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Effect of Administration of Subanaesthetic Doses of N-Methyl-D-aspartate Antagonist (ketamine) in Rats' Perception, Cognition, and Motor Response

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Abstract

Ketamine, an N-methyl –D-aspartate (NMDA) antagonist, has been abused as a recreational drug due to its euphoric, dissociative, and hallucinogenic characteristics. Series of studies have been carried out on the effect of ketamine on cognition and memory. However, there is dearth literature on the activities of ketamine as a recreational drug of abuse; its effect on motor response in association with cognitive behaviours in Wistar rat models. Hence, this study is necessary to investigate the effects of chronic administration of sub-anesthetic doses of ketamine on perceptual, cognitive, and motor responses in Wistar rats. 25 *Wistar* rats (160-180 kg) were randomly selected into five groups and treated for three weeks thus: Group 1 (control), Group 2 (0.2 mL Ketamin-i.p), Group 3 (0.4 mL Ketamin-i.p), Group 4 (0.6 mL Ketamin-i.p) Group 5 (0.5 mL Cerebrex-orally). Neurobehavioral (Barnes, rotarod, and handgrip) activities exhibited by the various groups were recorded and analyzed using ANOVA. In the Barnes maze test, there was a significant increase ($p<0.05$) in escape time from weeks 1, 2 and 3 in groups 2, 3 and 4 when compared to control. In week 2 and 3 of the handgrip test, animals in group 4 had a significant improvement ($p<0.05$) in grip strength when compared to control. In weeks 1 and 2 of the rotarod test, groups 2 and 4 animals respectively, showed a significant increase ($p<0.05$) in balance compared to control. Sub-anesthetic doses of ketamine inhibited cognitive function but not motor responses in Wistar rats.

Keywords: Ketamine; Barnes maze; Rotarod test; handgrip test; brain; cognition; spatial memory; N-methyl –D-aspartate (NMDA).

1.0 INTRODUCTION

1.1 Background to the study

In both human and veterinary surgical procedures, ketamine (ketamine hydrochloride) has been used as an anesthetic agent (Kurdi *et al*., 2014; Shi *et al*., 2021). It serves as a pharmaceutical model of depression and schizophrenia in academic studies (Uliana *et al*., 2022). Ketamine has consistently ranked high on lists of substances that are abused and used recreationally in many parts of the world (Chang *et al*., 2019). Due to its psychotropic effects, it is currently a restricted substance in many nations, yet its use as a recreational drug has spread globally (Morgan *et al*., 2013). After surgery or while treating burns, ketamine makes sedatives more effective and may reduce the need for addictive opioids like morphine (Abdolrazaghnejad *et al*., 2018). When abused, ketamine can alter your hearing and vision.

In the developing brains of a range of animals, including rats, general anesthetic administration at clinically relevant concentrations appears to cause a broad increase in neuronal death. (Iwanaga *et al*., 2021). They are long-lasting impacts. Behavior problems may persist even after a child has been exposed to anesthetics in childhood (Iwanaga *et al*., 2021), even while there is no longer a discernible rise in neuronal apoptosis (Iwanaga *et al*., 2021). Moreover, the potential for toxicity from ketamine usage has shown degenerative alterations in both human and animal organs (Orhurhu *et al*., 2023). They include its toxicity on the immune system, liver, pancreas, adrenal gland, gut, and central nervous system (CNS) (Orhurhu *et al*., 2023).

Pharmacologically, ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist that also affects opioid receptors and monoamine transporters

(Iadarola *et al*., 2015). Moreover, this receptor has been linked to memory and learning (Newcomer *et al*., 2022). According to some reports, ketamin may contribute to forgetfulness (Shi *et al.*, 2021). Moreover, research suggest that NMDA inhibition caused by ketamine usage may impair memory and learning (Newcomer *et al*., 2022).

Basic researchers have demonstrated for about a decade that the excitatory amino acid (EAA) receptor, NMDA, is crucial in experimental animals of severe pain (Nakazawa and Sapkota, 2020). To assess the analgesic effects of various NMDA receptor antagonists, such as ketamine, in individuals with chronic pain, these studies have more investigation in this field (Dahan *et al*., 2017). Animals with dopaminergic receptor depletion have been observed to have considerable locomotor stimulation when given NMDA receptor antagonists (Adell, 2020). Yet, investigators have noted contradictory findings after inhibiting the DA-induced circling habit in lesioned rats (Lane *et al*., 2006).

Although being frequently used as an anesthetic and analgesic, ketamine, a non-competitive NMDA receptor antagonist, has been shown to be toxic to the brain (Orhurhu *et al*., 2023). Ketamine has been abused as a recreational drug due to its euphoric, dissociative, and hallucinogenic characteristics, which has resulted in strict supervision of the pharmaceutical sector (Edinoff *et al*., 2023). Series of studies have been carried out on the effect of ketamine on cognition and memory. However, due to the dearth of information regarding the activities of ketamine as a recreational drug of abuse; its effect on motor response in association with cognitive behaviours in Wistar rat models have not been fully explored. More research to address this gap is needed. Hence, this study is necessary to investigate the effects of chronic administration of sub-anesthetic doses of N-methyl-D-aspartate receptor antagonist (ketamine), on perceptual, cognitive, and motor responses in Wistar rats. To achieve this aim, the following methods were adopted.

2.0 MATERIAL AND METHODS

2.1 Drugs and Chemicals

Ketamine hydrochloride injection and Cerebrex (Rotex Medica. Trittau. Germany) was procured from registered pharmacy store in Port Harcourt.

2.2 Experimental Animals and housing

25 Wistar rats of comparable sizes of 160 – 180g were bought from the Animal House of the Department of Physiology, Faculty of Basic Medical Sciences, College of Health Sciences, University of Port Harcourt, Nigeria. The animals were housed in a forced air facility before and during the experiment at the Animal House in the University of Port Harcourt. The animals were maintained in the cages at 23°C and 50 – 60% relative humidity, with maximum ventilation. The groups were kept in separate compartments of different plastic cages measuring 23.5 x 16.5 x 12cm (length, height, and width respectively) and were always given water and feeds *ad libitum*. The experiment described in this report was conducted in accordance with the National Institute of Health (2002) guide for the care and use of laboratory animals. These guides were approved by the institutional ethics committee for animal experiment.

2.2.1 Acclimatization of Animals

The rats used for the study were acclimatized for two weeks at the animal house to observe them before the commencement of the experiment under standard laboratory condition in a well-ventilated standard housing condition.

2.3 Ethical Statements

The experimental procedures and techniques used in the study were in accordance with acceptable principles for laboratory animal use and care by NIH, 1985 and EU directive of 1989:86/609/EEC. All conditions and handling of the animals were approved by the Ethical Committee of Faculty Basic Medical Sciences, University of Port Harcourt, Nigeria.

2.4 Preparation of Treatment

The drug, monosodium glutamate was bought in a mall and was used in this study. The monosodium glutamate was diluted in 20 ml of distilled water and was stored in a plastic bottle.

2.5 Experimental Design and animal grouping

0.2 mL of ketamine was interperitoneally administered 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. 0.4 mL of ketamine was interperitoneally administered to group 3 rats before the trial started. The rats slept immediately, and it lasted for 8 hours then after 2 hours the rats got its balance the test trial commenced. 0.6 mL of ketamine was interperitoneally administered to the rats slowly. Since it is an active drug, the rats slept immediately after the treatment it lasted for 24 hours. 0.5 mL of cerebrex was given to group 5 every day before the experiment. Investigating the cognitive Effects of N-methyl-D-aspartate receptor antagonist (ketamine) in Wistar rats using Handgrip test, Rotarod test, Banes Maze task.

Cognitive assessment was conducted weekly following the treatment of test groups with ketamine and cerebrex respectively. The test was conducted in 3 trials per week for the period of 3 weeks and was recorded accordingly.

Table 1: The experimental design showing the group, treatment, test, procedure, and duration

Groups	Treatment	Neuro-Behavioural test	Procedure and Duration
Group 1	Control 1 mL of distilled water (5 rats)	Handgrip test, Rotarod test, Barnes Maze task	The rats were exposed through the test without any drug treatment for 3 weeks
Group 2	0.2 mL of Ketamine (5 rats)	Handgrip test, Rotarod test, Barnes Maze task	The rats were exposed through the test with 0.2ml Ketamine treatment intraperitoneally for 3 weeks
Group 3	0.4 mL of Ketamine (5 rats)	Handgrip test, Rotarod test, Barnes Maze task	The rats were exposed through the test with 0.4ml Ketamine treatment intraperitoneally for 3 weeks
Group 4	0.6 mL of Ketamine (5 rats)	Handgrip test, Rotarod test, Barnes Maze task	The rats were exposed through the test with 0.6ml Ketamine treatment intraperitoneally for 3 weeks
Group 5	0.5 mL of Cerebrex (5 rats)	Handgrip test, Rotarod test, Barnes Maze task	The rats were exposed through the test with 0.5ml Cerebrex treatment orally for 3 weeks

2.6 Neuro-Behavioural studies

2.6.1 Barnes Maze

The Barnes maze is a tool used in psychological laboratory experiments to measure spatial learning and memory. The test subjects are rodents such as mice or lab rats. It is a visual-spatial learning and memory task designed for rats. It consists of an elevated circular surface with holes around the edge. It is an instrument used in psychological laboratory experiments to measure spatial and learning memory (Barnes, 1979). The study of spatial memory led to Barnes maze development, originally for rats and later adopted for mice (Bach *et al*., 1995; Barnes, 1979). Rodents utilize extra-maze visual cues to locate an escape hole and can escape from open space and bright light into a dark box beneath the maze. Time taken to locate the escape hole into the dark box beneath the maze is then recorded.

2.6.2 Rotarod Test

The rotarod also known as the rotarod test, is used as a basic assessment tool for coordination, endurance and balance in rodents and provides one measure of locomotors ability as originally described by Dunham and Miya, (1957) and modified by Crawley, (2003). Some of the functions of the test include evaluating balance, grip strength and motor coordination of the subjects; especially in testing the effect of experimental drugs or after traumatic brain injury (Mouzon *et al*., 2012).

2.6.3 Handgrip Test

The grip strength test is a simple non-invasive method designed to evaluate mouse muscle force in vivo, by taking advantage of the animals' tendency to grasp a horizontal metal bar or grid while suspended by its tail, this test is also used to measure grip-strength (i.e., peak force and time resistance) of forelimbs and hind limbs in rats. The modified method as described by (Takeshita *et al*., (2017) was used for this work.

2.7 Method of Data Analysis

Statistical data were analysed using GraphPad Prism 8 software (Graph-pad Software Inc., San Diego, USA). Multiple-group parametric data were analysed by one-way analysis of variance (ANOVA), expressed as mean ± standard error of mean (SEM); followed by a Tukey's *post hoc* test for multiple group comparisons. Data was considered statistically significant when $p \leq 0.05$.

3.0 RESULTS

3.1 Result summary

3.1.1 Barnes maze

In Fig 1, there was a significant increase ($p<0.05$) in the time taken for the rats administered with 0.4 mL and 0.6 mL of ketamine to locate the escape route in the Barnes maze task when compared to the control group.

In Fig 2, there was a significant increase ($p<0.05$) in the time taken for the rats administered with 0.2 mL and 0.4 mL 0.6 mL of ketamine to locate the escape route in the Barnes maze task when compared to the control group.

In Fig 3, there was a significant increase ($p<0.05$) in the time taken for the rats administered with 0.2 mL and 0.4 mL 0.6 mL of ketamine to locate the escape route in the Barnes maze task when compared to the control group.

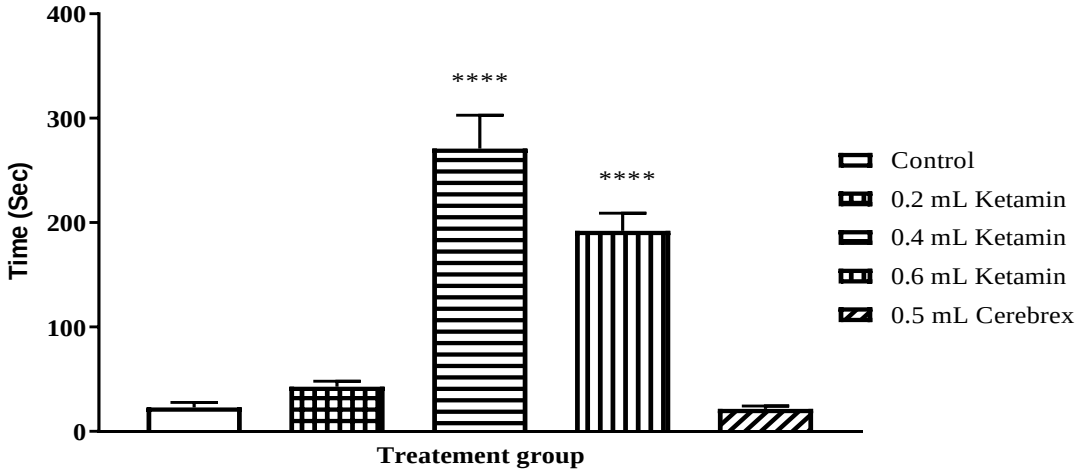

Fig 1: Subanesthetic effect of non-competitive N-Methyl-D-aspartate and ketamine in rats' perception, cognition, and motor response using Barnes-maze Test (Week 1). Results are presented as mean ± SEM. N=5, * Mean values are statistically significant when compared to the control group

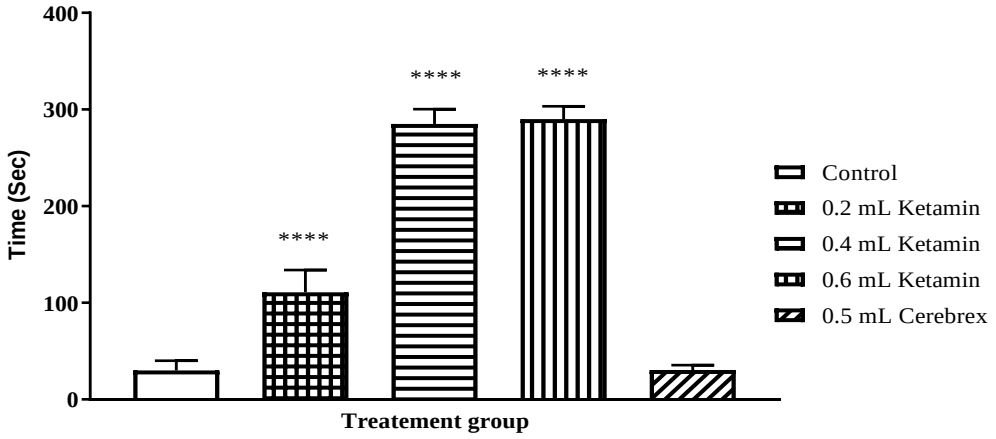

Fig 2: Subanesthetic effect of non-competitive N-Methyl-D-aspartate and ketamine in rats' perception, cognition, and motor response using Barnes-maze Test (Week 2). Results are presented as mean ± SEM. N=5, * Mean values are statistically significant when compared to the control group

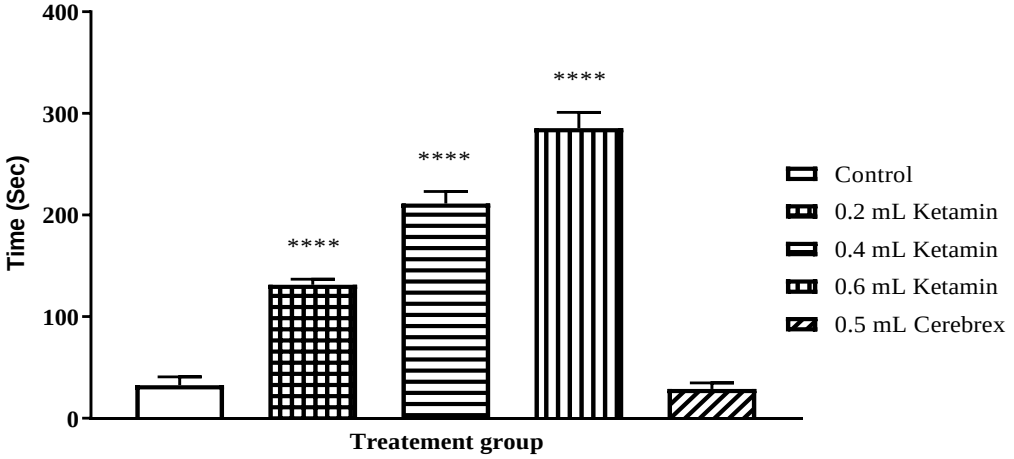

Fig 3: Subanesthetic effect of non-competitive N-Methyl-D-aspartate and ketamine in rats' perception, cognition, and motor response using Barnes-maze Test (Week 3). Results are presented as mean ± SEM. N=5, * Mean values are statistically significant when compared to the control group

3.1.2 Handgrip

In Fig 5, there was a significant increase ($p<0.05$) in time taken at which the rats administered with 0.6 mL was able grip as compared to control.

In Fig 6, there was a significant increase ($p<0.05$) in time taken at which the rats administered with 0.6 mL was able grip as compared to control.

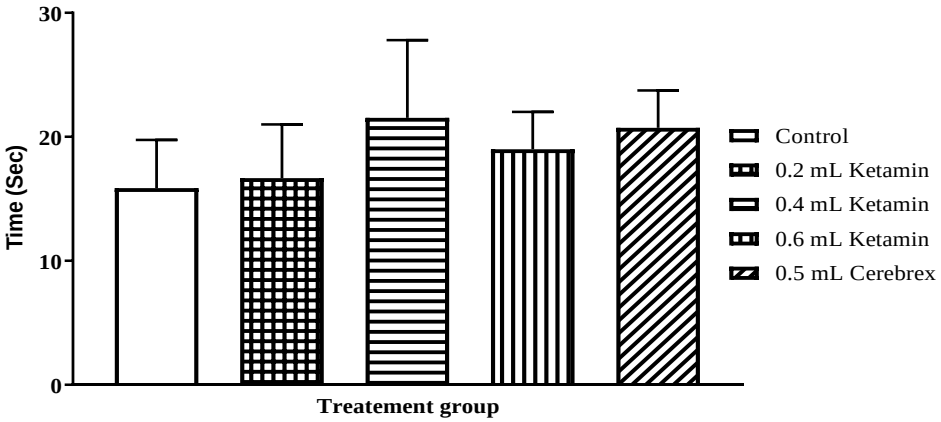

Fig 4: Subanesthetic effect of non-competitive N-Methyl-D-aspartate and ketamine in rats' perception, cognition, and motor response using handgrip test (Week 1). Results are presented as mean ± SEM. N=5

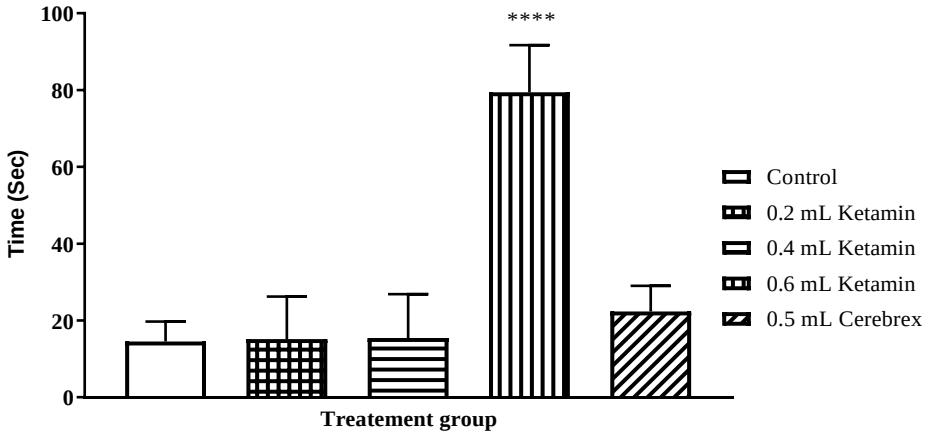

Fig 5: Subanesthetic effect of non-competitive N-Methyl-D-aspartate and ketamine in rats' perception, cognition, and motor response using handgrip test (Week 2). Results are presented as mean ± SEM. N=5, * Mean values are statistically significant when compared to the control group

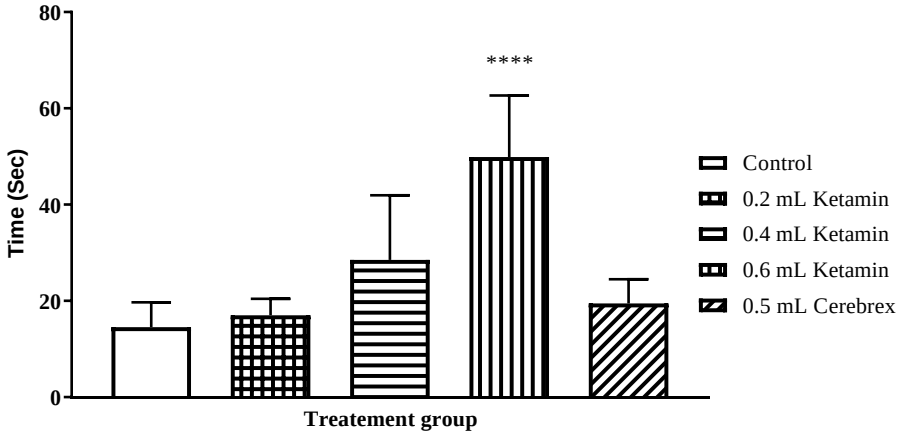

Fig 6: Subanesthetic effect of non-competitive N-Methyl-D-aspartate and ketamine in rats' perception, cognition, and motor response using handgrip test (Week 3). Results are presented as mean ± SEM. N=5, * Mean values are statistically significant when compared to the control group

3.1.3 Rotarod test

Rotarod test In Fig 7, there was a significant increase ($p<0.05$) in balance with respect to time taken for the rats administered with 0.2 mL ketamine as compared to control group

In Fig 8, there was a significant increase ($p<0.05$) in balance with respect to time taken for the rats administered with 0.6 mL ketamine as compared to control group.

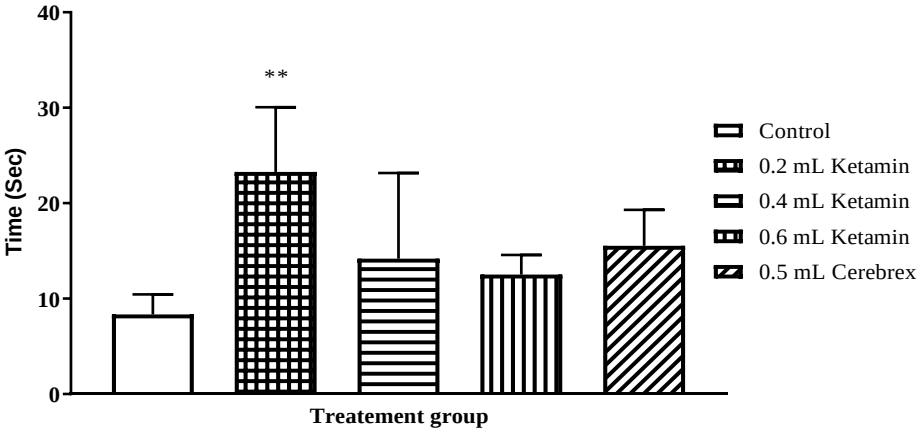

Fig 7: Subanesthetic effect of non-competitive N-Methyl-D-aspartate and ketamine in rats' perception, cognition, and motor response using rotarod test (Week 1). Results are presented as mean ± SEM. N=5, * Mean values are statistically significant when compared to the control group

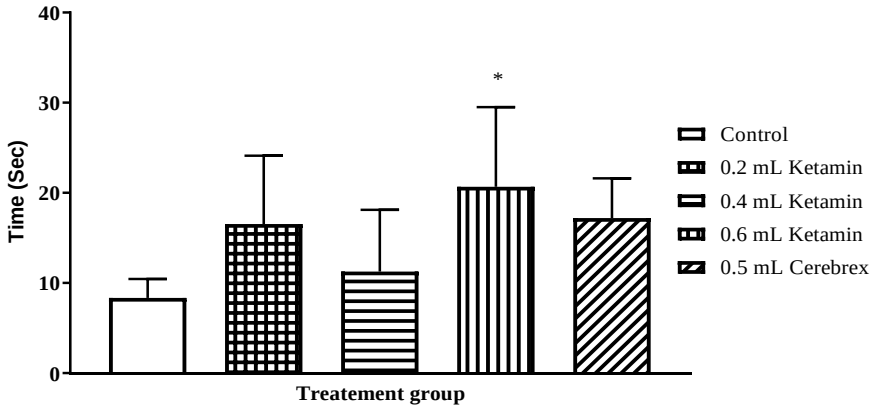

Fig 8: Subanesthetic effect of non-competitive N-Methyl-D-aspartate and ketamine in rats' perception, cognition, and motor response using rotarod test (Week 2). Results are presented as mean ± SEM. N=5, * Mean values are statistically significant when compared to the control group

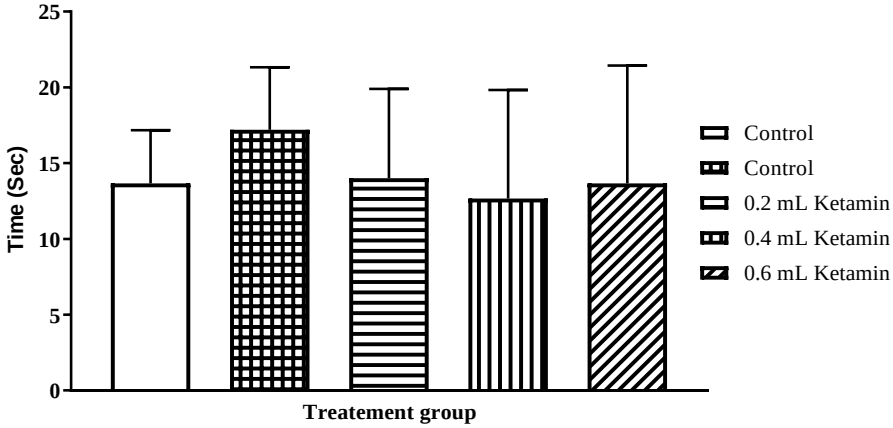

Fig 9: Subanesthetic effect of non-competitive N-Methyl-D-aspartate and ketamine in rats' perception, cognition, and motor response using rotarod test (Week 3). Results are presented as mean ± SEM. N=5

4.0 DISCUSSION

Ketamine is a clinically important drug commonly used in anaesthesia and perioperative analgesia (Ueyema *et al*., 2008). It is psychedelic properties make it also a popular drug of abuse (Muetzelfeldt *et al*., 2008). At subanaesthetic doses, (far lower than the normal dose range of anaesthesia) the role of ketamine, as a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, in blocking the processing of nociceptive inputs has led to its use in chronic pain syndromes management (Hocking and Cousins, 2003). However, ketamine use, both in preclinical studies (Imre *et al*., 2006) or in compulsive users was reported to induce cognitive impairments (Morgan and Curran, 2008). Acute subanaesthetic doses of ketamine were shown to induce a marked increase in glutamate release in the nucleus accumbens (Iskandrani *et al*., 2015). In turn, this facilitates synaptic flow of information from the prefrontal cortex (PFC) and amygdala (Razoux *et al*., 2007). This validates the hypothesis that ketamine acts preferentially to block NMDA receptors on inhibitory neurons leading to a state of disinhibition and increased glutamate release in the PFC and limbic regions (Razoux *et al.*, 2007). Thus, this study is to investigate the effect of subanaesthetic dose administration of N-methyl-D-aspartate receptor antagonist (ketamine) on cognitive function and motor responses in Wistar rats.

The result obtained from Barnes maze test in the study showed that there was an increase in the time spent in the performance of the visual-based memory task from week 1, week 2 and week 3 across all tests, after the rats were injected intraperitoneally with ketamine. During the first week of trials in medium and high dose of 0.4 and 0.6 of ketamine treated rats there was a decline in memory. Hence the more time taken to complete the task when compared to control. Also, mental retardation and dullness was observed across all test groups when compared to control group. In week 2 and week 3 trials, the mental dullness and decline in cognitive function occurred in a dose dependent manner, though not statistically different from each other (0.2, 0.4- and 0.6-mL doses of ketamine). The increase in time taken by the animals to locate the escape cues could be because of the toxicity of ketamine to the brain. This implies that subanesthetic doses of ketamine have an impact on cognitive activities of these experimental animals as it caused a decline in cognitive function of the experimental animals resulting in an increased time in performing the visual-based memory task. This finding agrees with Olorunfemi *et al*., (2022) who reported a distortion in performance of the visual scene-based memory task across the test groups when compared to the group treated with epinephrine in a dose- and time-dependent manner of effect. Hence, ketamine induced inhibitory effects on cognitive function and motor responses via blocking the NMDA receptors. This suggest that lower amounts of ketamine have less negative cognitive effect while higher amounts of ketamine may have a greater long-term effect on an individual's cognition (Davis *et al*., 2020). This is interesting as individuals under the influence of ketamine display impaired spatial working memory (Chan *et al*., 2012; Driesen *et al.*, 2013).

Assessment of Cognito-motor activities using handgrip test showed that experimental animals treated with 0.6 mL ketamine showed a very strong grip strength in week 2 and week 3 trials when compared to control. 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 2 and week 3, but not in a dose- and time dependent manner. Hence, subanaesthetic doses of ketamine did not cause dystrophy in experimental animals. Wojtas *et al*., (2022) study revealed that ketamine suppressed rat locomotor activity which did not affect animals' behavior. In the present study, 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 subanaesthetic doses of ketamine when compared to control.

Assessment of locomotive abilities using rotarod test showed that experimental animals treated with 0.2 mL ketamine showed better locomotive abilities when compared to control group in week 1. Also, animals treated with 0.6 mL ketamine showed improved coordination, endurance and balance in locomotive abilities when compared to control group in week 2, locomotive abilities improved in animals treated with subanaesthetic doses of ketamine when compared to control. Ketamine did not cause an inhibition in motor responses from this study, and it could be due to naivety of experimental animals (Wojtas *et al*., 2022). According to a study by Viktorov *et al*., (2022), they suggested that the effect of NMDA antagonists is limited when used on animals who are not subjected to any model of depression. On the other hand, our behavioral tests were performed after the administration of the drugs, and while that is enough to eliminate their acute effects, it might not be enough for the long-lasting effects to manifest fully, as Hibicke *et al*., (2020) reported an antidepressant effect observed 7 days post psilocybin administration.

5.0 CONCLUSION

In conclusion, this study investigated the effect of subanaesthetic administration of N-methyl-D-aspartate receptor (ketamine) antagonist on cognitive function and motor responses in Wistar rats. This revealed that sub-anesthetic does of ketamine inhibited cognitive function but not motor responses in Wistar rats. Hence, subanaesthetic doses of ketamine may impair cognitive function and improve motor responses in Wistar rats.

6.0 RECOMMENDATION

Although ketamine has been reported in some studies to inhibit cognitive function, spatial memory, and motor responses. However, from the findings of this study, it was observed to be otherwise in terms of cognitive function but improved motor response. Hence, further studies to corroborate our findings are highly recommended. Therefore, we recommend that more studies should be carried out using depression models to evaluate the cognitive and motor effect of subanaesthetic dose of ketamine.

7.0 ACKNOWLEDGEMENTS

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