Original Article

Effect of sugammadex on recovery from ketamine anesthesia: An experimental study

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Abstract

Aim: Previous studies have shown cyclodextrins bind to a variety of medications. The hypothesis in our study is to determine whether or not sugammadex interacts with the lipophilic medication of ketamine to shorten the effect duration and ensure earlier recovery.
Material and Methods: The study used 24 adult male Sprague-Dawley rats. Rats were randomly divided into 4 equal groups. Each rat was administered 75 mg/kg ketamine intraperitoneal (ip) bolus and then in the fifth minute rats was administered sugammadex at appropriate doses for their group through the lateral vein in the tail. Group C (control group) were administered 15 mL/kg physiologic serum (PS) (n=6), Group Sgdx 16 were administered 16 mg/kg sugammadex (n=6), Group Sgdx 100 were administered 100 mg/kg sugammadex (n=6) and Group Sgdx 1000 were administered 1000 mg/kg sugammadex (n=6). The heart rate, respiratory rate and recovery durations of the rats were recorded.
Results: The recovery duration in the Sgdx 100 group was statistically significantly shorter compared to the control group (p=0.026), while the recovery duration in the Sgdx 1000 group was statistically significantly shorter than the control group (p<0.001) and the Sgdx 16 group (p=0.015). Heart rate was statistically significantly low in the Sgdx 1000 group compared to the control group (p<0.05). Respiratory rates were similar.
Conclusion: Our study showed that 100 mg/kg and 1000 mg/kg sugammadex doses significantly shortened recovery. We conclude that there is a need for more research about the interaction between ketamine and sugammadex.

Keywords: Cyclodextrin; ketamine; recovery; sugammadex

INTRODUCTION

Ketamine, a highly fat soluble anesthetic medication, is one of the agents frequently used both in surgeries and for non-operating room outpatient procedures (1). Ketamine is an antagonist for the N-methyl-D-aspartate (NMDA) receptors in the central nervous system, which forms dissociative anesthesia by disrupting the coordinated working of the limbic cortex which ensures the thalamus is aware of the senses (2). The anesthetic and analgesic effects of ketamine are linked to antagonism of the excitatory neurotransmitter of NMDA, agony of the opioid mu receptor and interaction with voltage-sensitive sodium channels. As NMDA receptors are found in the central nervous system including the lumbar spinal cord ketamine is used with intrathecal or epidural administration for analgesic aims (3).

Recovery from ketamine varies depending on age, gender, personal traits and environment. During recovery, nearly 12% of cases experience hallucinations. After increased cerebral blood flow and intraocular pressure, secretion, nystagmus, amnesia, anxiety, delirium, insomnia, diplopia and tonic-clonic movements may develop. Sometimes vasodilatation and hypotension may form if the catecholamine stores in the body are emptied. Nausea-vomiting and hypersecretions that may be observed during recovery reduce the patient's comfort and may increase the possibility of complications (4). As a result, an agent who shortens the recovery from ketamine will be beneficial.

Sugammadex has modified g-cyclodextrin structure and binds completely with rocuronium and partially with vecuronium (encapsulation) reducing the free plasma concentration of these agents to rapidly reverse their effects. One of the most important clinical benefits of sugammadex is the rapid reverse of any degree of neuromuscular block, which is not possible with neostigmine. Additionally, there are potential benefits like increased patient safety and reducing the residual block incidence during recovery (5). During our literature scan,

we found no study related to the interaction between ketamine and sugammadex.

The hypothesis of our study is that sugammadex will interact with the lipophilic medication of ketamine to reduce the effect duration and ensure earlier recovery. To test this hypothesis, we aimed to assess the recovery duration of rats administered ketamine anesthesia with 16, 100 and 1000 mg/kg doses of sugammadex.

MATERIAL and METHODS

Ethical statement
The study was designed as a randomized, prospective, double blinded, placebo controlled was approved by the Hospital of Ankara animal welfare and ethics review board under the reference number 2019/568.

Animals
For the study, 24 adult male Sprague-Dawley rats weighing from 250-350 g were used. Their environment had 12-hour night 12-hour daytime period, with temperature 24±4°C, and humidity rate 50±5%. Rats were randomly divided into 4 equal groups and fed with standard feed.

Experimental design
Rats were weighed on a sensitive scale, with weight of the holder subtracted from brute weight to calculate net weight. Age (days) and weights (g) were recorded. Each rat was administered 75 mg/kg ketamine (Ketalar, Pfizer Drugs Company, Istanbul) intraperitoneal (ip) bolus and then in the fifth minute rats had appropriate sugammadex dose for their group administered through the lateral vein

in the tail. Group C (control group) were administered 15 mL/kg physiologic serum (PS) (n=6), Group Sgdx 16 were administered 16 mg/kg sugammadex (n=6), Group Sgdx 100 were administered 100 mg/kg sugammadex (n=6) and Group Sgdx 1000 were administered 1000 mg/kg sugammadex (n=6).

During the experiment, the heart rate (HR) and respiratory rate of each rat was recorded initially (T1), 3 minutes after ketamine administration (T2), 3 minutes after sugammadex administration (T3) and after recovery (T4). Recovery criterion was taken as the time when all rats could stand for the second time (stand on four paws).

Statistical analysis
For statistical analysis, the program Statistical Package for Social Sciences 15 (SPSS 15.0, Chicago, IL, USA) was used. The distribution of the data was examined using the Kolmogorov–Smirnov test. To evaluate the significance of the comparisons between groups, the Kruskal–Wallis. Statistical significance was accepted as $p < 0.05$.

RESULTS

In all groups, the weights and ages of rats were statistically similar. There were statistically significant differences between the groups in terms of recovery duration ($p < 0.05$) (Table 1).

When the HR of rats is assessed, at T1, T2 and T3 measurement times, there were no statistically significant differences between the control, Sgdx 16 and Sgdx 100 groups ($p > 0.05$).

Table 1. Demographic data and recovery times						
	Control (1) (n=6) (mean ± SD)	Sgdx 16 (2) (n=6) (mean ± SD)	Sgdx 100 (3) (n=6) (mean ± SD)	Sgdx 1000 (4) (n=6) (mean ± SD)	p value	Post hoc P
Age (day)	201.00 ± 11.40	194.16 ± 11.92	197.00 ± 9.16	195.50 ± 10.63	0.483	-
Weight (g)	328.83 ± 8.88	326.00 ± 10.99	328.16 ± 8.32	330.16 ± 10.26	0.938	-
Recovery Times (sec)	2905.33 ± 181.32	2562.50 ± 121.24	1349.83 ± 99.52	635.83 ± 62.67	<0.001*	1-3: 0.026* 1-4: <0.001* 2-4: 0.015*

*Kruskal-Wallis test, SD: Standart Deviation
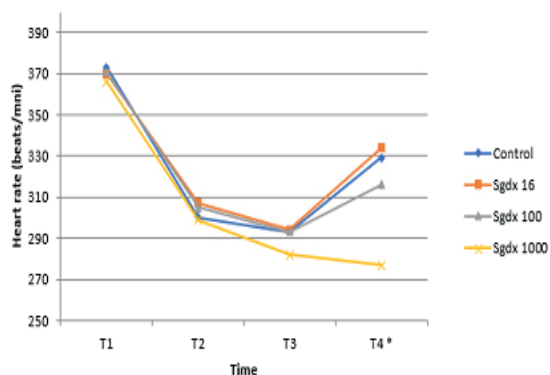
*: p<0.05 Compared of the Sgdx 1000 group with the control group
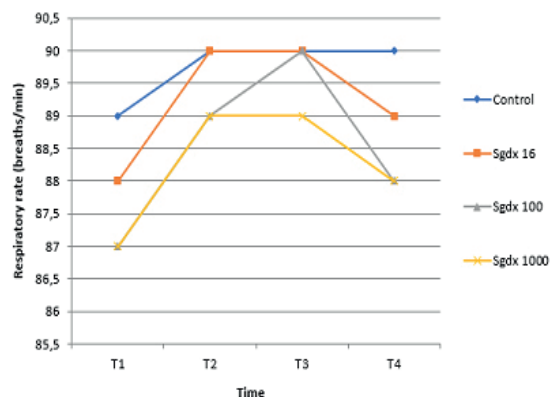
Figure 1. Heart Rate

Figure 2. Respiratory rate

At T4 measurements time, the HR in the control, Sgdx 16, Sgdx 100 and Sgdx 1000 groups were 366.16 ± 25.38, 299.83 ± 19.68, 282.83 ± 16.47 and 277.83 ± 14.67 beats/min, respectively. There was a statistically significant difference between the HR in the groups at time T4 ($p<0.05$). The HR in the Sgdx 1000 group was statistically significantly low compared with the control group ($p<0.05$) (Figure 1).

When respiratory rates are compared, there were no statistically significant differences between the groups at T1, T2, T3 and T4 (Figure 2).

The recovery durations are presented in Table 1. The recovery duration in the Sgdx 100 group was statistically significantly shorter compared to the control group ($p=0.026$), while the recovery duration in the Sgdx 1000 group was statistically significantly shorter than the control group ($p<0.001$) and the Sgdx 16 group ($p=0.015$) (Figure 3).
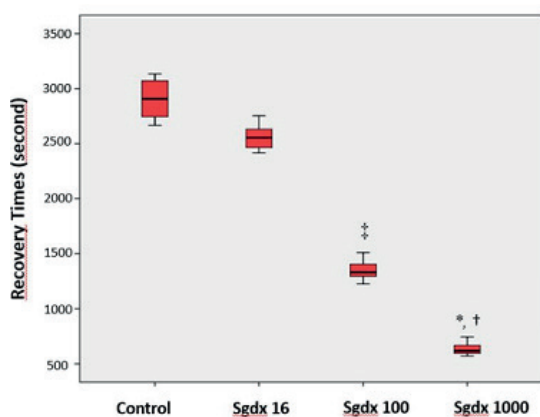
*:p<0.05 compared with group control
†: p<0.05 compared with group Sgdx16
‡: p<0.05 compared with group control

Figure 3. Recovery Time of Groups

DISCUSSION

From the results of our study, we concluded that sugammadex shortens the recovery time after ketamine anesthesia. This effect was most pronounced in the group administered 1000 mg/kg sugammadex.

Ketamine is an agent frequently used alone or in combination with other medications for non-operating room and outpatient anesthesia. Ketamine ensures unconsciousness and analgesia in dose-linked fashion. Due to high lipid solubility, it rapidly passes the blood brain barrier. After ketamine is administered, a cataleptic status forms with the patient's eyes open with pupils dilated and horizontal or vertical nystagmus observed. The cornea, cough and swallow reflexes continue. There is an increase in secretions, skeletal muscle tonus increases and purposeless movements of the head, arms, legs and trunk may be observed (6). Outpatient surgical procedures have advantages of increased patient comfort, early mobilization and reduced risk of nosocomial infection, along with economic gains (7). As a result, the target is for the patient to return to daily life in the shortest time possible.

A study researching the effect of methylphenidate on recovery of rats from isoflurane anesthesia defined the rat standing on four paws as recovery criterion (8). Wang et al. in a study researching the effect of caffeine on recovery from isoflurane anesthesia accepted the recovery time as the moment when rats could stand on all four paws (9). In our study, we used the second time rats could stand on all four paws as recovery criterion.

Different medications are used for recovery after ketamine anesthesia. Some of these include yohimbine and physostigmine. Hsu et al. in a study of cats stated that yohimbine increased the speed of the recovery from ketamine+xylazine anesthesia. Additionally, they stated that yohimbine reversed bradycardia and respiratory depression occurring after xylazine-ketamine and that yohimbine will be beneficial to control the anesthesia duration (10). Sontakke et al. in an animal study stated that yohimbine reversed the effect of xylazine due to alpha 2 adrenergic antagonisms after the combination of ketamine+xylazine (11). Hamilton et al. in a study divided patients recovering from ketamine anesthesia into two groups. The first group was administered physostigmine and the second group were given saline. The group administered physostigmine were observed to have significantly shortened recovery duration (12). Another study by Kubota et al. observed the use of physostigmine shortened the recovery from ketamine anesthesia and linked to this, reduced noradrenalin secretion in the prefrontal region (13). A study by Engelhardt et al. used ketamine with physostigmine and researched the effect on EEG changes. Ketamine was found to cause greater increase in total, delta, theta and beta amplitudes during anesthesia. During recovery there was a clear reduction in median and dominant frequencies on EEG waves. There was no difference between the physostigmine and placebo groups; however, they stated this may be linked to use of a low dose of physostigmine (14).

Sugammadex is a neuromuscular agent blocker, commonly used in recent years. However, studies have reported that sugammadex does not just bind to muscle relaxants but to many agents. Previous studies of sugammadex have reported interaction with more than forty lipophilic steroidal and non-steroidal medications. Among these medications are propofol, thiopental, fentanyl, remifentanil, vancomycin, gentamicin, salbutamol, aminophylline, atropine, ephedrine, phentolamine, verapamil, cortisone and hydrocortisone (15). Ketamine is among these medications; however, there is no study found about ketamine antagonism. A study by Hanci et al. stated that sugammadex administered to rats with theophylline-aminophylline intoxication significantly delayed toxicity and increased the mean lethal theophylline dose. They

stated that 16 mg/kg sugammadex dose was more effective for theophylline intoxication (16). Ozbilgin et al. found sugammadex delayed cardiotoxicity of digoxin in rats with induced digoxin intoxication. A dose of 1000 mg/kg sugammadex was stated to significantly lengthen the asystole time in digoxin intoxication (17). Another study by Ozbilgin et al. used 16 mg/kg dose of sugammadex in rats with induced verapamil intoxication and found it delayed verapamil cardiotoxicity. However, sugammadex at 1000 mg/kg dose was observed to increase the speed of verapamil cardiotoxicity (18). In our study, the results with 16 mg/kg dose of sugammadex were similar to the control group. Additionally, with 100 mg/kg and 1000 mg/kg doses of sugammadex, recovery durations were found to be significantly short.

One of the known side effects of sugammadex is that it lowers heart rate. A study by Kızılay et al. compared the hemodynamic effects of neostigmine with sugammadex in cardiac patients undergoing non-cardiac surgery. Blood pressure and heart rate were observed to be lower in the sugammadex group compared to the neostigmine group (19). Mesa et al. compared the effects of different doses of sugammadex in patients administered rocuronium infusion. Sugammadex doses of 2 mg/kg and 4 mg/kg were observed to have no different effects on heart rate, mean arterial pressure, diastolic and systolic blood pressure (20). In our study, the 1000 mg sugammadex group was observed to have significantly low heart rate.

One of the limitations of our study is that the ketamine concentrations in plasma and brain tissue were not measured. Similar studies measuring ketamine concentration in plasma and brain tissue using different doses of sugammadex will provide the opportunity for more healthy assessment. Apart from this, one of the topics that requires research is what results will be due to the effect of sugammadex using ketamine intoxication models in this type of study.

CONCLUSION

In this study with the aim of revealing whether sugammadex is beneficial to increase the speed of recovery from ketamine anesthesia, 100 mg/kg and 1000 mg/kg sugammadex doses were shown to significantly shorten recovery. Additionally, the heart rate in the group administered 1000 mg/kg sugammadex was determined to be significantly low compared to the other groups. Future studies should research the mechanisms in the relationship between ketamine and sugammadex.

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