The Effects of Memantine after Propofol Anaesthesia to Recovery on Cognitive Functions and Pain in Streptozotocin Induced Diabetic Rats

Streptozosin ile Diyabet Oluşturulan Ratlarda Propofol Anestezisi Sonrası Memantin Tedavisinin Derlenme, Kognitif Fonksiyon ve Ağrı Üzerine Etkileri

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ABSTRACT

Objective: The aim of this study is to research the neurocognitive, neuroprotective and analgesic effects of the memantine in diabetic rats after anaesthesia. Postoperative cognitive dysfunction is a frequent complication after anaesthesia. Although the reason of this hasn't been explained completely, there are numerous risk factors such as the increase of cognitive dysfunction during postoperative period. Being in older age, coexisting diseases, etc. are among these risk factors. Propofol, one of the anaesthetic agents, is an agent causing the postoperative cognitive dysfunction.Memantine has beneficial effects on memory deficits and learning process. Additionally, it is an agent which also has neuroprotective effects, and is used for the treatment of chronic pain syndromes. In this study, we aim to determine its effects on recovery, cognitive functions and pain of memantine after propofol anaesthesia.

Materials and Methods: Thirty Wistar rats were divided into 5 groups randomly. 0,9 % NaCl (1ml i.p.) were given to Group C on 31st day after normal nutrition period during 30 days. 0,9 % NaCl (1ml i.p.) was given to Group DC on 31st day after normal nutrition period during 30 days. 0,9 % NaCl (1ml i.p.) was given to Group DM on 31st day after oral memantine treatment (20 mg/kg/day) during 30 days. Propofol (150 mg/kg i.p.) was given to Group DP on 31th day after normal nutrition period during 30 days. Propofol (150 mg/kg i.p.) was given to Group DPM on 31th day after oral memantine treatment (20 mg/kg/day) during 30 days. Recovery, cognitive function and the pain level of the rats are evaluated with "tail pinch", "Radial Arm Maze" and "hot-plate" respectively.

Results: Recovery durations of the rats in Group DMP were shorter than rats in Group DP ($p< 0,0001$). Hot-plate values were significantly longer than control values in all groups, except for Group C, when compared in-group ($p<0,05$).

Conclusion: In conclusion, this study showed that memantine has beneficial effects on recovery, cognitive functions and pain after propofol anaesthesia in diabetic rats.

Key Words: Memantine, propofol, diabetes, postoperative cognitive dysfunction, pain, hot plate, radial arm maze

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ÖZET

Amaç: Bu çalışmanın amacı diyabet oluşturulan ratlarda propofol anestezisi sonrası uygulanan memantinin nörokognitif, nöroprotektif ve analjezik etkilerini araştırmaktır.Postoperatif kognitif disfonksiyon anestezi sonrasında sıklıkla görülen bir durumdur. Nedeni tam olarak belirlenememesine karşı postoperatif dönemde kognitif disfonksiyonu artıran pek çok risk faktörü vardır. İleri yaş; eşlik eden hastalıklar vb. bu risk faktörleri arasındadır. Anestezik ajanlardan propofol, postoperatif kognitif disfonksiyon yaptığı kanıtlanmış bir ajandır. Memantinin ise hafıza ve öğrenmeye olumlu katkıları olmasının yanında; nöroprotektif olduğu bilinen ve kronik ağrı tedavisinde kullanılan bir ajandır. Bu çalışmada memantinin, propofol anestezisi sonrasında derlenme, kognitif disfonksiyon ve ağrı düzeyine etkilerinin araştırılmasını amaçlamış bulunmaktayız.

Yöntem: Otuz adet Wistar cinsi yaşlı ratlar rastgele 5 gruba ayrıldı. Grup K nondiabetik ratlar 30 gün normal beslendikten sonra 31. gün % 0,9 NaCl (1 ml i.p.) verildi. Grup DK diabetik ratlar 30 gün normal beslendikten sonra 31. gün % 0,9 NaCl (1 ml i.p.) verildi. Grup DM diabetik ratlar 30 gün gün boyunca oral memantin (20 mg/kg/gün) tedavisi sonrası 31. gün % 0,9 NaCl (1 ml i.p.) verildi. Grup DP diabetik ratlar 30 gün normal beslendikten sonra 31. gün propofol (150 mg/kg i.p.) verildi. Grup DPM'de diabetik ratlar 30 gün gün boyunca oral memantin (20 mg/kg/gün) tedavisi sonrası 31. gün propofol (150 mg/kg i.p.) uygulandı. Ratların derlenmesi "tail pinch", kognitif fonksiyonları "Radial Arm Maze" ve ağrı düzeyleri ise "hot-plate" ile değerlendirildi.

Bulgular: Ratlarda derlenme süresi Grup DMP' de Grup DP' ye göre anlamlı kısa idi ($p<0.0001$). Hot-plate değerleri ise Grup K hariç bütün gruplarda, grup içi karşılaştırıldığında, kontrol değerlerine göre ileri haftalarda anlamlı olarak yüksek bulundu ($p<0,05$).

Sonuç: Sonuçta ise diyabet oluşturulan ratlarda memantinin propofol anestezisi sonrası derlenme, kognitif fonksiyonlar ve ağrı düzeyine olumlu etkileri olduğu kanaatindeyiz.

Anahtar Sözcükler: Memantin, propofol, diyabet, postoperatif kognitif disfonksiyon, ağrı, hot plate, radial arm maze

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INTRODUCTION

Postoperative cognitive dysfunction (POCD) is defined as postoperatively -also following anaesthesia- emerged regression of cognitive functions such as memory, ability of concentration, language and social communication skills. Frequency of POCD is varied between 33% and 83% (1). POCD may continue for hours, days, weeks or can result in permanent cognitive dysfunction (2,3).

Diabetes Mellitus (DM) is a well-known risk factor for cardiovascular diseases, blindness, and renal failure. Also DM leads structural damage and subsequent cognitive dysfunction in Central Nervous System (CNS) (4).

Memantine is an N-methyl D aspartate (NMDA) receptor antagonist whose effectiveness on Alzheimer disease has been proven. Previous studies have shown that memantine can reverse changes in memory disturbances and synaptic plasticity in animal models (5). Also there are several pre-clinical and clinical studies which indicate positive effects of memantine on learning capability and memory function (6,7). On the other hand, positive effects of memantine on pain management have been reported (8).

Propofol is a general anaesthesia agent applied by intravenous (iv). Although its effect mechanism has not been clearly defined, it is thought that it has an effect on decreasing the separation of gamma amino butyric acid (GABA) from the receptor as barbiturates do. Besides, excitatory in the CNS causes to emerge an extensive inhibition effect by blocking both the glutamate receptors, which are the subtypes of NMDA receptors, and slow calcium pathways (9).

In the present study, the effects of memantine on recovery, cognitive functions and pain management after propofol anaesthesia in streptozotocin (STZ) induced diabetic rats were investigated. We aimed to eliminate inhibitory activity of propofol on CNS using memantine's effect on glutamate pathway. We used Radial Arm Maze (RAM) test and hot plate tests on rats in order to evaluate cognitive functions and pain levels respectively.

MATERIALS and METHODS

Animals and experimental protocol

This study was conducted in the GUDAM Laboratory of Gazi University with the consent of the Experimental Animals Ethics Committee of Gazi University (G. Ü. ET. 13.047). All animals received human care in compliance with the "Principles of Laboratory Animal Care" formulated by the National Society for Medical Research and the "Guide for the Care and the Use of Laboratory Animals" prepared by the National Academy of Science and published by the National Institutes of Health (NIH publication Nr. 85–23, revised in 1985).

We used 30 Wistar albino old rats (>12 months) weighing between 125-200 g. Rats were housed under controlled conditions of light cycle (12 hours:12 hours light:dark) with free access to water and rat chow. On the day of the study, animals were fastened before night. Before studying the experiment, blood glucose levels and body weights of all animals were measured. 6 rats were in the control group (Group C), and in this group diabetes were not induced. Other 24 diabetic rats were randomly divided into 4 study groups (Group DC, Group DM, Group DP, and Group DPM).

Group C (Control Group): Rats were allowed free access to water and chow for 30 days, RAM and hot plate values were measured weekly. On the 31th day of experiment number and duration of entrance/exit and hot plate times at 0, 1 and 2nd hours were recorded as measured in other groups.

Induction of Diabetes: In diabetes groups, one single intraperitoneal injection of STZ (55 mg/kg) was done. 72 hours after injection, blood glucose levels were determined from blood collected from tail vein. Rats with a blood glucose level equal to or above 250 mg/dl were determined as diabetic. Rats were followed for 4 weeks in order to evaluate chronic effects of diabetes on organ systems.

Group DC (Diabetes Control Group): RAM and hot plate values were determined weekly. On the 31th day of experiment, number and duration of entrance/exit on RAM and hot plate times at 0, 1 and 2nd hours were recorded as measured in other groups.

Group DM (Diabetes Memantine Group): Memantine (20 mg/kg/day) was added in drinking water of rats for 30 days. Daily water consumption of rats was adjusted as 10-12 ml/100 gr body weight. Drinking water was refreshed weekly. RAM and hot plate values were determined weekly. On the 31th day of experiment, number and duration of entrance/exit and hot plate times at 0, 1 and 2nd hours were recorded as measured in other groups.

Group DP (Diabetes Propofol Group): RAM and hot plate values were determined weekly. On the 31th day of experiment, 150 mg/kg dose of propofol 1% (propofol 1%, Fresenius Kabi AB, Germany) was administered IP and the application time was recorded in all rats. The rats were left to recover, then recovery was evaluated with a tail pinch test (squeezing the tail 3–4 cm from the base for 30 seconds using "rubber dam" forceps) and the time for recovery was recorded. Recovery time after anaesthesia, number and duration of entrance/exit and hot plate times at 0, 1 and 2nd hours were recorded.

Group DPM (Diabetes Propofol Memantine Group): Memantine (20 mg/kg/day) was added in drinking water of rats for 30 days. Daily water consumption of each rat was adjusted as 10-12 ml/100 gr body weight. Drinking water was refreshed weekly. RAM and hot plate values were determined weekly. On the 31th day of experiment, 150 mg/kg dose of propofol 1% (propofol 1%, Fresenius Kabi AB, Germany) was administered IP and the application time was recorded in all rats. The rats were left to recover, then the recovery was evaluated with a tail pinch test (squeezing the tail 3–4 cm from the base for 30 seconds using "rubber dam" forceps) and the time for recovery was recorded. Recovery time after anaesthesia, number and duration of entrance/exit and hot plate times at 0, 1 and 2nd hours were recorded.

The radial arm maze: The radial arm maze is comprised of a Plexiglas central platform measuring 30 cm with eight equidistant arms radiating outwards (for example, 80 cm × 12.5 cm) with a height of 66 cm. The areas around the maze are visible to permit the orientation of rats, and rats move using those tips. For this study, the RAM was placed on a table top 90 cm from the floor.

Hot plate test: This is a test for acute pain evaluation. The aluminium hot plate surface was heated up to 55 °C. Glass cylinders were used to ensure that the rats remained in the heated region while not limiting capacity for movement. Movements such as foot raising, jumping, licking, and walking backwards were all accepted as positive, and the times from first placement until the first positive movement were recorded. The test was terminated after 25 sec to prevent tissue damage.

Statistical Analysis

Statistical analysis was performed using SPSS 20,0 packet program. Data was expressed as mean±standard deviation (min-max). $p<0.05$ was determined as statistically significant. Shapiro-Wilk test was used in order to determine normal/abnormal distribution of measured parameters. One-way ANOVA test was used to determine intergroup differences between normally distributed data in groups. Significant differences between groups were compared using Bonferroni test. Repeated data from hot plate and entry-exit to Radial Arm Maze (RAM) tests were analysed using Repeated Measures Analysis of Variance (RANOVA) test. Certain time points which significant differences identified were determined using Bonferroni correction.

RESULTS

In the study, when the body weight of the rats in the examined 5 groups comprising 30 subjects was compared, no significant difference and similar weight average in among the groups were determined ($p>0.05$), (Table 1).

Table 1. Mean body weights of rats in study groups [Mean ± SD, (Min-Max].

Weight (g)	Group C (n=6)	Group DC (n=6)	Group DM (n=6)	Group DP (n=6)	Group DPM (n=6)	p
Baseline	172,83±13,55 (159-192)	179,66±11,25 (169-194)	168,67±20,73 (131-193)	177,66±13,25 (159-197)	168,17±11,55 (156-185)	0,844
End of study	193,17±10,99 (181-211)	184,50±11,78 (165-200)	160,17±20,16 (128-188)	180,50±15,70 (156-205)	178,83±19,29 (154-198)	0,149

p value: achieved from multiple comparisons

Additionally, the blood glucose of the rats with diabetes were observed to have increased significantly in all groups compared to the ones without diabetes (p<0.0001), (Table 2).

Table 2. Mean blood glucose levels of rats in study groups [Mean ± SD, (Min-Max].

	Group C (n=6)	Group DC (n=6)	Group DM (n=6)	Group DP (n=6)	Group DPM (n=6)	P
Blood glucose levels (mg/dL))	106,33±5,68 (88-125)	454,50±98,81* (256-800)	493,17±73,02* (293-787)	340,33±86,21* (253-469)	597,33±84,2* (493-689)	<0,0001

p value: achieved from multiple comparisons

***:** p<0,05 (when compared with Group C)

In the Tail Flick test, which anaesthesia recovery period was evaluated, the period was examined to be significantly shorter in Group DPM than in Group DP (p<0,0001).

When hot plate weeks 1 and 2 measurement values were compared, no difference in groups were determined (Table 3). Measured hot plate values of Groups DM and DPM in the periods oral memantine was given, were determined to be significantly increased in week 3 when compared to Group C.

Table 3. Mean hot plate values of study groups [Mean ± SD, (Min-Max].

	Group C (n=6)	Group DC (n=6)	Group DM (n=6)	Group DP (n=6)	Group DPM (n=6)	P
Tail flick (min)				97,00±5,40 (90-105)	73,00±9,80 (63-87)	<0,0001
Hot plate week 1 (sec)	8,83±1,94 (6-11)	9,50±1,76 (7-12)	8,83±1,32 (7-10)	9,17±0,75 (8-10)	9,67±0,82 (8-10)	0,779
Hot plate week 2 (sec)	8,50±1,51 (6-10)	10,00±1,10 (8-11)	11,33±2,25 (9-14)	12,83±5,15 (6-18)	10,50±2,34 (8-15)	0,133
Hot plate week 3 (sec)	8,33±1,86 (5-10)	11,33±2,42 (10-16)	15,50±4,32*,+ (10-20)	11,17±1,94 (8-13)	15,17±3,43*,+ (10-20)	0,003
Hot plate week 4 (sec)	10,33±1,21 (9-12)	14,50±1,38* (13-16)	15,33±6,05* (10-25)	15,17±1,17* (14-17)	17,50±2,66*, ≠ (13-20)	0,009
Hot plate 0.hour (sec)	10,50±1,05 (9-12)	13,33±1,51 (12-15)	15,83±5,85* (10-25)	21,00±2,37*,+,&, ≠ (18-24)	24,00±2,45*,+,&, ≠ (19-25)	<0,0001
Hot plate 1. hour (sec)	10,50±0,55 (10-11)	14,66±2,34* (12-18)	15,00±4,47* (10-20)	19,00±2,00*,+,&, ≠ (16-21)	23,33±2,88*,+,&,?, ≠ (18-25)	<0,0001
Hot plate 2. hour (sec)	10,67±2,16 (8-13)	15,83±1,17* (14-17)	14,17±3,76* (10-20)	15,17±1,47* (14-18)	21,00±3,74*,+,&,?, ≠ (15-25)	<0,0001

***: p<0,05** Compared to Group C

+: p<0,05 Compared to Group DC

&: p<0,05 Compared to Group DM

?: p<0,05 Compared to Group DP

≠: p<0,05 Compared to week 1. measurement

Hot plate values measured in week 4, when oral memantine was given, were determined to be significantly increased in Groups DC, DM, DP and DPM, when compared to Group C (Table 4). Hot plate values measured after propofol application period were found to be significantly increased at 0, 1st and 2nd hour measuring times in Groups DP and GPM when compared to Group C.

Furthermore, when Group DP was compared to Group DC, it was determined to be significantly increased at 0 and 1 hour measuring times in Group DP and 0.,1st and 2nd hour measuring times in Group DPM. Similarly, it increased significantly in Group DP at 0. and 1st hour and at 0., 1st and 2nd hour measuring times in Group DPM when compared to Group DM. Besides, it was found to be increased at 1st and 2nd, hour measurement periods in Group DPM when compared to Group DP.

Table 4. Mean number of Radial Arm Maze (RAM) entry-exit of study groups [Mean ± SD, (Min-Max].

	Group C (n=6)	Group DC (n=6)	Group DM (n=6)	Group DP (n=6)	Group DPM (n=6)	P
Week 1 (entry-exit)	10,00±0,63 (9-11)	9,17±1,17 (8-11)	9,50±1,52 (7-11)	9,33±1,37 (7-11)	9,83±1,47 (8-12)	0,777
Week 2 (entry-exit)	8,00±1,55 (6-10)	5,50±1,22*,≠ (5-8)	6,83±1,83* (5-9)	5,83±0,75*, ≠ (5-7)	6,33±1,21* (5-8)	0,034
Week 3 (entry-exit)	8,50±0,55 (8-9)	5,50±0,55*,≠ (5-6)	7,67±2,50+ (5-11)	5,50±1,05*, ≠ (4-7)	8,33±1,51+ (6-10)	0.001
Week 4 (entry-exit)	6,33±0,52 (6-7)	4,33±0,52*,≠ (4-5)	6,50±1,05+ (5-8)	5,00±0,63*,≠ (4-6)	7,00±0,63+ (6-8)	<0.0001
Hour 0 (entry-exit)	6,67±0,82 (5-7)	4,33±0,82*,≠ (3-5)	7,00±1,55+ (6-10)	1,50±0,84*,+,&,≠ (0-2)	3,00±1,55*,&,?,≠ (2-5)	<0.0001
Hour 1 (entry-exit)	6,83±0,75 (6-8)	4,50±0,55*,≠(4-5)	6,00±0,63+ (5-7)	2,83±0,98*,+, &,≠ (2-5)	4,33±1,21 *,&,?,≠ (3-6)	<0.0001
Hour 2 (entry-exit)	7,00±0,63 (6-8)	4,33±1,21*,≠(3-6)	6,00±1,26+ (5-8)	4,00±0,63*,&,≠ (3-5)	5,83±1,17+,? (5-8)	<0.0001

***: p<0,05** Compared with Group C
+: p<0,05 Compared with Group DC
&: p<0,05 Compared with Group DM
?: p<0,05 Compared with Group DP
≠: p<0,05 Compared with week 1 measurement

When hot plate data were compared within the group, basal measurement times were determined to be similar to the hot plate measuring times in Groups C and DC. 0. and 1st hour measurement times, after anaesthesia, were determined to be significantly more in Group DP than basal measurement period. Hot plate measurement times in Group DPM, which was given oral memantine, were found to be significantly increased in week 4 and after anaesthesia when compared to basal measurement period.

In the first week measurements, after diabetes, the number of entry-exit of the rats were determined to be similar among the groups. In the second week measurements, entry-exit of the rats were determined to be significantly decreased in all groups compared to the control group. As for the third and fourth weeks, entry-exit decreased significantly in DC and DP groups compared to the control group. In the groups which memantine were given, entry-exit were found to be similar to the control group.

When compared to Group C, entry-exit in were found to have decreased significantly at 0, 1. and 2. hour measuring times. In Group DPM, at 0. and 1. hour measuring times, entry-exit decreased significantly in comparison with those of Group C. In Group DP, at 0. and 1. hour measuring times, entry-exit decreased significantly compared to Group DC. In Group DPM, at 2. hour measuring times, entry-exit increased significantly compared to Group DC. In Group DP, at 0., 1. and 2. measuring times, entry-exit decreased significantly compared to Group DM. In Group DPM, at 0. and 1. hour measuring times, entry-exit decreased significantly compared to Group DM. In Group DPM, at 0., 1. and 2. hour measuring times, entry-exit increased significantly compared to Group DP.

According to in-group evaluation, when 1st week measuring time and other measuring times were compared, entry-exit were found to be similar. As for Group DC and DP, when 1st week measuring times and other measuring times were compared, entry-exit decreased significantly. In Group DPM, when 1st week measurement time and other measurement times were compared, 0. and 1st hour entry-exit decreased significantly after anaesthesia.

DISCUSSION

In this study we observed positive effects of memantine – a NMDA receptor antagonist- on postoperative recovery, cognitive functions and acute pain after propofol in STZ induced diabetic rats.

In literature, there are studies a lot of risk factors related with POCD are indicated. When POCD occurrence etiology is considered, patient induced factors (old age, cerebrovascular damage, low education level and chronic diseases such as diabetes), operational and anaesthetic factors can be counted (10,11).

Different results related with the effects of DM on cognitive functions have been reported. In many studies, diabetic patients were determined to have poorer performance in neuropsychometric tests, including, word fluency, oral and audio learning phases compared to control groups. In Launer's wide-population based survey, it has been noted that the subjects having DM background have significantly low MMDM scores (21 and less) (12). Nonetheless, in Rotterdam research, Breteler et al reported that MMDM scores of diabetic and non-diabetic patients don't have a significant difference, however, subjects having high glucose level after glucose load have a low MMDM score. Another possibility noted by Breteler is the thought that cognitive disorder is more related with the increased glucose level in blood than diagnosed diabetes (13). In Rotterdam population research, dementia, particularly Alzheimer's type dementia, in female diabetic patients diagnosed as type 2 receiving insulin treatment are noted to be more frequently seen (14).

In histopathological studies, metabolic oxidation products related with DM and hypoglycaemia, progressive glycosylation post products (PGPP) were indicated in senile plaque and the structure of neurofibrillary tangles of the post-mortem samples of the patients diagnosed as Alzheimer's disease (15).

We aimed to include rats having a lot of risk factors related with POCD occurrence (old, diabetic and having had anaesthesia) in our study. Our study has similarities with the previous studies including diabetes, as well. In the 4-week follow-ups, before any process had been realized, Group DC including diabetes with STZ and not given memantine, when Group DP and Group C including non-diabetes and not given memantine compared, RAM entrance and exist numbers were found to be similar to those of the control group in the first measurements. However, in the measurements after the 2nd week, a significant decrease was determined in the diabetic group in comparison with the control group. This fact led us to a conclusion that diabetes causes a negative effect on the cognitive functions and memory of the rats. In our study, we determined that RAM entrance and exit numbers declined significantly in the rats with diabetes; however, memantine application increased the entrance and exit numbers.

The reason for our selecting propofol as an anaesthetic agent is that it has an effect mechanism creating extensive inhibition on $GABA_A$ receptors and Ach receptors, and the hypothesis that some of these effects can be reversed by memantine which is an NMDA antagonist to create an anaesthetic effect. It creates an anaesthetic effect occurred through propofol NMDA and GABA receptors. Memantine's having an effect as NMDA receptor antagonist and its affecting on common receptor with propofol is the main factor of the cause of our selection.

Memantine, an uncompetitive NMDA antagonist, is a medicine used for the treatment of cognitive dysfunction, Alzheimer's disease – degree of disease ranging between tolerable to severe- comprising behavioural disorder, and was approved by FDA with this indication in 2003 (16). We thought that memantine may well have positive effects on recovery, POCD and acute pain, based upon the positive effects of memantine on learning process and memory, its neuroprotective effect and usage in pain treatment. The reason for our using oral memantine form is the application of memantine (Ebixa®) also orally on clinical patients. We consider that in this was, it will be easier to apply the research in clinic.

The role of surgery and anaesthesia in the occurrence of POCD remains uncertain. However, in theories about its anaesthetic effects, direct toxicity, difference in calcium homeostasis, systematic inflammatory effect, suppression in the neural stem cell functions related with age, the momentum of endogen neurodegenerative phase, direct toxicity and apoptosis have been asserted (17,18). In cell culture studies, it has been indicated that volatile anaesthetics (isoflurane, sevoflurane and desflurane) triggers apoptosis and increases the occurrence of amyloidal-beta in the presence of hypoxia (17,19). Fodale et al., have founded that iv anaesthetics such as propofol and thiopental doesn't change amyloidal precursor proteins (19).

Clinical effect of anaesthetics agents on molecular cellular mesh and structural anatomic levels comprise a lot of competent. These competent neurotransmitter mediated ion pathways especially GABA, glutamate and NMDA pathways are modulated by many anaesthetics and can be diagnosed as the targets of receptors and anaesthetics agents in both synaptic and extra-synaptic areas (20).

When we examine the effect mechanism of propofol used in this research, its sedative effects were found connected with its potentiation of chlorine flow by connecting $GABA_A$ receptor ß sub-unit in the hippocampus and with blocking Ach oscillation on hippocampus and prefrontal cortex. In addition to this, propofol creates extensive inhibition on NMDA receptors which are the subtypes of the modulation of door mechanism of sodium pathways and glutamate receptors (21). The modulation of these receptors' creating POCD is known. Kunimatsu et al., (22) notes that when propofol is used as an anaesthetic agent on patients having had oral surgery, postoperative POCD occurs. In another study, supporting this, Nishikawa et al. (23) compared patients having had laparoscopic surgery administered epidural anaesthesia and the ones given propofol and sevoflurane anaesthesias, and determined that in the group given propofol anaesthesia besides epidural anaesthesia, delirium stocks are more compared with the other group.

We observed that the recovery after propofol anaesthesia of the diabetic ats administered oral memantine for 1 month (Grup DP :97,00±5,40 min, Grup DPM:73,00±9,80 min p<0,0001) was much faster. Generally, recovery from anaesthesia is determined by the rate at which the anaesthetic agent concentrations in the brain tissue decrease, and by the elimination rate of the drug (24). It can be deduced from the present study that early recovery from propofol anaesthesia, which was the case in this study in memantine-administered rats, is due to the common interaction of both agents on the NMDA receptor rather than to an increase in the elimination rate. In a study supporting the effect of this interaction on the level of anaesthesia, Brosnan et al., (25) used picrotoxin, which is a $GABA_A$ receptor antagonist, on rats that had been anaesthetized with isoflurane, and then they administered an NMDA receptor antagonist, MK-801 (Dizocilpine), to the rats. When they analysed the isoflurane minimum alveolar concentration (MAC) value using a standard tail clamping test, the picrotoxin was found to increase isoflurane MAC while the IV MK-801 decreased isoflurane MAC. The authors concluded that NMDA receptor inhibition played a major role in anaesthetic immobilization and that the use of NMDA antagonists affected MAC. In a study by Kuroda et al., (26) on the effects of the NMDA receptor antagonist dizocilpine on isoflurane MAC, the MK-801 was found to decrease isoflurane MAC due to the receptor interaction through GABA. Similar to our study Emik et al., used intravenous memantine, 30 minutes before the propofol anaesthesia, and they showed that memantine-administered rats were more rapidly recovered from propofol anaesthesia (27).

Another part of our study comprises the evaluation of the effect of memantine on acute pain. With the indication of the role of NMDA receptors in neuropathic pain, NMDA receptor antagonists have created a new hope for pain treatment in clinical usage. In the study by Chen et al., antinociceptive effect of chronic administration of memantine, neramexane and gabapentine which are of NMDA receptors was examined. Diabetic rats, induced 2-3% STZ, were given neramexane, memantine ((20mg/kg/day)) and gabapentine for 2 weeks in the form of subcutaneous infusion with a mini-pump placed on the back of the animals with isoflurane anaesthesia. Mechanic hyperalgesia and allodynia in the rats were observed, and it was concluded in the study that chronic memantine and neramexane administration have beneficial effects on diabetic neuropathic pain (28).

In another study by Alexander et al., neurologic damage was created in 8-10 week-old rats by straining the neurons for 60 minutes. Respectively, memantine 20 mg/kg i.p. mifepristone 50 mg/kg, corticosterone 1,5 mg/kg were given, and it was observed that corticosterone increased allodynia in the rats on which neurologic damage was created, whereas memantine prevents allodynia in the same group (29).

Hot plate method, which has a standard temperature of 52°C, was used for creating an acute pain. In the study, before starting memantine treatment, basal pain levels of all the groups were measured, and the results were found similar in all. Measurement times were significantly longer in diabetic groups, being more significant in memantine administered groups. When regular measurements were noted hourly following the consciousness after anaesthesia, measurement times of basal values of in-groups and in comparison with the values of the control group, the measurement times of each memantine, propofol and memantine+propofol groups were significantly longer ($p<0.0001$). This result leads us to assume that memantine affects acute pain. As known, propofol, has some analgesic effect (30) and this may well explain the indifference intergroup. In the study protocol, we let the rats stay 25 seconds at maximum on hot plate for the examination of analgesic effect. As we observed the analgesic effect for just 2 hours, its effect on the analgesic period couldn't be exactly evaluated.

CONCLUSION

Oral memantine long time administration in diabetic rats before the administration of propofol anaesthesia was observed to facilitate recovery from anaesthesia and to have positive effects on cognitive functions and acute pain. This subject may benefit from further evaluation in future studies.

Conflict of interest

No conflict of interest was declared by the authors.

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