Rev Bras Anestesiol. 2016;66(5):485–491

REVISTA
BRASILEIRA DE
ANESTESIOLOGIA
Publicação Oficial da Sociedade Brasileira de Anestesiologia
www.sba.com.br

SCIENTIFIC ARTICLE

The effects of memantine on recovery, cognitive functions, and pain after propofol anesthesia

Ulku Emik, Yusuf Unal, Mustafa Arslan*, Cengiz Bekir Demirel

Department of Anesthesiology and Reanimation, School of Medicine, Gazi University, Ankara, Turkey

Received 15 December 2014; accepted 10 March 2015
Available online 20 January 2016

KEYWORDS
Memantine;
Anesthesia;
Recovery;
Propofol;
POCD

Abstract
Objectives: Postoperative cognitive dysfunction refers to the problems associated with thought and memory that are often experienced after major surgery. The aim of this study is to evaluate the effects of intraperitoneally administered memantine on recovery, cognitive functions, and pain after propofol anesthesia.
Methods: The study was conducted in Gazi University Animal Research Laboratory, Ankara, Turkey in January 2012. Twenty-four adult female Wistar Albino rats weighing 170–270 g were educated for 300 s in the radial arm maze (RAM) over three days. Group P was administered 150 mg kg^{-1} of intraperitoneal (IP) propofol; Group M was given 1 mg kg^{-1} of IP memantine; and Group MP was given 1 mg kg^{-1} of IP memantine before being administered 150 mg kg^{-1} of IP propofol. The control group received only IP saline. RAM and hot plate values were obtained after recovery from the groups that received propofol anesthesia and 30 min after the administration of drugs in other two groups.
Results: The duration of recovery for Group MP was significantly shorter than Group P ($p < 0.001$), and the number of entries and exits in the RAM by Group MP was significantly higher during the first hour when compared to Group P ($p < 0.0001$). Hot plate values, on the other hand, were found to be significantly increased in all groups when compared to the control values, aside from Group C ($p < 0.0001$).
Conclusion: In this study, memantine provided shorter recovery times, better cognitive functions, and reduced postoperative pain. From this study, we find that memantine has beneficial effects on recovery, cognitive functions, and pain after propofol anesthesia.

* Corresponding author.
E-mails: marslan36@yahoo.com, mustarslan@gmail.com (M. Arslan).

http://dx.doi.org/10.1016/j.bjane.2015.03.002

PALAVRAS-CHAVE
Memantina;
Anestesia;
Recuperação;
Propofol;
DCPO

Efeitos da memantina sobre a recuperação, funções cognitivas e dor após a anestesia com propofol

Resumo
Objetivos: A disfunção cognitiva no pós-operatório refere-se a problemas associados ao pensamento e à memória que são frequentemente manifestados após uma cirurgia de grande porte. O objetivo deste estudo foi avaliar os efeitos da memantina administrada por via intraperitoneal sobrea recuperação, funções cognitivas e dor após a anestesia com propofol.
Métodos: O estudo foi realizado no Laboratório de Pesquisa com Animais da Universidade de Gazi, Ankara, Turquia, em janeiro de 2012. Vinte e quatro ratos albinos do sexo feminino, adultos, da linhagem Wistar, pesando 170-270 g, foram treinadosdurante 300 segundos no labirinto radial de oito braços (LRB) durante três dias. O Grupo P recebeu 150 mg/kg^{-1} de propofol por via intraperitoneal (IP); o Grupo H recebeu 1 mg/kg^{-1} de memantina IP e o Grupo MP recebeu 1 mg/kg^{-1} de memantina IP antes daadministração de 150 mg/kg^{-1} de propofolPI. O grupo controle recebeu apenas solução salina IP. Os valores doLRB e da placa quente foram obtidos após a recuperação dos grupos que receberam propofol e 30 minutos após a administração dos fármacos nos outros dois grupos.
Resultados: O tempo de recuperação do Grupo MP foi significativamente menor que o do Grupo P ($p < 0,001$), eo número de entradas e saídas do LRBdo Grupo MP foi significativamente maior durante a primeira hora,em comparação com o Grupo P ($p < 0,0001$). Os valores da placa quente, por outro lado, foram significativamente maiores em todos os grupos, em comparação com os valores dogrupo controle, exceto pelo Grupo C ($p < 0,0001$).
Conclusão: No presente estudo, memantina proporcionou tempos mais curtos de recuperação, funções cognitivas melhores e reduziu a dor no pós-operatório. A partir deste estudo, descobrimos que a memantina tem efeitos benéficos sobre a recuperação, funções cognitivas e dor após anestesia com propofol.

Introduction

Postoperative cognitive dysfunction (POCD) refers to disorders affecting attention, consciousness, orientation, perception, judgment, and insight that develop during the postoperative period. Although the etiology of POCD has yet to be adequately explained, many factors have been found to be responsible. Most recently, disequilibrium in the neurotransmitter systems during the preoperative period, such as acetylcholine, serotonin, glutamate, and aspartate, has been one of the most commonly blamed factors.[1–3]

The effects of the nicotinic system on learning, memory, and cognition have been shown in studies of both humans and animals.[4] This directly influences attention while also affecting learning and memory by facilitating acetylcholine, glutamate, dopamine, noradrenaline, serotonin, and gamma-aminobutyric acid (GABA) releases from the presynaptic nicotinic acetylcholine receptors (nAChRs).[4]

Propofol is a frequently used hypnotic agent that works by potentializing the chloride flow of GABA by connecting to the β-subunit in the GABA receptor. The alpha and gamma (γ_2) subunits also seem to contribute to the modulation of the effect of propofol on the GABA receptor. As a result of this effect on the $GABA_A$ receptors in the hippocampus, propofol inhibits ACh release in the hippocampus and prefrontal cortex. This seems to be significant in the sedative effects of propofol. Propofol diffuses inhibition on N-methyl-D-aspartate (NMDA) which is a subtype of glutamate receptor, by modulating the gate mechanism in the sodium channels and thus contributing to the central nervous system (CNS) effects. Propofol is also effective on the $GABA_A$ and glycine receptors on the dorsal horn of the spinal cord, and modulation of these receptors is known to result in cognitive dysfunction. Propofol is reported to inhibit cognitive functions for up to 6 h.[5,6]

Memantine is a non-competitive receptor antagonist with a low affinity that inhibits the pathological activation of NMDA receptors without changing their physiological functions.[7] Memantine has demonstrated an ability to reverse the changes that develop in the synaptic plasticity of animal models after its use was suggested for various neurological disorders.[8] The use of memantine has yielded positive results on learning, memory, pain, and neuroprotective effects in clinical studies.[9] As a result, it was sent to the Food and Drug Administration (FDA) in 2003 for approval for the treatment of Alzheimer's disease. There have also been studies investigating the use of memantine in the treatment of chronic pain,[10] in which it has been shown to decrease diabetic neuropathy pain in rats.[11]

In the present study, the effects of memantine administration prior to propofol anesthesia on recovery, cognitive functions, and acute pain are evaluated.

Materials and methods

Animals and experimental protocol

This study was conducted in the animal research laboratory of Gazi University in January 2012 with the consent

of the Experimental Animals Ethics Committee of Gazi University. All of the procedures were performed according to the accepted standards of the Guide for the Care and Use of Laboratory Animals.

Twenty-four adult female Wistar Albino rats weighing 170–270 g were used. The rats were kept in lightened and darkened mediums for alternating 24 h periods until the beginning of the study to allow them to adapt to the medium. The subjects were left in a light- and heat-standardized medium and fed with standard pellet feed. There was no restriction on access to water; however, the rats were deprived of food for 2 h before the study.

All rats were weighed and the results were recorded for all groups. After being deprived of food for 2 h prior to the study, pellet food was placed at the end of each arm of a radial arm maze (RAM). The rats were educated in the RAM for 300 s over the first three days of the study, and the entry and exit times of the rats at the arms of the RAM were recorded. The RAM and hot plate basal values were measured for all rats on the fourth day of the study, after which the rats were randomly allocated into four groups.

Group C (Control group, $n = 6$): each rat was administered 1 ml of 0.9% sodium chloride (saline) intraperitoneally (IP). Rats were placed in the RAM 30 min after the administration of saline IP, and the entry and exit times at the arms at beginning T_0, 1 h (T_1), and 2 h (T_2), as well as the durations on the hot plate, were measured and recorded.

Group M (Memantine group, $n = 6$): 1 mg kg^{-1} dose of memantine (memantine hydrochloride, Sigma–Aldrich Chemie, St. Louis, MO, USA) in 1 ml saline was administered IP. Thirty minutes after the administration of memantine, the rats were placed in the RAM. The entry and exit times at the arms at T_0, T_1, and T_2, and the durations on the hot plate, were measured and recorded.

Group P (Propofol group, $n = 6$): 150 mg kg^{-1} 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 s using ''rubber dam'' forceps)[12] and the time for recovery was recorded. The rats were placed in the RAM after recovery. The first measurement after recovery was recorded as 0 (T_0) hour, after which the first hour (T_1) and second hour (T_2) measurements were obtained and recorded.

Group MP (Memantine + propofol group, $n = 6$): 1 mg kg^{-1} dose of memantine was applied IP and 30 minutes later 150 mg kg^{-1} of propofol was injected IP. Propofol application time was recorded in all rats. The rats were left to recover, recovery was evaluated with a tail pinch test, and the time for recovery was recorded. The rats were placed in the RAM after recovery. The first measurement after recovery was recorded as 0 (T_0) hour, after which the first hour (T_1) and second hour (T_2) measurements were obtained and recorded.

The radial arm maze

The radial arm maze is comprised of a Plexiglass 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 tabletop 90 cm from the floor.

Hot plate test for acute pain evaluation

The aluminum 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 s to prevent tissue damage.

Statistical analysis

A statistical evaluation was performed using the SPSS 12.0 computer program utilizing the following tests. Statistical analysis data was presented as the mean ± standard deviation (minimum–maximum); $p < 0.05$ was accepted as significant in all statistical analyses; and $p < 0.033$ (0.1/3) value was accepted as significant in evaluations of Bonferroni corrections. A Kolmogorov–Smirnov test was performed for the measurable parameters to identify normal or abnormal distributions.

In independent groups, the differences between the groups were tested using a Kruskal–Wallis test and a Mann–Whitney U test, with a Bonferroni correction used to detect the groups that generated differences when any were identified.

Results

The body weights of the subjects (g) were similar in all groups.

The time period in the tail pinch test was significantly shorter in Group MP when compared to Group P (Table 1).

The basal measurements of the hot plate were similar in all groups (Table 1). The hot plate values were found to be significantly increased in all measured time periods in groups M, P, and MP when compared to Group C.

The RAM values were found to be similar between the groups on the days before the administration of anesthesia (Table 2).

The entry and exit times at hours T_0, T_1, and T_2 were found to be significantly decreased in Group P when compared to Group C ($p < 0.0001$, $p < 0.0001$, $p = 0.029$, respectively). Only in Group MP were the entry and exit times at T_0 significantly decreased when compared to Group C ($p = 0.001$).

The entry and exit times at T_0 and T_1 were found to be significantly decreased in Group P when compared to Group M ($p < 0.0001$, $p < 0.0001$, respectively). Only in Group MP were the entry and exit times at T_0 significantly decreased when compared to Group M ($p < 0.0001$), and only in Group MP were the entry and exit times at T_1 significantly decreased when compared to Group P ($p = 0.030$).

The results for the evaluation of each group are as follows:

Table 1 Tail pinch and hot plate data for all groups [mean ± SD (minimum–maximum)].

	Group C ($n=6$)	Group M ($n=6$)	Group P ($n=6$)	Group MP ($n=6$)	p
Tail pinch (min)	–	–	229.50 ± 25.11 (215–278)	152.20 ± 25.13[b] (125–175)	0.001
Hot plate basal (s)	4.82 ± 2.03 (2.3–8.2)	5.50 ± 2.63 (3.1–9.9)	6.98 ± 1.82 (4.6–9)	6.08 ± 2.03 (3.6–9.5)	0.374
Hot plate T_0 (s)	6.03 ± 2.23 (3.3–8.6)	17.94 ± 8.26[a,c] (7.7–25)	22.98 ± 4.94[a,c] (12.9–25)	23.40 ± 3.58[a,c] (17.0–25)	<0.0001
Hot plate T_1 (s)	5.83 ± 1.99 (3.3–7.9)	23.98 ± 2.95[a,c] (18–25)	17.42 ± 7.66[a,c] (5.5–25)	20.00 ± 7.87[a,c] (7–25)	<0.0001
Hot plate T_2 (s)	5.73 ± 1.91 (3.3–7.9)	24.17 ± 2.04[a,c] (20–25)	18.67 ± 6.65[a,c] (8–25)	17.30 ± 8.95[a,c] (6–25)	<0.0001

[a] $p < 0.05$ (compared to Group C).
[b] $p < 0.05$ (compared to Group P).
[c] $p < 0.05$ (compared to hot plate basal measurement).

1. Entry and exit times were found to be similar between the first day measurements and other measurements in Group C and Group M.
2. In Group P, the entry and exit times at T_0 and T_1 were significantly decreased ($p = 0.011$, $p = 0.011$, respectively).
3. In Group PM, the entry and exit times were significantly reduced only at T_0 ($p = 0.006$) (Table 2).

Discussion

This study evaluating the effects of memantine on postoperative recovery and pain in rats has revealed a decrease in recovery time and in the recovery of cognitive functions. It was also found to be effective in the management of acute pain.

A standardization of perioperative and postoperative factors is difficult in clinical studies associated with postoperative cognitive functions due to the different parameters involved, including the type of surgery, the distribution of age, the interaction of anesthesia, the presence of bleeding resulting from surgery, and the possibility of infection. While the effects of anesthesia on cognitive functions have been demonstrated in previous experimental studies,[13] this study has adopted the RAM method, in which only the parameter of the anesthetic agent is changed and all other factors are standardized.

RAM is a frequently used method for the evaluation of cognitive functions in experimental animal models.[13] Culley et al.,[13] used a RAM with 12 arms in a study evaluating the effects of nitrous oxide on learning disorders in rats. As in the present study, they also left the rats for 10 min for three consecutive days on the RAM to measure levels

Table 2 Data of entry and exits of the radial arm maze in all groups [mean ± SD (minimum–maximum)].

	Group C ($n=6$)	Group M ($n=6$)	Group P ($n=6$)	Group MP ($n=6$)	p
Day 1 (entry–exit) (s)	7.50 ± 3.21 (2–11)	6.33 ± 1.63 (4–8)	7.67 ± 2.58 (5–12)	7.50 ± 4.03 (0–11)	0.858
Day 2 (entry–exit) (s)	5.50 ± 3.27 (1–11)	6.17 ± 3.13 (3–11)	8.00 ± 4.19 (4–15)	5.83 ± 3.49 (0–10)	0.625
Day 3 (entry–exit) (s)	5.67 ± 2.16 (2–8)	4.00 ± 1.41 (2–6)	6.00 ± 4.60 (0–11)	6.50 ± 4.76 (0–11)	0.649
Time T_0 (entry–exit) (s)	6.00 ± 2.97 (3–11)	6.83 ± 2.48 (3–10)	0.17 ± 0.40[a,b,d] (0–1)	0.00 ± 0.00[a,b,d] (0–0)	<0.0001
Time T_1 (entry–exit) (s)	5.67 ± 2.33 (3–9)	5.50 ± 1.38 (3–7)	0.0 ± 0.0[a,b,d] (0–0)	2.60 ± 2.07[c] (0–5)	<0.0001
Time T_2 (entry–exit) (s)	5.50 ± 2.07 (3–8)	4.17 ± 1.72 (2–7)	2.17 ± 1.83[a] (0–5)	2.40 ± 1.52 (0–4)	0.017

[a] $p < 0.05$ (compared with Group C).
[b] $p < 0.05$ (compared with Group M).
[c] $p < 0.05$ (compared with Group P).
[d] $p < 0.05$ (compared with 1st day measurement).

of adaptation and education, from which they were able to deduce that general anesthesia reversibly impaired the previously learned spatial memory in older rats.

Postoperative cognitive dysfunction is attributed to the use of both IV and inhaled anesthetics, which are believed to cause long-term structural changes in the CNS since they can no longer be identified in the blood several days after administration. Anesthetic agents administered during surgery change the behavioral status of the patient and affect brain activity in at least two mechanisms. The first of these is described as the dose-dependent effect on the brain, and the second is the inhibition of region-specific neuronal activity, disruption of functional relations, and disruption of the neural plexus.[14] These component neurotransmitter-mediated ion channels, especially the GABA, glutamate, and NMDA channels, are modulated by many anesthetic agents and are diagnosed as targets of the anesthetic agents and receptors in both synaptic and extra-synaptic areas.[15]

An analysis of the propofol used in this study reveals that its sedative effects are related to its potentialization of chloride flow through the connection to the $GABA_A$ receptor β subunit of the hippocampus and the prevention of ACh release from the hippocampus and prefrontal cortex. In addition, propofol encourages diffuse inhibition in the NMDA receptors, which are the subtypes of glutamate receptors, by modulating the gate mechanism of the sodium channels.[5] Modulation of these receptors is known to produce POCD; consequently, there are many studies confirming the role of propofol in the development of POCD. Kunimatsu et al.,[16] observed POCD in patients undergoing oral surgery under propofol anesthesia. In another study supporting this finding, Nishikawa et al.,[17] identified a higher postoperative delirium score in a group of patients who had been administered propofol and who had been given an epidural anesthesia in their comparison of propofol, sevoflurane, and epidural anesthesia in patients undergoing laparoscopic surgery. Larsen et al.,[18] conducted a study of cognitive functions and recovery after propofol, desflurane, and sevoflurane in 60 patients with ASA I–II; the results of this study showed that the patients in the propofol group awoke and recovered faster than those that had been anesthetized with desflurane or sevoflurane. Desflurane and sevoflurane anesthesia showed similar effects, although the eye-opening time was shorter among those anesthetized with desflurane. In light of these studies, the intention here has been to carry out this study using propofol anesthesia, which is known to cause POCD and which allows for early recovery from anesthesia. Another reason for choosing propofol as the anesthetic agent was its mechanism affecting the diffuse inhibition of NMDA receptors, $GABA_A$ receptors, and ACh receptors, and the hypothesis that these effects are reversed by memantine, which is an NMDA receptor antagonist.

A search of previous studies garnered no data on the effect of memantine on cognitive dysfunction following recovery from propofol anesthesia. For this reason, the intention has been to evaluate the effects of memantine after recovery from propofol anesthesia on cognitive functions and pain in a rat model with a minimal variation in variables and with a single variable parameter using propofol as the anesthetic agent.

Memantine, a NMDA antagonist, was first tested on animal models by Bigamous, who demonstrated improvements in cognitive functions and deficits in neuron plasticity.[19] Memantine is a NMDA receptor antagonist that is a non-dissociative anesthetic. It features rapid channel opening kinetics and is a powerful voltage-dependent channel blocker with a lesser affinity to the NMDA receptor channel.[20] In contrast to other NMDA receptor antagonists with dissociative anesthetic effects, it has different pharmacological properties. This unique property of memantine allows it to activate pathological NMDA receptors, while having no effect on the physiological NMDA receptors that have a critical role in memory and learning.[21]

Memantine was approved for the treatment of Alzheimer's disease by European medicines Agency (EMEA) in Europe in 2002 and by the FDA in the United States in 2003.[8] Since then, memantine has been shown to improve performance in studies of various pharmacological learning and memory models and was found to be useful in patients with Alzheimer's disease.[22] The effect of memantine on cognitive functions in cases of neurodegenerative diseases, such as Alzheimer's, is studied using different application methods and in different doses. An acute administration of memantine in a $5\,mg\,kg^{-1}$ dose had no effect on behavior or motor functions[23]; however, the administration of a $10\,mg\,kg^{-1}$ dose resulted in hyperlocomotion and deterioration in a ''food-motivated task'' test. A single dose of $20\,mg\,kg^{-1}$ of memantine causes ataxia.[24,25]

When memantine was administered in $10\,mg\,kg^{-1}$ and $20\,mg\,kg^{-1}$ doses prior to the learning period in a passive avoidance test, it was shown to deteriorate learning behavior and deter memory.[26] These results suggest that memantine produces beneficial results in low doses but has harmful effects on behavior in high doses.[27] In a study that involved the administration of donazepil and rimonabant, which are known to cause cognitive disorders, learning behaviors were tested using RAM. Memantine doses of $0.1\,mg\,kg^{-1}$, $0.3\,mg\,kg^{-1}$, and $0.56\,mg\,kg^{-1}$ were found to decrease errors in the RAM test; however, doses of $1.0\,mg\,kg^{-1}$, $3.0\,mg\,kg^{-1}$, and $10\,mg\,kg^{-1}$ were found to increase deficits.[28]

The present study involved the administration of $1\,mg\,kg^{-1}$ IP doses of memantine; however, the effects of other doses cannot be predicted, and a similar study with different doses of memantine should be performed.

Generally, recovery from anesthesia is determined by the rate at which the anesthetic agent concentrations in the brain tissue decrease, and the elimination rate of the drug.[29] It can be deduced from the present study that early recovery from propofol anesthesia, 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 anesthesia, Brosnan et al.,[30] used picrotoxin, which is a $GABA_A$ receptor antagonist, on rats that had been anesthetized with isoflurane and then administered an NMDA receptor antagonist, MK-801 (Dizocilpine), to the rats. When they analyzed 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 anesthetic immobilization and that the use of NMDA antagonists affected MAC. In a

study by Kuroda et al.,[31] 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.

This study has also analyzed the effects of NMDA receptor antagonists on cognitive functions. When the cognitive functions were analyzed on the RAM configuration in 1-hour intervals after awakening, no searching movement was observed in the rats that had been administered only propofol; however, searching movements were observed during the first hour in Group MP ($p < 0.0001$). Searching movements started in the propofol group during the second hour, with no noticeable differences between the groups. In a study to evaluate cognitive recovery through a series of tests of attention span, planning, late memory, and speech, Sanou et al.,[6] found that cognitive recovery from propofol took between 1 and 3 h following general anesthesia and that recovery to a pre-anesthetic state took 6 h. Marshall et al.,[32] in a similar study of propofol and alfentanil, found that levels of word memory were decreased for 5 h. Although the last study was performed on humans, recovery from propofol in our study started during the first hour in the memantine-administered rats and during the second hour in the rats that had not been given memantine. Measurements in this study were limited to 2 h after recovery from anesthesia, meaning that the time needed to reach a pre-anesthetic state was not evaluated.

It can be deduced from this study that NMDA receptors play a significant role in the formation of neuronal networks during memory, learning, and development in the mammalian brain. Since this takes place in some physiological functions, such as synaptic plasticity and synapsis formation, the receptors are beneficial in explaining POCD. This study has revealed that the administration of memantine is beneficial in the recovery of cognitive functions after anesthesia.

Another subject of our study was the effect of memantine on acute pain. Grande et al.[33] have shown in a clinical study that memantine is effective in eliminating neuropathic pain in patients after a metastatic spinal tumor resection.[11,33] The potential uses of memantine in the treatment of chronic and neuropathic pain raised the question of whether it may also be effective in the treatment of stress-related pain. The hot plate method, with a standard heat of 52 °C, was used to administer acute pain, and the measured basal pain levels before the administration of memantine were similar in all groups. Serial measurements at 1-hour intervals were taken, from which it was demonstrated that the duration of pain response in the memantine, propofol, and memantine + propofol-administered groups were significantly longer when compared to the basal values in each group and when compared to the control group ($p < 0.0001$); however, there was no significant difference between the memantine, propofol, and memantine + propofol-administered groups. This clinical picture reveals that memantine is also effective in the treatment of acute pain. As propofol is also known to have some analgesic properties,[5] this may explain the similarity between the groups.

In the study design, the rats were permitted to stay on the hot plate for a maximum of 25 s when evaluating the analgesic effects of the drugs, which meant that it was not possible to identify with any certainty whether propofol and memantine possess any additive analgesic effects. No interpretation was possible since the times of the three groups were similar. As the analgesic effects were followed up for only 2 h, the effects of the drugs on analgesia times could not be evaluated clearly. In a study evaluating the effects of memantine on acute pain, Park et al.[34] demonstrated that memantine, given in an IP dose of 10 mg kg^{-1} (10 times the dose used in our study) 30 min before performing a trigeminocervical pain model with a formalin injection, resulted in a decrease in pain scores. In contrast to the present study, in a study of rats by Zhan and Brennan,[35] in which memantine was used for postoperative pain control, plantar incisions were produced in rats and memantine was applied intrathecally through an intrathecal catheter with no beneficial results. In a comparative study to evaluate the local anesthetic effects of memantine, Chen et al.,[36] suggested that memantine produced better local analgesic effects when compared to lidocaine and that NMDA receptors contributed to this analgesic effect.

Conclusion

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

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Dodds C, Allison J. Postoperative cognitive deficit in the elderly surgical patient. Br J Anaesth. 1998;81:449–62.
2. Wu CL, Hsu W, Richman JM, Raja SN. Postoperative cognitive function as an outcome of regional anesthesia and analgesia. Reg Anesth Pain Med. 2004;29:257–68.
3. Selnes OA, McKhann GM. Cognitive changes after coronary artery bypass surgery. Curr Opin Pscychiatry. 2002;15:285–90.
4. Işık B. Relation of the anesthesia and cognitive functions. Turkiye Klinikleri J Anest Reanim. 2004;2:94–102.
5. Miller RD. Miller's anesthesia. Intravenous anesthetics, 7th ed; 2010. p. 317–77 [Chapter 26].
6. Sanou J, Goodall G, Capuron L, Bourdalle-Badie C, Maurette P. Cognitive sequelae of propofol anaesthesia. Neuroreport. 1996;7:1130–2.
7. Parsons CG, Danysz W, Quack G. Memantine is a clinically well tolerated N-methyl-D aspartate (NMDA) receptor antagonist – a review of preclinical data. Neuropharmacol. 1999;38:735–67.
8. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. Cochrane Libr. 2009;1:1–43.
9. Berrino L, Oliva P, Massimo F, Aurilio C, Maione S, Grella A, et al. Antinociceptive effect in mice of intraperitoneal N-methyl-D-aspartate receptor antagonists in the formalin test. Eur J Pain. 2003;7:131–7.
10. Lipton SA. Paradigm shift in NMDA receptor antagonist drug development: molecular mechanism of uncompetitive inhibition by memantine in the treatment of Alzheirme's disease and other neurologic disorders. J Alzheimers Dis. 2004;6:61–74.
11. Villetti G, Bergamaschi M, Bassani F, Bolzoni PT, Maiorino M, Pietra C, et al. Antinociceptive activity of the

N-methyl-D-aspartate receptor antagonist N-(2-Indanyl)-glycinamide hydrochloride (CHF3381) in experimental models of inflammatory and neuropathic pain. J Pharmacol Exp Ther. 2003;306:804–14.
12. Katz RJ, Roth K. Tail pinch-induced stress arousal facilities brain stimulation reward. Physiol Behav. 1979;42:193–4.
13. Culley DJ, Baxter M, Yukhananov R, Crosby G. The memory effects of general anesthesia persist for weeks in young and aged rats. Anaesth Analg. 2003;96:1004–9.
14. Heinke W, Koelsch S. The effects of anesthetics on brain activity and cognitive function. Curr Opin Anaesthesiol. 2005;18:625–31.
15. Hemmings HC Jr, Akabas MH, Goldstein PA, Trudell JR, Orser BA, Harrison NL. Emerging molecular mechanisms of general anesthetic action. Trends Pharmacol Sci. 2005;26:503–10.
16. Kunimatsu T, Misaki T, Hirose N, Tsuboi E, Takahashi I, Ohki H, et al. Postoperative mental disorder following prolonged oral surgery. J Oral Sci. 2004;46:71–4.
17. Nishikawa K, Nakayama M, Omote K, Namiki A. Recovery characteristics and post-operative delirium after long-duration laparoscope-assisted surgery in elderly patients: propofol-based vs. sevoflurane-based anesthesia. Acta Anaesthesiol Scand. 2004;48:162–8.
18. Larsen B, Seitz A, Larsen R. Recovery of cognitive function after remifentanil-propofol anesthesia: a comparison with desflurane and sevoflurane anesthesia. Anesth Analg. 2000;90:168–74.
19. Möbius HJ. Pharmacologic rationale for memantine in chronic cerebral hypoperfusion, especially vascular dementia. Alzheimer Dis Assoc Disord. 1999;3:172–8.
20. Parsons CG, Quack G, Bresink I, Baran L, Przegalinski E, Kostowski W, et al. Comparison of the potency, kinetics and voltage-dependency of a series of uncompetitive NMDA receptor antagonists in vitro with anticonvulsive and motor impairment activity in vivo. Neuropharmacology. 1995;34:1239–58.
21. Zajaczkowski W, Quack G, Danysz W. Infusion of (+)-MK-801 and memantine – contrasting effects on radial arm maze learning in rats with entorhinal cortex lesion. Eur J Pharmacol. 1996;296:239–46.
22. Reisberg B, Doody R, Stoffler A, Schmitt F, Ferris S, Mobius HJ, Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med. 2003;348:1333–41.
23. Van Dam D, Abramowski D, Staufenbiel M, De Deyn PP. Symptomatic effect of donepezil, rivastigmine, galantamine and memantine on cognitive deficits in the APP23 model. Psychopharmacology (Berl). 2005;180:177–90.
24. Creeley C, Wozniak DF, Labruyere J, Taylor GT, Olney JW. Low doses of memantine disrupt memory in adult rats. J Neurosci. 2006;26:3923–32.
25. Sukhanov IM, Zakharova ES, Danysz W, Bespalov AY. Effects of NMDA receptor channel blockers. MK-801 and memantine, on locomotor activity and tolerance to delay of reward in Wistar–Kyoto and spontaneously hypertensive rats. Behav Pharmacol. 2004;15:263–71.
26. Réus GZ, Valvassori SS, Machado RA, Martins MR, Gavioli EC, Quevedo J. Acute treatment with low doses of memantine does not impair aversive, non-associative and recognition memory in rats. Naunyn Schmiedebergs Arch Pharmacol. 2008;376:295–300.
27. Yuedea CM, Dong H, Csernansky JG. Anti-dementia drugs and hippocampal dependent memory in rodents. Behav Pharmacol. 2007;18:347–63.
28. Wise LE, Lichtman AH. The uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist memantine prolongs spatial memory in a rat delayed radial arm maze memory task. Eur J Pharmacol. 2007;575:98–102.
29. Morgan G, Mikhail M, Murray M. Clinical anesthesiology. 4th ed. Los Angeles: McGraw-Hill Companies Inc.; 2008. p. 155–78.
30. Brosnan RJ. GABA(A) receptor antagonism increases NMDA receptor inhibition by isoflurane at a minimum alveolar concentration. Vet Anaesth Analg. 2011;38:231–9.
31. Kuroda Y, Strebel S, Rafferty C, Bullock R. Neuroprotective doses of N-methyl-D-aspartate receptor antagonists profoundly reduce the minimum alveolar anesthetic concentration (MAC) for isoflurane in rats. Anesth Analg. 1993;77:795–800.
32. Marshall CA, Jones RM, Bajorek PK, Cashman JN. Recovery characteristics using isoflurane or propofol for maintenance of anaesthesia: a double-blind controlled trial. Anaesthesia. 1992;47:461–6.
33. Grande LA, O'Donnell BR, Fitzgibbon DR, Terman GW. Ultra-low dose ketamine and memantine treatment for pain in an opioid-tolerant oncology patient. Anesth Analg. 2008;107:1380–3.
34. Park JW, Suh GI, Shin HE, Park GE. Influence of memantine on nociceptive responses of the trigeminocervical complex after formalin injection. Cephalalgia. 2012;32:308–16.
35. Zahn PK, Brennan TJ. Lack of effect of intrathecally administered N-methyl-D-aspartate receptor antagonists in a rat model for postoperative pain. Anesthesiology. 1998;88:143–56.
36. Chen YW, Chu CC, Chen YC, Wang JJ, Hung CH. The local anesthetic effect of memantine on infiltrative cutaneous analgesia in the rat. Anaesth Analg. 2011;113:191–5.