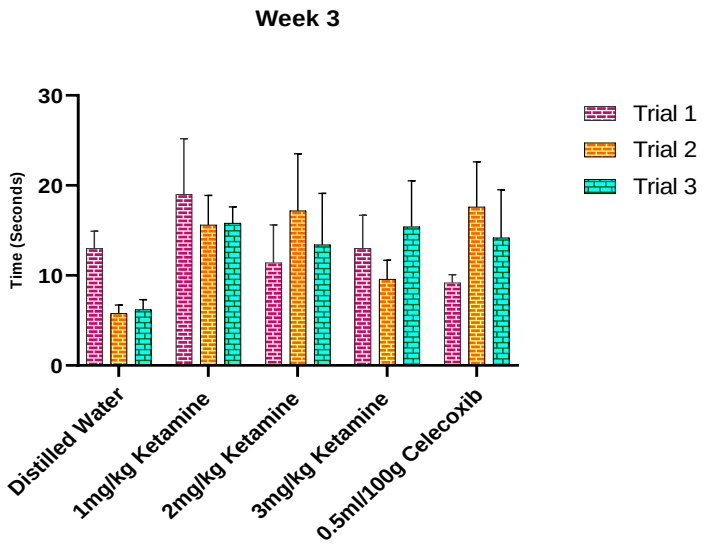


Fig. 3. Profile of Cognito-Motor Assessment Using Rotarod Test in the Test and Control Groups week 1 to week 3. Values are presented in Mean ± SEM; n=5, *means values are statistically significant at p<0.05 when compared to the control values

control (see Fig. 3). There increase in the time spent on the rotarod in week 2 and week 3. This increase in time spent on the rortarod before falling off was significant ($p<0.05$) in the second and third trial in week 2. No significant increase in the time spent on the rotarod in the three trials in week 3when compared to contro (see Fig. 3). Animals treated with celecoxib showed increase in time spent on the rotarod before falling off in the three trials in week 1 and 2. The increase in the time spent on the rotarod was significant ($p<0.05$) in the first and second trial in week 1 and significant ($p<0.05$) in the three trials in week 2. In week 3, significant {$p<0.05$) increase in the time spent on the rotarod was observed in the second and third trial, while an insignificant ($p>0.05$) was observed in the first trial (see Fig. 3).

4. DISCUSSION

“Ketamine is a therapeutically significant medication that is extensively used in anesthesia and perioperative analgesia, particularly in resource-constrained nations” [26,27]. Given its hallucinogenic qualities, it is also a popular recreational drug [28]. “Ketamine's role as a noncompetitive N-Methyl-D-Aspartate (NMDA) receptor antagonist in blocking the processing of nociceptive signals at sub-anesthetic levels has led to its usage in the therapy of chronic pain syndromes” [29,30]. However, both in preclinical research and in compulsive users, ketamine has been shown to cause cognitive deficits [31,32]. “Ketamine has shown to induce a significant increase in glutamate release in the nucleus accumbens, facilitating synaptic flow of information from the prefrontal cortex (PFC) and amygdala, which is consistent with the hypothesis that ketamine acts preferentially to block NMDA receptors on inhibitory neurons, resulting in disinhibition and increased glutamate release in the PFC and limbic regions” [33,34]. Consequently, the purpose of this study was to investigate the effect of sub-anesthetic ketamine administration on cognitive function and motor responses in Wistar rats.

The results of the Barnes maze test in the current study, as shown in Table 2 and Fig. 1, showed that there was an increase in the time spent performing the visual-based memory task across test groups from week 1, week 2, and week 3 when compared to the control group and celecoxib treated group. When compared to the control group, no significant decline in memory, mental retardation, or dullness was observed across test groups, except in the celecoxib-treated group, which showed dullness and a decline in cognitive performance. This implies that sub-anesthetic doses of ketamine did not impact on cognitive activities of experimental animals; instead, it caused an unexpected boast in cognitive function in experimental animals resulting in an increased time in performing the visual-based memory task. This finding contradicts the findings of Olorunfemi et al. [19] who observed that performance on the visual scene-based memory task was skewed throughout the test groups as compared to the epinephrine-treated group in a dose- and time-dependent pattern; and as well as studies by Venâncio et al. [35]. As a result, ketamine did not reduce spatial learning and memory by inhibiting NMDA receptors [34,35]. Davis et al. [36] also found that low-ketamine dosed rats had considerably better spatial memory recall than high-ketamine dosed rats. The rats in the high-ketamine group appeared to struggle with working memory more than the rats in the low-ketamine and control groups. This suggests that lower doses of ketamine have little to no detrimental cognitive effect, however higher doses of ketamine may have a stronger long-term influence on an individual's cognition [36]. This is intriguing because people under the effect of ketamine have been shown to have poor spatial working memory [37,38].

Assessment of Cognito-motor activities using handgrip test on ketamine, celecoxib treated rats and control groups as presented in Table 3 and Fig. 2, showed that experimental animals treated with 1mg/kg ketamine showed a very strong grip strength in trial 1 of week 1 when compared to the grip strength in other experimental groups (2mg/kg and 3mg/kg ketamine treated group), as well as the control group and celecoxib treated group. Assessment of the grip strength of other trials in week 1 showed that grip strength of ketamine treated animals was not as strong as that of the celecoxib treated group but stronger than control animals.

A drop in grip strength was observed in experimental animals treated with 1mg/kg and 2mg/kg ketamine respectively in week 2 when compared with celecoxib treated group but the grip was stronger than the control group across all trials except in trial 1 of week 2. Experimental animals treated with 3mg/kg ketamine showed stronger grip strength when compared to control and celecoxib treated group in week 2.

Also, when compared to the control group and trial 3 of the celecoxib-treated group, experimental rats given 1mg/kg, 2mg/kg, and 3mg/kg of ketamine had greater grip strength throughout all trials in week 3.

From the assessment of the hand grip strength, there was an improvement in handgrip capacity of experimental animals treated with sub-anesthetic doses of ketamine from week 1 to week 3, but not in a dose- and time dependent manner. Hence, sub-anesthetic doses of ketamine did not cause dystrophy in experimental animals or compromise motor function through other mechanisms. Wojtas et al. [39] revealed that ketamine suppressed rat locomotor activity which did not affect animals' behavior. The finding of their study was contrary to that of this present study, since ketamine did not suppress motor responses, but rather amplified it somewhat. This was further proved by the improvement in locomotive abilities of experimental animals treated with sub-anesthetic doses of ketamine when compared to control as (Table 3 and Fig. 2). Assessment of locomotive abilities using rotarod test showed that experimental animals treated with 1mg/kg ketamine showed better locomotive abilities when compared to control group in week 1. Also, animals treated with 2mg/kg and 3mg/kg ketamine showed improved coordination, endurance and balance in locomotive abilities when compared to control group in week 1. From week 2 to week 3, locomotive abilities improved in animals treated with sub-anesthetic doses of ketamine and celecoxib when compared to control.

Ketamine did not cause an inhibition in cognitive function and motor responses from this study and it could be due to naivety of experimental animals [39]. According to a study conducted by Viktorov et al. [40] the effect of NMDA antagonists in animals not subjected to any model of depression is limited. On the other hand, our behavioral tests were conducted after the drugs were administered, which, while sufficient to eliminate their acute effects, may not be sufficient for the long-term effects to manifest fully, as Hibicke et al. [41] reported an antidepressant effect 7 days after psilocybin administration. The improvement in cognitive function and motor responses from this study is well supported by the systematic review of by Souza-Marques [42]. Out of 14 review studies, five found increases in processing speed, verbal memory, visual memory, working memory, or cognitive flexibility following ketamine treatment, whereas only one indicated cognitive impairment in processing speed and verbal memory after ketamine treatment. As a result, ketamine does not appear to have substantial negative neurocognitive consequences in patients with treatment-resistant depression, either in the short or long term.

5. CONCLUSION

The effect of sub-anesthetic ketamine treatment on cognitive function and motor responses in Wistar rats was examined in this study. This revealed that sub-anesthetic does of ketamine did not inhibit, rather, it improved cognitive function and motor responses in Wistar rats. Also, celecoxib showed similar trend when compared to control. Hence, sub-anesthetic doses of ketamine improve cognitive function and motor responses in normal Wistar rats.

6. RECOMMENDATION

Further studies to corroborate or contradict our findings are highly recommended. Such studies may evaluate the objectives of this present study for a period beyond three weeks (which was done in this study. Additionally, animal models of depression or other mental diseases may be employed to assess the effect of ketamine on cognitive and motor functions in these animals.

CONSENT

It is not applicable.

ETHICAL CONSIDERATION

All methods in this study were carried out in accordance with the University of Port Harcourt Research Ethics Committee's guiding principles for animal research and Standards for Care and use of Laboratory Animals.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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