The Effects of Memantine on Cognitive Function and Pain after Sevoflurane and Desflurane Anesthesia in Streptozotocin Induced Diabetic Rats

Streptozosin Uygulanan Diyabetik Ratlarda Memantin Kullanımının Sevofluran ve Desfluran Anestezisi Sonrası Kognitif Fonksiyonlar ve Ağrı Üzerine Etkileri

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ABSTRACT

Objective: Postoperative cognitive dysfunction (POCD) refers to a wide range of alterations which effect memory, information processing and executive function after anesthesia and, the mechanism is still not properly defined. Diabetes is a chronic metabolic disease which has a negative impact on cognitive function and leads to impairment of perception of pain by causing peripheral neuropathy. Sevoflurane and desflurane are anesthetic agents which are shown to cause POCD in many studies. Memantine is an agent which has a positive contribution on memory and learning; also known as neuroprotective and used in chronic pain treatment. In this study, we aim to investigate the effects of memantine, after sevoflurane and desflurane anesthesia on cognitive dysfunction and pain levels in diabetic rats.

Materials and Methods: In our study, we used 42, old (>12 months) Wistar Albino rats, 6 of them were grouped as control group (Group C). We have injected 55 mg/kg streptozotocin (i.p) in the other wistar rats and measured blood glucose and weight. Diabetic 36 rats were randomized into 6 groups (n=6) and groups were defined as Group DC, Group DM, Group DS, Group DD, Group DSM, Group DDM and control group Group C. During 30 days we added 20 mg/kg memantine into the drinking water of Group DM, Group DSM and Group DDM's rats. We measured radial arm maze (RAM) and hot plate values of 30 days-followed up rats weekly. At the end of 30 days we gave anesthesia to sevoflurane and desflurane groups in 2 hours-long period and after that we measured 0. 1. and 2. hours RAM and hot plate values of this rats and other rats.

Results: In the groups of which only variant was diabetes (until the study day Group C and Group DC, Group DS and Group DD, groups which weren't given memantine), we compared the results and we conclude that diabetes has negative impact on cognitive function. Similarly, in the groups of which only variant was sevoflurane (Group DS and Group DC) or was desflurane (Group DD and Group DC) we compared the results and we conclude that our inhaler agents effect cognitive functions negatively. And yet, in the groups of which only variant was just inhaler agents (Group DS and Group DD; Group DSM and Group DDM), inhaler agents have similar effects on cognitive function and recovery. And finally, in the rat groups of which only variant was memantine (Group DC and Group DM, Group DSM and Group DS, Group DDM and Group DD), we observe that memantine fasten recovery time and has a positive effects on cognitive functions. In addition to that, we compared the hot plate measurements between 30 days followed-up diabetic rats which were not given memantine (Group DC, Group DS and Group DD) and diabetic rats which were given memantine (Group DM, Group DSM, Group DDM) and between the groups on the study day which had only variant memantine (Group DSM and Group DS; Group DDM and Group DD). The hot plate values show us memantine has an analgesic effect.

Conclusion: In conclusion, administration of memantine in diabetic rats has positive effect on recovery, cognitive functions and pain levels after anesthesia with sevoflurane or desflurane.

Key Words: Memantine, desflurane, sevoflurane, diabetes mellitus, RAM, POCD, hot plate

ÖZET

Amaç: Postoperatif kognitif disfonksiyon (POKD), anestezi sonrası bellek, bilgi işleme ve yürütme işlevini etkileyen çok çeşitli değişiklikleri ifade eder ve mekanizma hala tam olarak tanımlanmamıştır. Diyabet, kognitif fonksiyon üzerinde olumsuz bir etkisi olan ve periferik nöropatiye neden olarak ağrı algısının bozulmasına yol açan kronik bir metabolik hastalıktır. Sevofluran ve desfluran, birçok çalışmada POKD'ye neden olduğu gösterilen anestezik ajanlardır. Memantin hafıza ve öğrenmeye olumlu katkıda bulunan bir ajandır; nöroprotektif olarak da bilinir ve kronik ağrı tedavisinde kullanılırBu çalışmada, memantinin sevofluran ve desfluran anestezisinden sonra diyabetik sıçanlarda kognitif disfonksiyon ve ağrı düzeyleri üzerine etkilerini araştırmayı amaçladık.

Yöntem: Çalışmamızda, 6'sı kontrol grubu (Grup K) olarak gruplandırılan 42 adet yaşlı (> 12 ay) Wistar Albino sıçan kullanıldı. Kontrol grubu dışındaki Wistar sıçanlarına 55 mg/kg streptozosin (i.p) enjekte edildi ve kan şekeri ve ağırlığı ölçüldü. Diyabetik 36 sıçan 6 gruba (n=6) randomize edildi ve gruplar Grup DK, Grup DM, Grup DS, Grup DD, Grup DSM, Grup DDM ve kontrol grubu Grup K olarak tanımlandı. 30 gün boyunca Grup DM, Grup DSM ve Grup DDM sıçanlarının içme suyuna memantin 20 mg/kg eklendi. Radial arm maze (RAM) ve 30 günlük hot plate değerleri haftalık ölçüldü. 30 günün sonunda sevofluran ve desfluran gruplarına 2 saat süren anestezi uygulandı ve bundan sonra bu sıçanların ve diğer sıçanların 0. ve 2. saat RAM ve hot plate değerleri ölçtüldü.

Bulgular: Sadece diyabet olan gruplarda (memantin verilmeyen gruplar; Grup K ve Grup DK, Grup DS ve Grup DD) sonuçları karşılaştırıldı ve diyabetin bilişsel işlev üzerinde olumsuz etkisi olduğu sonucuna vardık. Benzer şekilde, sadece sevofluran (Grup DS ve Grup DK) veya desfluran (Grup DD ve Grup DK) olan gruplarda sonuçlar karşılaştırıldı ve inhaler ajanların kognitif fonksiyonları olumsuz etkilediği sonucuna vardık. Yine de, sadece inhaler ajanları olan gruplarda (Grup DS ve Grup DD; Grup DSM ve Grup DDM), inhaler ajanlarının kognitif fonksiyon ve iyileşme üzerinde benzer etkileri vardır. Son olarak, sadece varyantı memantin olan sıçan gruplarında (Grup DK ve Grup DM, Grup DSM ve Grup DS, Grup DDM ve Grup DD), memantinin iyileşme süresini hızlandırdığını ve kognitif fonksiyonlar üzerinde olumlu etkileri olduğunu gözlemledik. Buna ek olarak, 30 günlük takip edilen diyabetik ve memantin verilmeyen gruplar (Grup DK, Grup DS ve Grup DD) ile diyabetik ve memantin verilen gruplar (Grup DM, Grup DSM, Grup DDM) ve çalışma gününde sadece memantinli gruplar arasında (Grup DSM ve Grup DS; Grup DDM ve Grup DD) hot plate değerlerini karşılaştırdık. Hot plate değerleri memantinin analjezik bir etkiye sahip olduğunu göstermektedir.

Sonuç: Sonuç olarak, diyabetik sıçanlarda memantin uygulamasının, sevofluran veya desfluran ile anestezi sonrası iyileşme, kognitif fonksiyonlar ve ağrı seviyeleri üzerinde olumlu etkisi vardır.

Anahtar Sözcükler: Memantin, desfluran, sevofluran, diabetes mellitus, RAM, POKD, hot plate

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INTRODUCTION

Postoperative cognitive dysfunction (POCD) is defined as postoperatively –also following anesthesia- 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 be continued 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, renal failure. Also DM leads structural damage and subsequent cognitive dysfunction in central nervous system (CNS) (4).

Memantine is a N-methyl D aspartate (NMDA) receptor antagonist that its 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 indicate positive effects of memantine on learning capability and memory function (6, 7). On the other hand positive effects of memantine on pain management has been reported (8).

In the present study effects of memantine on recovery, cognitive functions and pain management after sevoflurane or desflurane anesthesia in streptozotocin (STZ) induced diabetic rats was investigated. We aimed to eliminate inhibitory activity of sevoflurane or desflurane 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. 13.084). 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 42 Wistar Albino old rats (>12 months) weighing between 150-200 g. Rats were housed under controlled conditions of light cycle (12 hours:12 hours light:dark) with free access to water and rat chow. The study day study animals were fastened before night. Before studying the experiment blood glucose levels and body weights of all animals were measured. 6 rats were control group (Group C) and in this group diabetes were not induced. Other 36 rats were randomly divided into 6 study groups (Group DC, Group DM, Group DS, Group DD, Group DSM and Group DDM).

Group C (Control Group): Rats were allowed free access to water and chow for 30 days, RAM and hot plate values were measured weekly. At 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. At 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 DM (Diabetes Memantine Group): Memantine (20 mg/kg/day) (Ebixa® Lundbeck İlaç Tic. Ltd. Şti, İstanbul, Türkiye) was added in drinking water of rats for 30 days. Daily water consumption of rats were adjusted as 10-12 ml/100 gr body weight. Drinking water was refreshed weekly. RAM and hot plate values were determined weekly. At 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 DS (Diabetes Sevoflurane Group): RAM and hot plate values were determined weekly. At the 31th day of experiment, rats were given 1 MAC of sevoflurane 2% (Sevorane 250 ml, Abbott, İstanbul, Türkiye) (100% oxygen mixture at 4 L/min flow rate) for 2 hours in a bell jar with a gas entrance/exit hole. Recovery time after anesthesia, number and duration of entrance/exit and hot plate times at 0, 1 and 2nd hours were recorded.

Group DD (Diabetes Desflurane Group): RAM and hot plate values were determined weekly. At the 31th day of experiment, rats were given 1 MAC of desflurane 6% (Suprane 240 ml, Baxter) (100% oxygen mixture at 4 L/min flow rate) for 2 hours in a bell jar with a gas entrance/exit hole. Recovery time after anesthesia, number and duration of entrance/exit and hot plate times at 0, 1 and 2nd hours were recorded.

Group DSM (Diabetes Sevoflurane 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. At the 31th day of experiment, rats were given 1 MAC of sevoflurane 2% (100% oxygen mixture at 4 L/min flow rate) for 2 hours in a bell jar with a gas entrance/exit hole. Recovery time after anesthesia, number and duration of entrance/exit and hot plate times at 0, 1 and 2nd hours were recorded.

Group DDM (Diabetes Desflurane 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. At the 31th day of experiment, rats were given 1 MAC of desflurane 6% (100% oxygen mixture at 4 L/min flow rate) for 2 hours in a bell jar with a gas entrance/exit hole. Recovery time after anesthesia, number and duration of entrance/exit and hot plate times at 0, 1 and 2nd hours were recorded.

Statistical Analysis

Statistical analysis was performed using SPSS 20.0 packet program. Data was expressed as mean±standard deviation (SD). $p<0.05$ 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 RAM tests were analyzed using Repeated measures analysis of variance (rANOVA) test. Certain time points which significant differences identified were determined using Bonferroni correction.

RESULTS

Weights of rats in all groups before and after induced diabetic state were similar ($p>0.05$), (Table 1).

Table 1. Mean body weights of rats in study groups [Mean ± SD].

Weight (g)	Group C (n=6)	Group DC (n=6)	Group DM (n=6)	Group DS (n=6)	Group DD (n=6)	Group DSM (n=6)	Group DDM (n=6)	P
Baseline	172,83±13,55	179,66±11,25	168,67±20,73	178,00±10,79	170,33±16,43	171,83±14,68	177,50±19,10	0,844
End of study	193,17±10,99	184,50±11,78	160,17±20,16	194,00±10,64	186,33±25,18	191,23±25,92	187,67±35,42	0,149

p value: achieved from multiple comparisons

Blood glucose levels of diabetic rats were significantly higher than those measured in non-diabetics ($p<0.0001$), (Table 2).

Table 2. Mean blood glucose levels of rats in study groups [Mean ± SD].

	Group C (n=6)	Group DC (n=6)	Group DM (n=6)	Group DS (n=6)	Group DD (n=6)	Group DSM (n=6)	Group DDM (n=6)	P
Blood glucose levels (mg/dL)	106,33±5,68	454,50±98,8*	493,17±73,02*	282,00±23,12*	321,00±40,0*	359,00±33,02*	475,50±63,49*	<0,0001

p value: achieved from multiple comparisons
***:** p<0,05 (when compared with Group C)

Hot plate measurements at first week were similar between groups (Table 3). Hot plate measurements at 2, 3 and 4th weeks in memantine treated groups (Group DM, Group DDM and Group DSM) were significantly higher than that in Control Group (Group C) and Diabetic Control Group (Group DC). Hot plate values in Group DS and Group DD were lower than those measured in Group DM.

Table 3. Mean hot plate values of study groups [Mean ± SD].

Hot plate (sec.)	Group C (n=6)	Group DC (n=6)	Group DM (n=6)	Group DS (n=6)	Group DD (n=6)	Group DSM (n=6)	Group DDM (n=6)	P
1.week	8.83±1.94	10.00±1.26	8.33±1.86	10.83±2.92	8.16±0.41	8.67±1.75	10.17±0.98	0,080
2. week	7.50±1.22	9.17±0.75	12.83±5.15*	11.83±0.75	9.33±2.16	12.50±2.17*	13.17±2.04*	<0,0001
3. week	8.33±1.86	11.50±1.76	14.50±1.38*,=	11.83±2.48	10.83±0.98	15.00±2.76*,=	13.50±1.05*,=	<0,0001
4. week	10.33±1.21	10.17±1.47	17.50±2.66*,+,=	12.83±2.56	11.83±1.17&	15.67±1.37*,+,=	16.67±1.97*.+,?,=	<0,001
0.hour	10.50±1.05	11.33±2.25	15.83±1.17*,+,=	19.00±2.61*,+,=	15.67±1.37*,+,=	25.00±0.00*,+,=,&,**	20.66±0.82*,+,&,?,=	<0,0001
1.hour	10.50±0.55	13.17±0.75*	15.33±6.05*,=	16.83±1.60*,=	12.67±2.50*	23.67±2.16*,+,=,&,**	18.67±1.21*.+?,=	<0,0001
2.hour	10.67±2.16	12.50±4.50	15.00±4.47*.=	15.17±1.47*	13.33±2.42*	19.50±1.52*,+,=	16.67±6.05*.=	0.005

p value: achieved from multiple comparisons
:** p<0,05 (when compared with Group C), **+:** p<0,05 (when compared with Group DC), **&:** p<0,05 (when compared with Group DM), **?:** p<0,05 (when compared with Group DD), *:** p<0,05 (when compared with Group DS), **=:** p<0,05 (when compared with 1. week),

Hot plate values measured at 0th hour after desflurane or sevoflurane administration in Group DM, Group DD, Group DDM, Group DS and Group DSM were significantly higher than that measured in Group C. Similarly when compared with Group DC, values measured in those groups were found significantly higher. Additionally hot plate values measured at 0th hour after desflurane or sevoflurane administration in Group DDM and Group DSM were significantly higher than that in Group DM. Also values measured in Group DDM were higher than that measured in Group DD. Similar results were found between Group DSM and Group DS.

Hot plate values measured at 1st hour after desflurane or sevoflurane administration in all study groups were significantly higher than that measured in Group C. Values measured in Group DDM and Group DSM were significantly higher than those measured in Group DC. Similarly values in Group DSM were significantly higher than those in Group DM. Values measured in Group DDM were higher than those measured in Group DD. A similar correlation was found between Group DSM and Group DS.

Hot plate values measured at 2nd hour after desflurane or sevoflurane administration in all study groups –except Group DC- were significantly higher than that measured in Group C. Additionally values in Group DSM were significantly higher than those measured in Group DC.

Within group comparisons of hot plate values revealed that values at all time points in Group C and Group DC were similar with baseline values. Values measured 0th hour after anesthesia in Group DD were higher than baseline values. In Group DS, values measured at 0th and 1st hours were significantly higher than baseline values. Hot plate values measured at all time points -except 2nd week- in all memantine treated groups were significantly higher than baseline values.

Mean entry-exit numbers 1st week after diabetes induction were similar between all study groups. The mean numbers 2nd week after diabetes induction in all study groups were significantly lower than those measured in control group. Mean numbers at 3rd and 4th weeks in Group DC, Group DD and Group DS were significantly lower than those recorded in control group. Results in all memantine treated groups were similar with control group (Table 4).

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

Radial Arm Maze (entry-exit)	Group C (n=6)	Group DC (n=6)	Group DM (n=6)	Group DS (n=6)	Group DD (n=6)	Group DSM (n=6)	Group DDM (n=6)	P
1.week	10.00±0.63	9.67±1.03	10.50±2.07	12.17±2.40	11.00±2.19	10.83±2.23	10.17±2.32	0,396
2. week	8.00±1.55	5.50±1.22*,=	5.83±0.75*	5.83±0.41*,=	5.83±0.75*	6.00±0.63*	6.00±0.63*	0,001
3. week	8.50±0.55	5.50±0.55*,=	7.67±2.50	6.67±1.57*	7.00±1.10*	8.50±1.05+	9.50±0.55+	<0,0001
4. week	6.33±0.52	4.33±0.52*,=	5.50±0.55	5.17±0.41*,=	4.50±0.84*,=	5.33±0.52	5.17±1.72	0,006
0.hour	6.67±0.82	4.23±0.82*,=	7.00±1.55+	1.50±0.55*,+,=,&	1.00±0.63*,+,=,&	3.67±0.52*,+,=,&,?,**	3.17±0.41*,+,&,=	<0,0001
1.hour	6.83±0.75	4.50±0.55*,=	6.00±0.63+	3.00±0.89*,+,=,&	3.67±1.03*,=,&	3.33±0.52*,=	4.67±0.52*	<0,0001
2.hour	7.00±0.63	4.33±1.21*,=	6.00±1.26	4.50±0.55*,=	4.33±0.82*,=	5.50±0.84	5.67±0.52	<0.0001

p value: achieved from multiple comparisons
:** p<0,05 (when compared with Group C), **+:** p<0,05 (when compared with Group DC), **&:** p<0,05 (when compared with Group DM), **?:** p<0,05 (when compared with Group DD), *:** p<0,05 (when compared with Group DS), **=:** p<0,05 (when compared with 1. week)

Mean entry-exit numbers at 0th, 1st and 2nd hours in Group DC, DD and DS were lower than those measured in Group C. Mean numbers recorded at 0th and 1st hours in Group DDM and DSM were lower than those measured in Group C.

Mean entry-exit numbers at 0th hour in Group DD were lower than Group DC. Mean entry-exit numbers at 0th and 1st hours in Group DS were lower than Group DC. Mean entry-exit numbers at 0th and 1st hours in Group DM were higher than Group DC.

Mean entry-exit numbers at 0th and 1st hours in Group DD and Group DS were lower than those measured in Group DM. Mean entry-exit numbers at 0th hour in Group DDM and Group DSM were significantly lower than those measured in Group DM.

Mean entry-exit numbers at 0th hour in Group DDM were significantly higher than those measured in Group DD. Similarly mean numbers at 0th hour in Group DSM were higher than those measured in Group DS.

Within group comparisons of mean entry-exit numbers revealed that numbers at 1st week and other time points were similar in Group C and Group DM. In Group DC all measurements were decreased when compared with measurements at 1st week. In Group DD mean numbers of entrance-exit at 4th week and after anesthesia period were significantly lower when compared with numbers measured at 1st week. In Group DD and DS mean numbers of entry-exit at 2nd, 4th week and after anesthesia period were significantly lower when compared with numbers measured at 1st week. In Group DDM numbers measured only 0th hour after anesthesia were lower when compared with numbers measured at 1st week. In Group DSM mean numbers of entry-exit at 0th and 1st hours after anesthesia period were significantly lower when compared with numbers measured at 1st week.

DISCUSSION

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

We found significantly decreased RAM entrance-exit numbers after 2nd week in diabetic rats (Group DC, Group DS and Group DD) when compared with Control Group (non-diabetic and untreated group). This result indicates that diabetes induces cognitive dysfunction and memory disturbances in rats. There are contrary reports related with correlation between diabetes and cognitive functions (9,10). However many of these studies showed lower word fluency, verbal and auditory learning performance in diabetics when compared with normal controls (11,12). In general, diabetes may negatively affect perception and lead Alzheimer or dementia-like clinical outcomes. The results of present study –that investigates cognitive functions in diabetic rats are compatible with previous studies conducted with diabetic animals.

We observed negative effects of inhalation agents on cognitive functions using results of RAM settings. We found similar levels of POCD after sevoflurane or desflurane anesthesia. However according to our results we can not make any certain implication regarding superiority of these agents to each other. Anesthetic agents did not determined in circulation several days after operations however its thought that these agents present much longer periods in CNS and so they may induce structural changes in CNS. Several animal and laboratory experiments showed inhalation anesthetic induced POCD via resulting increased levels of oligomerization of Alzheimer related peptides and subsequent cytotoxicity (13,14).

Agents used in Alzheimer disease target cholinergic and glutamatergic pathways. Although effects of these agents on pathogenesis are unclear, they are useful in symptomatic relief. Memantine is a non-competitive NMDA antagonist that targets the glutamatergic system. Memantine can be used in patients with moderate to severe Alzheimer diseases with cognitive and behavioral dysfunction. The drug was approved from FDA for indications mentioned above (15). Due to its positive effects on learning processes and memory of patients with Alzheimer disease also proven neuroprotective and analgesic effects, we postulated that memantine may have positive effects on POCD and acute postoperative pain. Because of the single form that clinically accessible is oral form, we used oral form of memantine (Ebixa®) and so results of our study can be adapted to clinical studies.

Minkeviciene et al. (6) showed increased learning capability and memory following 3 weeks of memantine treatment (30 mg/kg/day) in APP and PS1 gen mutated old (8 months) mice. Authors added memantine in drinking water and evaluated cognitive functions using Morris water tank model. They observed increased results in Morris water tank model however they couldn't show any effects of memantine on locomotor activity (swimming ability in water tank etc.)

Wise et al. (16) investigated effects of different memantine doses (low dose -0.3 vs 0.56 mg/kg i.p. and high dose 3 vs 10 mg/kg i.p.) on learning capability and memory using RAM model in old male rats (12-16 months). Low doses of memantine was found related with -0.3 and 0.56 mg/kg i.p.- decreased number of entrance-exit and improved memory. In contrast RAM results were deteriorated in high dose groups. In 3 mg/kg treated group; only 1 rat entered both of 8 limbs, another one entered 4 limbs while others did not enter/exit to limbs. In 10 mg/kg memantine treated group none of the rats entered limbs. The authors concluded that effects of memantine on cognitive functions are dose dependent.

In another study Zajaczkowski et al. (17) compared effects of a newly developed NMDA receptor antagonist (+)-5-Methyl-10,11-dihydro-5H-dibenzosiklohepten-5,10-imine maleate (MK-801) and memantine on cognitive functions of normal rats and rats with damaged cortex -which mimics Alzheimer disease-. In order to achieve certain serum and blood concentration, both of agents were administered via subcutaneously. Authors observed negative effects of MK-801 (0.312 mg/kg/day) on learning capability of normal rats. In contrast memantine (20 mg/kg/day) was found in relation with reversal of damage induced memory loss and augmentation of cognitive dysfunction.

There is no established standard dose for memantine in different studies investigating effects of memantine for various indications. Also to our knowledge there is no study in literature investigating effects of memantine on cognitive functions during sevoflurane or desflurane anesthesia. So we chose 20 mg/kg/day oral dose of memantine and after a 30 days period we aimed to achieve a plasma drug concentration. On the other hand due to lack of blood memantine plasma level measurement, we can't make any implication regarding the sufficiency of drug dose.

We observed significant difference between RAM results of diabetic groups at first week versus second week. RAM results were significantly decreased at second week and this conclusion indicates negative effects of diabetes on cognitive functions. On the other hand RAM results measured at 3rd and 4th weeks in memantine treated groups were significantly increased and this result indicates positive effects of memantine on cognitive functions even in diabetic background.

Similar to results achieved in diabetic groups, we found higher RAM results in memantine treated sevoflurane/desflurane exposed groups than those measured in only inhalation anesthetic administered groups. We suggest that, this is an interesting and important result that indicates positive effects of memantine on POCD.

NMDA receptor antagonists are promising agents in pain management after finding of new evidences related with role of NMDA receptors among neuropathic pain mechanisms. Ketamine is the most commonly used agent however several side effects such as psychotomimetic, sedative and hallucinogenic effects limit use of ketamine. Memantine is a well-tolerated new agent and becomes a promising drug in pain management (18). Chen et al (19) investigated effects of three different NMDA receptor antagonist –neramexane, memantine (20 mg/kg/day) and gabapentin- on hyperalgesia and allodynia in streptozotocin induced diabetic rats. Three agents were administered subcutaneously via a mini-pump placed in the back of animals. Experiments were performed under 2-3% isoflurane anesthesia for 2 weeks. At the end of the study authors concluded that memantine and neramexane are effective agents against diabetic neuropathic pain.

Alexander et al. (20) induced neural injury via 60 minutes of stretching in mice (8-10 weeks) followed by memantine (20 mg/kg i.p.), mifepristone (50 mg/kg), corticosterone (1.5 mg/kg) administrations. They found increased allodynia in corticosterone treated group. In contrast memantine has prevented stress induced allodynia.

In a case report by Hacworth et al. (21) positive effects of memantine (20-45 mg/kg/day) added to morphine (100 mg/day) has been reported in two soldiers with phantom pain. Authors concluded that memantine can be used as an adjuvant in pain management and maximum effect can be achieved dependent on early start of memantine treatment.

Grande et al. (22) reported a case of neuropathic pain arised following metastatic spinal tumor resection. After a 1 month period of opioid infusion followed by ketamine infusion, authors discontinued infusion of two agents and started to administer a combination of memantine (20 mg/kg/day), methadone, gabapentin and naproxen. This regimen provided a 3 month pain-free period until the patients' death. In another study Viletti et al. (23) investigated effects of three NMDA receptor antagonists -N-(2-Indanyl)-glycinamide Hydrochloride (CHF3381), memantine and gabapentin- on neural injury of rat spinal cord. They found that memantine and CHF3381 equally have anti-nociceptive effects and memantine (10-15 mg/kg i.p.) can reverse thermal and mechanical hyperalgesia. Authors of these studies suggested that early start of memantine treatment in patients undergoing surgery –that may result in neuropathic pain- can be effective in pain treatment before developing a pain memory.

During the planning period of present study we thought that memantine can be effective against surgical stress after analyzing evidence indicate therapeutic role of memantine on diabetic and neuropathic pain. Stress –even psychological stress- induces kinase phosphorylation that regulates neuropathic extracellular signals. This induction activates glutamatergic system that is a target of memantine. And there are evidence that indicate resolution of stress related allodynia after memantine treatment (20).

We firstly compared the analgesic efficacy of memantine in diabetic rats and memantine treated diabetic rats using hot plate analgesia meter. Baseline hot plate values in all groups were similar however during later phases of study, hot plate values in diabetic rats were significantly increased when compared with control group. Also in memantine treated groups, hot plate values at 3rd and 4th weeks were significantly increased and these results indicate analgesic efficacy of memantine in this experimental setting.

Additionally we performed inter-group comparisons between sevoflurane exposed diabetic group (Group DS) and memantine treated sevoflurane exposed diabetic group (Group DSM). Also same comparisons were made between Group DS and DSM. In sevoflurane exposed groups we couldn't find any difference between hot plate values while in Desflurane exposed groups, increased hot plate values at 0th and 1st hours were noted in memantine treated group (Group DDM). However hot plate values at 3rd hour were similar in both groups. These results -again- indicate analgesic effect of memantine in this experimental setting.

CONCLUSION

We found that memantine -used in Alzheimer disease- produces positive effects on cognitive functions and pain management after sevoflurane and desflurane anesthesia. We suggest that memantine -when administered in patients with high POCD risk- can reduce POCD incidence. Future clinical studies are needed in order to evidence possible various effects of memantine on POCD and anesthesia.

Conflict of interest

No conflict of interest was declared by the authors.

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