

Piracetam And Citicoline Effect on The General Anesthesia Animals Model

Ahmed Maki Radeef¹, Ali S. Wadday², Ali Mohammed Obayes³, Aiman Mohammed Baqir Al-Dhalimy⁴, Baraa Akaal Al-Hasan⁵, Ghadeer Sabah Bustani⁶

¹M. Sc student major anesthesia, Tehran university of medical science, Middle Euphrates hospital, Iraq

²Department of Animal Husbandry, Faculty of Agricultural and Food Sciences and Environmental Management, University of Debrecen, Debrecen, Hungary.

³National University of Science and Technology-Health and medical technologies.

⁴College of Nursing, Altoosi University College, Najaf, Iraq.

⁵Medical Laboratory Technology Department, College of Medical Technology, The Islamic University, Najaf, Iraq.

⁶College of Nursing, Altoosi University College, Najaf, Iraq.

Email: makkiahmed950@gmail.com

Abstract

H Introduction: The brain is the target organ for both general anesthetic drugs and some drugs that are used to treat nervous disorders which cause brain activation such as piracetam and citicoline however, they work in contrast to each other.

Objective: Our study set out to determine the effect of piracetam and citicoline on the anesthetic induction time.

Method: For 10 days 24 mice had been treated with piracetam and citicoline in three groups (piracetam group, citicoline group, and mix group). In addition, 7 mice were used as a control group. All mice were assessed with open field test and underwent right reflex and pain reflex tests.

Results: The statistical results showed there is a highly significant relationship between the groups that received drugs in comparison to the control group during assessment by open field test (during the first three sequences) with P-value (0.000, 0.039, 0.008), also a non-significant association relationship between the right reflex test and the drug (piracetam with citicoline). On the other hand, there was a highly significant association relationship between the pain reflex test and the drug (piracetam with citicoline) with P-value(0.009).

Conclusion: the time required to achieve the surgical anesthesia stage had been delayed by the influence of piracetam and citicoline use.

Keywords: Piracetam, Citicoline, Somazina, Nootropil, general anesthesia, animal model.

INTRODUCTION

General anesthesia (GA) are those agents which cause the reversible loss of consciousness and also produce amnesia and analgesia with or without reversible muscle paralysis[1]. General anesthesia is used to make the patient safer and more comfortable during surgery. General anesthesia occurs in four stages that were first introduced and described at the 1930s these four stages remained essentially the same over[2].

Address for correspondence: Ahmed Maki Radeef,

Tehran university of medical science, Middle Euphrates hospital, Iraq

Email: makkiahmed950@gmail.com

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The first stage is known as induction it is simply a period during which the patient goes from a state of consciousness to a state of unconsciousness. Followed by the stage known as excitement at this stage depression of inhibitory neurons in the CNS leads to increased excitement involuntary muscle movement, heart rate, blood pressure, and respiration[2][3].

On other hand when a patient is fully unconscious, unresponsive to surgery, and has regular breathing this is the ideal stage for surgery so this is known as a surgical anesthetic stage. At this period careful monitoring is necessary to prevent further progression to stage four known as medullary paralysis or overdose. Otherwise, the patient will progress to failure of respiratory and cardiovascular then which lead to death if the patient cannot be revived [4]. Based on previous studies that showed using groups of specific drugs will enhance anastatic stages and reduce complications. Some of theis drugs that used to treat the nerves system disorder cause a brain activation such as piracetam and citicoline both of these medications activate the nerves system and both of them also metabolized in the liver. On other hand Theis drugs were discovered at middle of 20th century and since that time, many studies have focused on mechanism of action and there side effect on central nervous system and patients [5].

Piracetam is the original member of the racetam family of synthetic nootropics or "cognition-enhancing" compounds. Discovered in 1964[6]. Piracetam (2-oxopyrrolidine acetamide) belongs to a class of drugs that act on the central nervous system. It is a cyclic derivative of γ -aminobutyric acid (GABA) itself is a neurotransmitter and from it rremove one molecule of water It decreases by cyclisation. However, piracetam does not exist characteristics of GABA similar[7]. The nervous effect at the level of neurons in animals, Piracetam enhances a variety of types of neurotransmission, primarily through postsynaptic modulation of receptor density and activity. Piracetam protects and restores cognitive abilities in animals and humans after various brain insults such as hypoxia, poisoning, and electroconvulsive therapy. Prevents hypoxia changes in brain function and performance as assessed by an electroencephalogram (EEG) and psychological assessments[8].

Cytidine-5'-diphosphocholine (citicoline or CDP-choline)[9], There are two variants of the same substance

covered by the name "citicoline." First, "citicoline sodium," which is traditionally considered a pharmaceutical substance, which, in the Anatomical Therapeutic Chemical classification of drugs (ATC).The second one, "citicoline inner salt" (or "citicoline free base"), is Formally considered as a food ingredient (since 2009 2) in United States and in the European Union(since2013 3)[10]. Citicoline has shown beneficial effects in several CNS injury models, neurodegenerative diseases, ophthalmology, and psychiatry. Citicoline is widely available as a dietary supplement. It is often used to enhance cognitive functions[11][12][13]. It indicates for patients with cerebral vascular disease[14], head trauma (HT) of varying severity, cognitive disorders of different causes [15].

Method

Design: comparative experimental case control study. Thirty one adult Albino mice with weighed between 20 to 30 g were used in this study. The mice were divided into four groups of each group with males and females. For 10 days, the first group(n=8) mice received 400mg/kg oral piracetam daily with concentration (29.9mg/ml), the second group(n=8) mice received 500mg/kg oral citicoline daily with concentration (30mg/ml), the third group(n=8) received oral piracetam (400mg/kg) and citicoline (500mg/kg) orally daily. Lastly, the fourth group (control group) (n=7) of mice was left untreated.

Anesthesia plan was as following: the mixture of ketamine and xylazine has long been a popular combination as an injectable anesthetic for use in laboratory animals around the world. we use a combination of anesthetic drugs and dependent on the previous study, we use a ketamine-xylazine-midazolam combination we dose 100/10/5mg/kg intra-peritoneum(IP)[16][17]. We should mention that all groups of mice were assisted before starting anesthesia by an open field test assessment. The depth of anesthesia was assisted by right reflex test and Pain reflex test.[16][17]. Inclusion criteria are English articles and studies, Healthy adult albino mice and Appropriate temperature and environment. Exclusion criteria are Ill mice, Mice with previous experiments and Articles and studies in a language other than English

Results

Table 1: Distribution of the administration of Piracetam (Nootropil) with Citicoline (Somazina) on the general Anesthesia

Data	Groups	Freq.	Perc. %	Mean ± SD
Gender	Male	15	48.4	1.51 ± 0.54
	Female	16	51.6	

Drug group	Piracetam	8	25.8	2.45 ± 0.67
	Somazina	8	25.8	
	Mix	8	25.8	
	Controle	7	22.6	
Assessment (open filed test):- time (second)	0.5 – 2 second	29	93.5	1.12 ± 0.49
	2.5 – 4 second	0	00.0	
	4.5 - 5 second	2	6.5	
Assessment (open filed test):- clean	0 – 2 clean	19	61.3	1.45 ± 0.62
	3 – 4 clean	10	32.3	
	5 – 6 clean	2	6.5	
Assessment (open filed test):- run	0 – 11 run	7	22.6	1.87 ± 0.56
	12 – 23 run	21	67.7	
	24 – 34 run	3	9.7	
Assessment (open filed test):- square	3 – 43 square	4	12.9	2.06 ± 0.57
	44 – 84 square	21	67.7	
	85 – 125 square	6	19.4	
Right reflex test (minute)	1 – 2 minute	19	61.3	1.45 ± 0.63
	2.5 – 3.5 minute	10	32.3	
	4 – 5.5 minute	2	6.5	
Pain reflex test (minute)	2 – 5 minute	25	80.6	1.22 ± 0.23
	6 – 9 minute	5	16.1	
	10 – 12 minute	1	3.2	

Table (1) this table showed the majority of the study sample was gender, the majority of the study sample was female (51.6%) with mean and standard deviation equal 1.51 ± 0.54, regarding of the equal some drug group within the (Piracetam, Somazina, Mix) was (25.8%), with mean and standard deviation equal to 2.45 ± 0.67. The assessment (open filed test):- time (second), the majority of the study sample was (0.5 – 2 second) (93.5%), with mean and standard deviation equal to 1.12 ± 0.49. Moreover, assessment (open filed test):- clean, the majority of the study sample was (0 – 2 clean) (61.3%) with mean and standard

deviation equal to 1.45 ± 0.62. The majority of the study sample was assessment (open filed test):- run within the (12 – 23 Run) (67.7%), with mean and standard deviation equal to 1.87 ± 0.56. And the equal of the study sample type of assessment (open filed test):- square were 44 – 84 squares (67.7%) with mean and standard deviation equal to 2.06 ± 0.57. Moreover, right reflex test (minute), the majority of the study sample was 1 – 2 minute (61.3%), with mean and standard deviation equal to 1.45 ± 0.63, regarding pain reflex test (minute) 2 – 5 minute was (80.6%), with mean and standard deviation equal to 1.22 ± 0.23.

Table 2: Relationship between the Gender and the Drug

Data	Groups	Drug group				Freq.	Perc. %	Chi-Square			
		Piracetam	Somazina	Mix	Controle			χ ²	d.f	P-value	Sig.
Gender	Male	5	4	3	3	15	48.4	1.112	3	0.865	N.S
	Female	3	4	5	4	16	51.6				
	Total					31	100.0				

Table (2) this table showed that there was a non-significant association relationship between the gender and the drug {Piracetam (Nootropil) with Citicoline (Somazina)} on the general anesthesia, animal model at more than 0.05.

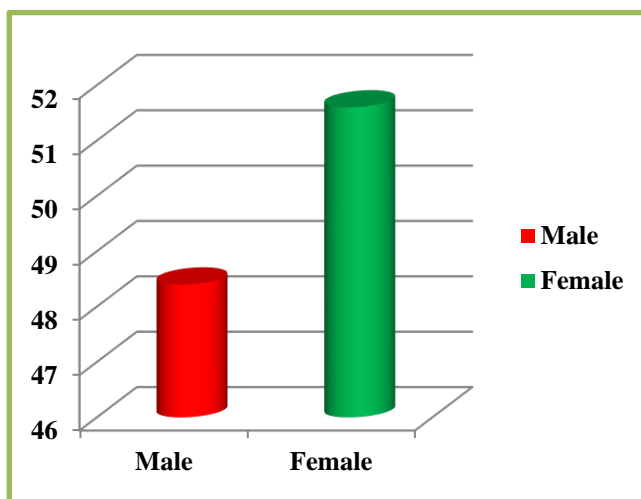


Figure (1) Distribution of the study subjects by their relationship between the gender and the drug

Table 3: Relationship between the open field test and the drug

Data	Groups	Drug group				Freq.	Perc. %	Chi-Square			
		Piracetam	Somazina	Mix	Controle			χ^2	d.f	P-value	Sig.
Assessment (open filed test):- time (second)	0.5 – 2 second	7	8	7	7	29	93.5	42.004	3	0.000	H.S
	2.5 – 4 second	0	0	0	0	0	00.0				
	4.5 - 5 second	1	0	1	0	2	6.5				
Assessment (open filed test):- clean	0 – 2 clean	4	6	5	4	19	61.3	16.756	6	0.039	S
	3 – 4 clean	2	2	3	3	10	32.3				
	5 – 6 clean	2	0	0	0	2	6.5				
Assessment (open filed test):- run	0 – 11 Run	3	1	2	1	7	22.6	42.952	6	0.008	H.S
	12 – 23 Run	4	6	6	5	21	67.7				
	24 – 34 Run	1	1	0	1	3	9.7				
Assessment (open filed test):- square	3 – 43 Square	3	0	1	0	4	12.9	9.977	6	0.122	N.S
	44 – 84 Square	5	7	4	5	21	67.7				
	85 – 125 Square	0	1	3	2	6	19.4				

□ H.S = High significant (p-value less than 0.01), S = Significant (p-value less than 0.05), N.S = Non significant (p-value more than 0.05).

Table (3) this table showed that there was a high significant of the relationship between the open field test and the drug {Piracetam (Nootropil) with Citicoline (Somazina)} on the general anesthesia, animal model within their (assessment (open filed test):- time (second), assessment (open filed test):- run) at p-value less than 0.01. There was a significant (assessment (open filed test):- clean) at p-value less than 0.05, moreover no-significant association with their (assessment (open filed test):- square) at p-value more than 0.05.

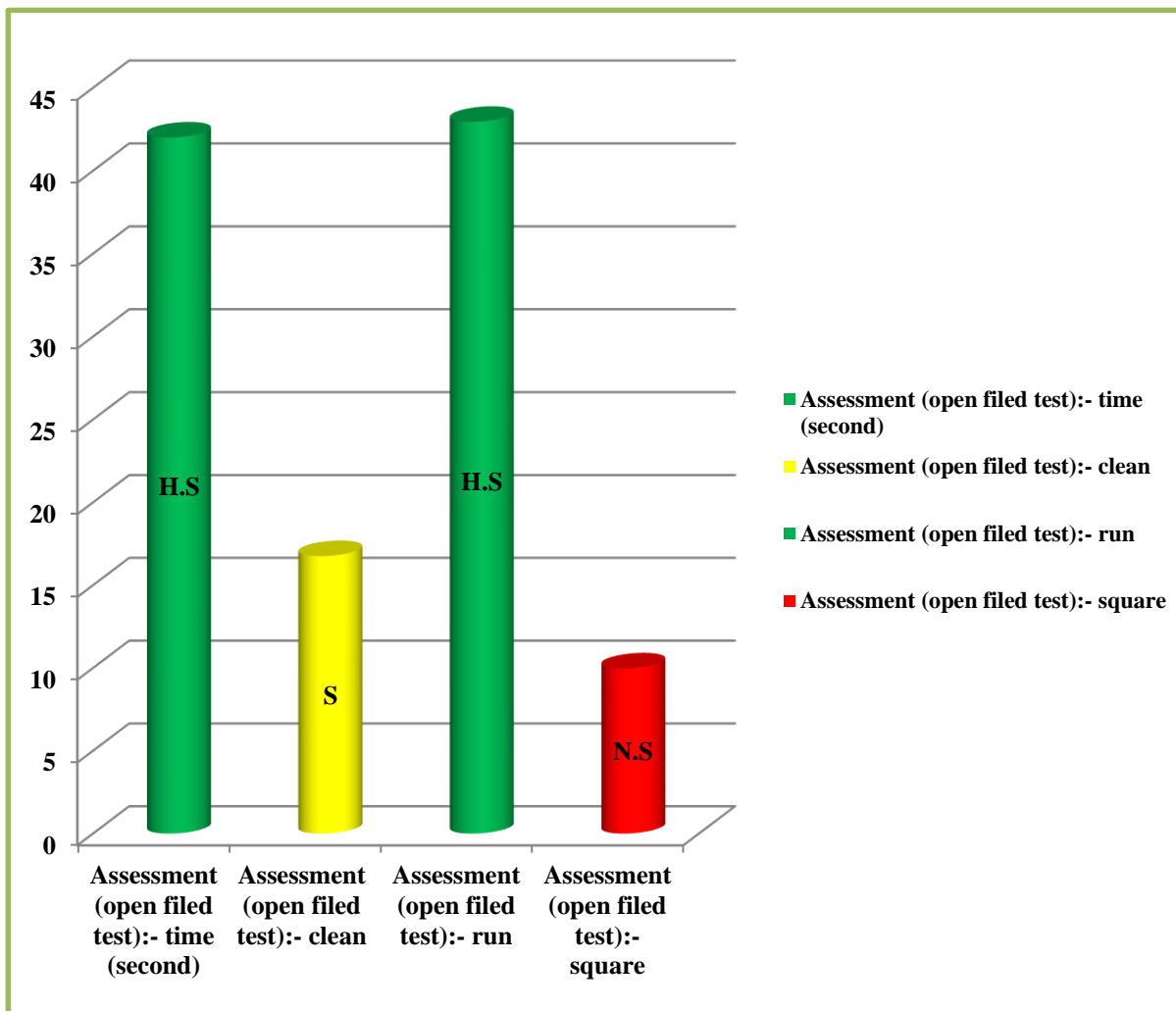


Figure (2) Distribution of the study subjects by their relationship between the open field test and the drug.

Table 4: Relationship between the right reflex test and the drug

Data	Groups	Drug group				Freq.	Perc. %	Chi-Square			
		Piracetam	Somazina	Mix	Controle			χ^2	d.f	P-value	Sig.
Right reflex test (minute)	1 – 2 minute	4	6	5	4	19	61.3	3.656	6	0.804	N.S
	2.5 – 3.5 minute	3	1	3	3	10	32.3				
	4 – 5.5 minute	1	1	0	0	2	6.5				
	Total					31	100.0				

Table (4) this table showed that there was a non-significant association relationship between of the right reflex test and the drug {Piracetam (Nootropil) with Citicoline (Somazina)} on the general anesthesia, animal model at more than 0.05.

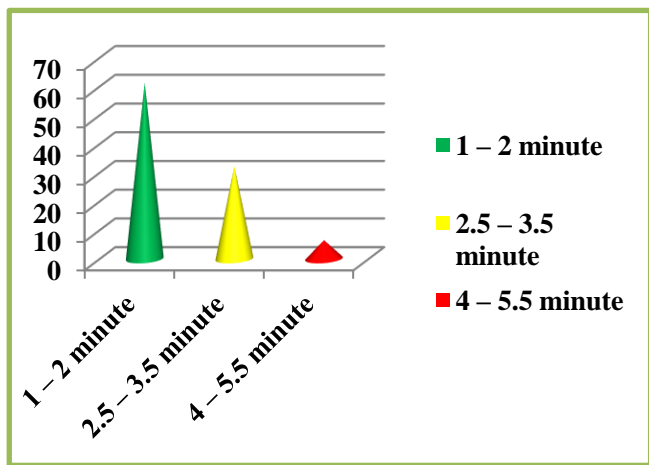


Figure (3) Distribution of the study subjects by their relationship between of the right reflex test and the drug.

Table 5: Relationship between the pain reflex test and the drug

Data	Groups	Drug group				Freq.	Perc. %	Chi-Square			
		Piracetam	Somazina	Mix	Controle			χ^2	d.f	P-value	Sig.
Pain reflex test (minute)	2 – 5 minute	6	6	6	7	25	80.6	45.270	6	0.009	H.S
	6 – 9 minute	2	2	1	0	5	16.1				
	10 – 12 minute	0	0	1	0	1	3.2				
	Total					31	100.0				

Table (5) this table showed that there was a high significant association relationship between of the pain reflex test and the drug {Piracetam (Nootropil) with Citicoline (Somazina)} on the general anesthesia, animal model at more than 0.05.

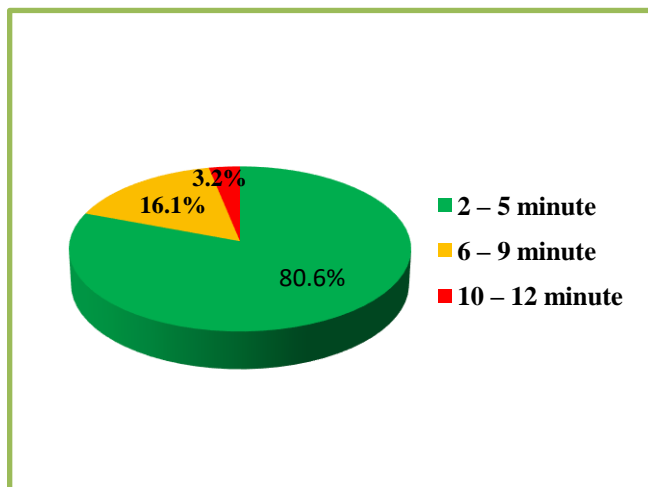


Figure (4) Distribution of the study subjects by their relationship between of the pain reflex test and the drug

Discussion

Several preclinical and clinical studies have shown the relationship of Piracetam (Nootropil) with Citicoline (Somazina) on the general anesthesia, animal model and some variables. However, the studied the combinational actions of these two substances on relationship between. Therefore, the present study investigated the effects of general anesthesia with Piracetam (Nootropil) with Citicoline (Somazina) as single agents and compared this with their combinational actions on an animal model. Participants of the animal are evaluate effectiveness of the administration the Piracetam (Nootropil) with Citicoline (Somazina) on the general anesthesia about (31) mice through the use of an instrument which is created through intensive review of relevant literatures and studies. The study shows the majority of the study sample was gender; the majority of the study sample was female. These results are consistent with [18] who studied the response of important factors affecting anesthetic choices are strained, gender of the mice, age, surgeon’s skill, and anesthesia duration/plane it is recommend giving a range of doses to allow for anesthetic protocol. Drug group of the general anesthesia who are found at study sample are most equal (Piracetam, Somazina, and

Mix) were percentage is (25.8%) of them is Mean \pm SD (2.45 \pm 0.67). These results indicate that there is specific drug group in mouse anesthesia has the majority to dominant as mouse under anesthesia [2], [19]; Because A common anesthesia theme is the use of balanced, multimodal anesthesia, where multiple anesthetic drugs with complementary modes of action are used to minimize the dose of each drug required. In regarding to the subjects assessment (open filed test):- time (second), the study results indicate that many of them are 0.5 – 2 second (93.5%). the time of assessment was determined by the anesthetist, considering the mouse studies were placebo-controlled with a Piracetam comparator group (open label) and included co-treatment with the analgesic with result of study conducted by [20] that found that most of the conclusion was reached for all studies that Piracetam was safe and effective for sedation during the procedures with rapid onset of effect and recovery. Concerning with the assessment (open filed test):- clean it is indicated that the great percentages of mouse were neither 0 – 2 clean (61.3%). This result is consistent with [21] found the amount of continue to monitor animals until they are fully recovered; recover animals on paper towels (without bedding) in a clean cage. Regard to Assessment (open filed test):- run the study results indicate that many within 12 – 23 run were (67.7%). In addition, the general anesthesia level was controlled with Citicoline of the animal; this result is inconsistent with that of [22] who study of the murine system the predominant function of LDH is the catalyzation of the reversible reaction of pyruvate to lactate. NAD⁺ is generated concomitantly alongside this process and is essential for the continuous generation of ATP to keep glycolysis running.

In some studies, assessment (open filed test):- square was used and the operation was performed in around 44 – 84 square. The open-field test of the square is a widely adopted paradigm to assess the animal's anxiety and general locomotion under the influence of test treatments [23]. Other study mentioned Right reflex test (minute) for general anesthesia effect in animals as it provides similar duration of analgesia with a shorter duration at 1 – 2 minute, it also provides adequate level of sensory block for the surgery with minimal intraoperative and postoperative side effects and stable hemodynamics throughout the surgery [24]. Continuously monitor the animal during the induction process: the animal should lose its righting reflex, and its breathing pattern should change (slower, deeper respiration). Gently tilt the box if unsure if animal is unconscious, to see if it reacts and tries to right itself; once the animal is unable to do so, it is unconscious and may be transferred to the facemask for maintenance of anesthesia,[25]. The study shows that, the pain reflex test (minute) is acceptable for a large proportion of the (2 – 5 minute) was (80.6%). These results are consistent with[26]; who studied the clinical outcomes of pain reflex test (minute) in mouse who underwent general anesthesia were similar to those achieved with the same dose of drugs.

According to the results, the study indicates for results are a high significant of the relationship between the open field test and the drug {Piracetam (Nootropil) with Citicoline (Somazina)} on the general anesthesia, animal model within their (assessment (open filed test):- time (second), assessment (open filed test):- run) at p-value less than 0.01. There was a significant (assessment (open filed test):- clean) at p-value less than 0.05, moreover no-significant association with their (assessment (open filed test):- square) at p-value more than 0.05[27] it is depicted that the effects of compound in intact animals with assessment (open filed test):- time (second) effects of compounds are necessary for the treatment of neurodegenerative disorders and play a huge role in memory dysfunction management. Here we compared the effects of compound with piracetam as a positive control and used normal saline as a negative control. Other study has found consistent findings with some study; There was high significant difference observed compared to the piracetam group. According assessment (open filed test):- run of these results, compound has better neurotropic activity than piracetam, as it reduces the immobility time and improves the number of center sector crossings and vertical activity, reduced the time in the light compartment[28]. onther one which studied to significant assessment (open filed test):- clean of compare between some variables and hemodynamic effects based on mice, the study mentioned to assess potential adverse events with the use of Citicoline, associated with both the surgical and the anesthetic procedures[29].

Regarding the aspect of no-significant association with their (assessment (open filed test):- square) at p-value more than 0.05. [30] said that survival rates were estimated within 28 days after the first administration of compound, piracetam, or saline. Kaplan–Meier survival curves are presented in assessment (open filed test):- square. The comparison of experimental groups was made by the log-rank test and showed no significant differences in the survival of animals. In each group, there was one death case on day 1 after MCAO and one animal per group reached a humane endpoint on day two. One animal from the compound group was humanely killed on day two after MCAO. Thus, there was no significant difference observed in viability and all deaths were not associated with administered compounds. The data analysis has revealed non-significant association relationship between of the right reflex test and the drug {Piracetam (Nootropil) with Citicoline (Somazina)} on the general anesthesia, animal model at more than 0.05, also another study [17] who indicate that effect is typically not significant in other species due to the comparatively small doses used in combination with other drugs. This result constant with study result of [31] who found that there is non-significant relationship between of the right reflex test and the drug of action general anesthesia, multiple factors affect the selection of a dose range for these cocktails, including the mouse's age and strain, the duration of a surgical plane required, the supportive care provided to the mouse, and the surgeon's experience. previous study is depicted that the Anesthetic recovery is associated with risk. By providing heat and a suitable environment, these risks are

diminished and increase the odds of a successful recovery. Once the animal has regained its righting reflex and is able to stand, recovery is complete; return the animal to its home cage [27,32]. The study shows that high significant association relationship between of the pain reflex test and the drug {Piracetam (Nootropil) with Citicoline (Somazina)} on the general anesthesia, animal model at more than 0.05. This result is consistent with that of [33,34] who studied here are main general anesthesia components: unconsciousness, amnesia, immobility/muscle relaxation, and analgesia. Sedation, hypnosis, and tranquilization are frequently used terms when discussing anesthesia, but are specific terms separate from the main general anesthesia components. The result is consistent with that of [35,36] general anesthesia may be used for surgical and non-surgical procedures and is also referred to as surgical anesthesia. Properly induced and maintained general anesthesia with effective monitoring is vital to maintaining animal welfare and creating reproducible studies. It allows the performance of lengthy and otherwise potentially painful and invasive procedures, including laparotomies, orthopedic manipulations, xenograft transfers, embryo derivation, and cranial implants, by rendering an animal unconscious and immobile for a procedure. study was mentioned these signs often require familiarizing oneself with the animal's appearance prior to carrying out painful procedures. Refer to the Mouse Grimace Scale, which provides a reliable and quantifiable means to evaluate pain in the mouse using facial feature [37]

Conclusion

This research has discussed the effect of piracetam and citicoline which cause brain activation on the anesthetic induction time.

1. According to the results, there are highly significant relation between the groups that received drugs in comparison to the control group during assessment by open field test (during the first three sequences).
2. Regarding pain reflex tests also there are highly significant relationship between the first three groups and the control group.

According to that, we can conclude our project result by Chronic use of these drugs significantly affect the brain activity of mouse and influence the surgical stage (third stage) of anesthesia, the longer time required to lose pain reflex completely with nearly no change in the first stage of anesthesia. It is therefore recommended to adjust the analgesic dose for a patient using one of these drugs.

Limitations

- Period of the research only 10 days of treatment, we had a deadline.

- Number of samples because of unavailability and dying in the preparation phase.

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