Comparison of Pre-Emptive Pregabalin with Placebo and Diclofenac Combination for Postoperative Analgesia and Cognitive Functions After Laparoscopic Cholecystectomy

Laparoskopik Kolesistektomi Sonrası Postoperatif Analjezi ve Kognitif Fonksiyonlar; Preemptif Pregabalin ile Plasebo ve Diklofenak Kombinasyonu Karşılaştırılması

Tülin AKARSU, MD, Msc, [a]
Hülya TÜR, MD, Msc, [a]
Cihan BOLAT, MD, Msc, [a]
İsmail ÖZKAYNAK, MD[a]

[a]Clinic of Anesthesiology and Reanimation, Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital, İstanbul

Geliş Tarihi/*Received:* 25.06.2011
Kabul Tarihi/*Accepted:* 14.01.2012

This study was presented as a poster at the 30th Annual Meeting of the ESRA, 7-10 September 2011, Dresden, Germany .

Yazışma Adresi/*Correspondence:*
Tülin AKARSU, MD, Msc
Kartal Koşuyolu Yüksek İhtisas Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, TÜRKİYE/TURKEY
akarsu.dr@gmail.com

ABSTRACT Objective: This study was conducted to evaluate the efficacy of pre-emptive pregabalin compared with plasebo and diclofenac combination for attenuating postoperative pain, analgesic consumption and cognitive function after laparoscopic cholecystectomy. **Material and Methods:** Sixty adults with ASA physical status I-III of either sex undergoing elective laparoscopic cholecystectomy were included in this prospective, randomized placebo controlled, single-blind study. Subjects were divided into two groups being 30 pat.ents in each to receive either a matching placebo or pregabalin 300 mg, administered orally 1 h before surgery. Intramuscular 75 mg diclofenac sodium was given to placebo patients 15-20 minutes before the estimated finishing time of surgery for pain relief after surgery. In the first 15 minutes after extubation, Aldrete Score and Ramsay Sedation Scale were evaluated. Mini mental test (MMT) was performed 1 hour and 6 hours after extubation. Postoperative pain was assessed by visual analogue scale (VAS). Time to first analgesic requirement, total analgesic dose and side effects were recorded. **Results:** The difference between preoperative 1st h and 6th h MMT values was not statistically significant between the two groups. VAS scores were significantly higher in Group C compared to Group P ($p < 0.01$). In Group P, the time to first analgesic rescue dose was significantly longer than in Group C ($p<0.01$). Total analgesic doses were significantly lower than in Group C patients ($p<0.01$). Sedation was significantly higher in Group P ($p<0.05$). **Conclusion:** We conclude that administration of 300 mg of pregabalin 1 hour before surgery lengthens recovery time minimally, prolongs first analgesic requirement time, reduces total analgesic consumption and does not impair cognitive functions.

Key Words: Cholecystectomy, laparoscopic; anesthesia recovery period; pain; delirium, dementia, amnestic, cognitive disorders

ÖZET Amaç: Preemptif pregabalinin plasebo ve diklofenak kombinasyonu ile karşılaştırıldığı laparoskopik kolesistektomi operasyonlarında, postoperatif ağrı, analjezik tüketimi ve bilişsel işlevler üzerindeki etkinliğinin değerlendirilmesi planlandı. **Gereç ve Yöntemler:** Elektif laparoskopik kolesistektomi uygulanacak ASA I-III sınıfı 60 yetişkin olgu prospektif, randomize, plasebo kontrollü, tek kör çalışma kapsamına alındı. Olgular 30'ar kişilik iki gruba ayrıldı, cerrahiden bir saat önce oral olarak ya bir plasebo (Grup C) veya pregabalin (Grup P) 300 mg verildi. Plasebo alan hastalara tahmini ameliyat bitiminden 15-20 dakika önce intramüsküler 75 mg diklofenak sodyum verildi. Operasyon bitiminde, ekstübasyon saati, göz açma, komutlara yanıt verme ve oryantasyon zamanı kaydedildi. Ekstübasyondan sonra hastalar Aldrete ve Ramsey Sedasyon Skoru ile değerlendirildi. Ekstübasyondan 1 ve 6 saat sonra mini mental test (MMT) uygulandı. Ağrı, vizuel analog skala ile değerlendirildi, ilk analjezik zamanı toplam analjezik dozları kaydedildi. Yirmi dört saat içerisinde görülen yan etkiler kaydedildi. **Bulgular:** Grup P'deki olguların göz açma zamanı (dk) ve komutlara yanıt verme (dk) süreleri, Grup C'deki olgulara göre anlamlı olarak yüksek bulundu. ($p<0,01$). Grup C ve Grup P'deki olguların Aldrete Skorları arasındaki fark istatistiksel olarak anlamlı değildi ($p>0,05$).Group P'deki olguların 30. dk (%33,3) ve 45. dk (%53,3) tamamen uyanık ve koopere olmaları Group C'ye göre anlamlı olarak düşük bulundu ($p<0,01$). Grup C ve Grup P'deki olguların preoperatif, 1. saat ve 6. saat MMT değerleri açısından gruplar arasında istatistiksel olarak anlamlı fark yoktu ($p>0,05$). **Sonuç:** Preemptif pregabalin uygulaması, derlenmeyi minimal geciktmekte, ancak kognitif fonksiyonları bozmamakta ve ağrı ve analjezik tüketimini azaltmaktadır.

Anahtar Kelimeler: Kolesistektomi, laparoskopik; anestezi toparlanma dönemi; ağrı; deliryum, demans, amnestik, bilişsel bozukluklar

doi:10.5336/medsci.2011-25368

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Turkiye Klinikleri J Med Sci 2012;32(4):963-70

Pregabalin (S-aminomethyl-5-methylhexaninacid) was designed as a more potent successor of gabapentin. Although mechanism of action is not fully understood, pregabalin has the same binding area and a similar pharmacological profile.[1] Both gabapentin and pregabalin are alkalinized aminobutyric acid analogues developed as anticonvulsants. These drugs bind to the alpha2delta (α2δ) subunit of the presynaptic voltage-dependent calcium channel present throughout the peripheral and central nervous systems, and prevent release of nociceptive neurotransmitters such as glutamate, substance P and noradrenaline.[2-7] Possible areas of action are peripheral, primary afferent neurons, spinal neurons and supraspinal areas.[8] It is thought that the postoperative pain has a temporary neuropathic pain component and both gabapentin and pregabalin are beneficial in reducing the central neuronal sensitization in postoperative pain.[9-13] Pregabalin's binding affinity to α2δ subunit is six times stronger than that of gabapentin.[14] Luo and colleagues showed that α2δ subunit up-regulation may play an important role in the process of hyper-sensitization in a study on rats with spinal nerve injuries.[15]

With preemptive application of drugs, prevention of central sensitization process and achieving a better quality of analgesia post-operatively is intended.[16-19] To obtain maximum clinical benefit, intraoperative complete noxious stimulus block should be achieved and this block should continue during the postoperative period. Thus, use of preemptive analgesia especially to prevent central sensitization with multimodal analgesic interventions, can reduce both acute and chronic postoperative pain.[20]

After laparoscopic surgeries, pain is the most frequent complaint and the most common cause for postoperative morbidity.[21,22] Pain associated with outpatient laparoscopic surgery may be moderate or even severe for some patients, and may require opioid treatment.

Diclofenac sodium is a phenylactic acid derivative which is formulated for oral, intramuscular and rectal use.[23] It is an effective analgesic given after operation.[24]

Long-term cognitive and psychomotor impairment after anesthesia, although rare, is a serious problem. Postoperative deterioration of cognitive functions and psychomotor abilities often last short-term and are temporary. These symptoms can be observed even after very short anesthesia applications. In the period after anesthesia, memory in young patients and mental organizations in elderly are more frequently affected.[25,26]

The effect of preemptive pregabalin on early postoperative cognitive functions has not been investigated in previous studies.

In our study, we have aimed to evaluate the efficacy of a single preemptive 300 mg dose of pregabalin on postoperative recovery, pain, analgesic consumption (postoperative 24 hours) and cognitive function after laparoscopic cholecystectomy in patients undergoing total intravenous anesthesia (TIVA).

MATERIAL AND METHODS:

After the Institute's Ethics Committee approval, written informed consent was obtained from patients scheduled to undergo elective laparoscopic cholecystectomy between February 2011 and July 2011. Sixty subjects, ASA physical status I-III of both sexes were recruited for this single-blinded (research team members), prospective, randomized, controlled clinical trial.

Patients were eligible for participation if they were at least 18 years old and weighed more than 40 kg. Exclusion criteria included known allergy, sensitivity, or contraindications to pregabalin, diclofenac sodium and pethidine, or any NSAID, renal insufficiency, severe coronary, pulmonary, hepatic disease, history of previous neurological disease or seizure disorder, a history of peptic ulcer, a history of alcohol or substance abuse, ongoing therapy with sustained-release opioids, pregnancy, history of intake of non-steroidal anti-inflammatory and antidepressant drugs within 24 h before surgery and ASA IV classification status.

All the patients were examined and informed about the applicable anesthesia at the outpatient clinic one day before the surgery. During the pre-

anesthetic round, the patients were trained in the use of the visual analogue scale (VAS) pain score (0 for no pain and 10 for extremely intense pain). Mini mental test (MMT) was performed. All patients were also followed for possible side effects that may have occurred.

STUDY DESIGN

Study medications were pregabalin 300 mg capsules and placebo capsules. Patients were assigned to one of two treatment groups in single-blind randomized manner. Each new patient was assigned a consecutive study number. The study medications were administered on the day of surgery by a nurse.

1. Pregabalin group (Group P, n=30) received 300 mg pregabalin capsules (Lyrica ® capsule) 1 h before induction.

2. Placebo group (Group C, n=30) received empty capsules of similar color, taste and appearance but filled only with rice bran 1 h before the anesthetic induction.

None of the cases received any premedication.

1000 mL Ringer lactate solution was administered through the antecubital intravenous line in the operating room. Systolic, diastolic and mean blood pressures, heart rate/min and peripheral arterial SpO_2 values were recorded noninvasively with standard monitoring.

Patients were induced with remifentanil 1 μg kg^{-1} as IV bolus in 30-60 sec, followed by 0.25 μg kg^{-1} infusion. Orotracheal intubation was facilitated 2 min after IV infusion of propofol 1.5 mg kg^{-1} and Rocuronium 0.1 mg kg^{-1}. Anesthesia was maintained with propofol 100 μg kg^{-1} and remifentanil 0.25 μg kg^{-1}. The lungs were ventilated with oxygen-air (40-60%) mixture. Lung ventilation was controlled so end-tidal CO_2 value was kept between 30-35 mm Hg. Remifentanil infusion was continued at 0.25 μg kg^{-1} dose. Remifentanil infusion was regulated with 25-50% increase or decrease in remifentanil rate every 2-5 minutes for appropriate depth of anesthesia. In case of non-deep anesthesia, bolus remifentanil was administered with 2-5 minutes intervals at 0.5 μg kg^{-1} dose. For the treatment of hypotension (mean arterial pressure falls below 20% of baseline value before induction) and/or bradycardia (HR<40 beats/min) during deep anesthesia, remifentanil infusion rate was reduced by 50% and ephedrine 5 mg IV or atropine 0.5 mg IV was administered when required. Propofol infusion rate was continued unchanged.

Remifentanil and propofol infusions were reduced by 50% when skin sutures were started. Infusions were terminated after last skin suture was placed. At the end of surgery, residual neuromuscular paralysis was antagonized with neostigmine 0.05 mg kg^{-1} and atropine sulfate 0.015 mg $kg^{-1.}$

Extubation time, eye opening, response to commands and orientation time were recorded. Aldrete Recovery Score (ARS) values were recorded at 5^{th}, 10^{th} and 15^{th} min. Ramsey Sedation Score (RSS). was performed 1^{st}, 3^{rd} and 6^{th} h postoperatively and MMT was performed 1^{st} and 6^{th} h.

For pain relief after surgery, a single 75 mg of dose intramuscular diclofenac sodium was given to Group C patients 15-20 minutes before the estimated ending time of surgery.

The postoperative pain intensity was measured on a VAS (VAS 0=no pain, 10=worst imaginable pain). VAS≥4 level was decided based on their need for additional analgesics. The nursing staff was allowed to provide analgesia if indicated. Pethidine 0.35 mg/kg IV was given up to 6 times per day.

First VAS value in the recovery room after surgery was determined as 1^{st} h VAS. 1^{st} h, 4^{th} h, 8^{th} h, 12^{th} h and 24^{th} h VAS scores, 24 hour total analgesic consumption (mg), time to first analgesic request by the patient and side effects were recorded.

STATISTICAL ANALYSIS

SPSS (Statistical Package for Social Sciences) for Windows 10.0 program was used for statistical analysis of the findings of this study.

Besides descriptive statistical methods (mean, standard deviation), Kolmogorov-Smirnov test was used to evaluate normal distribution.

Chi-square test or Fisher's exact test were used for comparison of categorical variables Mann-

Whitney U test was used for comparisons of non-normal quantitative data between the groups.

For intra-group comparisons of parameters, Wilcoxon signed rank test and Mc Nemar test were used. The Wilcoxon signed-rank test using Bonferroni correction was used to prevent Type I error. Results were evaluated at 95% confidence interval, with $p<0.05$ significance and $p<0.01$ further significance level.

RESULTS

This study included a total of 60 patients, 24 (40%) women and 36 (60%) men, between the ages of 44-68 years. Demographic data such as age, height and weight averages were similar and no statistically significant differences were found between the groups ($p>0.05$) (Table 1).

There was no statistically significant difference between the groups with regard to demographic data ($p>0.05$) (Table1).

There was no statistically significant difference between the groups with regard to extubation time (min) ($p>0.05$). There was a very significant statistical difference ($p=0.000$), between the groups with regard to time of eye opening (min) and time to respond to commands (min) (Table 2). When ARS were compared between the groups, there was no statistically significant difference with regard to after extubation, 5th min, 10th min and 15th min values ($p> 0.05$) (Table 3).

TABLE 1: Distribution of demographic characteristics.

		Group C		Group P		
		mean ±	SD	mean ±	SD	p
Age		58.20	6.65	58.77	5.67	0.724
Height (cm)		166.47	10.47	167.33	9.29	0.736
Weight (kg)		74.40	12.46	78.40	10.56	0.185
		n	%	n	%	
Sex	Female	12	40	12	40	0.999
	Male	18	60	18	60	
ASA	I	3	10	7	23.3	
	II	23	76.7	19	63.3	0.371
	III	4	13.3	4	13.3	

Group C: Control group; Group P: Pregabalin group.

TABLE 2: Distribution of extubation time, time of eye opening, time to respond to commands.

	Group C		Group P		
	mean ±	SD	mean ±	SD	p
Extubation Time (min)	3.367	0.490	3.467	0.571	0.538
Time of Eye Opening (min)	3.700	0.651	5.367	0.765	0.000*
Time to respond to commands (min)	4.800	0.761	8.167	1.341	0.000*

*p<0. 01.

Group C: Control group; Group P: Pregabalin group.

TABLE 3: Distribution of aldrete recovery scores.

	Group C		Group P		
	mean ±	SD	mean ±	SD	p
ARS after extubation	7.733	0.828	7.633	0.890	0.621
ARS (5.min)	8.400	0.814	8.233	0.728	0.372
ARS (10.min)	9.067	0.907	8.967	0.850	0.653
ARS (15.min)	9.633	0.556	9.667	0.547	0.792

Group C: Control group; Group P: Pregabalin group; ARS: Aldrete recovery score.

Comparing RSS between groups, no statistically significant difference was found between the 15th min averages after extubation ($p>0.05$). 30th (33.3%) and 45th (53.3%) min values of being fully awake and cooperative were significantly lower in Group P patients compared to Group C ($p<0.01$) (Table 4).

Patients were evaluated by preoperative, postoperative 1st-6th h MMT and neurological examination. At the end of the examination, no major neurological disorders or moderate and severe levels of cognitive impairment were detected. There was no statistically significant difference between preoperative MMT values ($p>0.05$) (Table 5).

The difference between preoperative 1st h and 6th h MMT values of Group C and Group P was not statistically significant ($p>0.05$) (Table 5).

The decrease in the MMT values of 1st h regarding to preoperative value was found statistically significant in Group P ($p<0.05$). The increase in the value of 6th h regarding to 1st h value was found statistically significant ($p<0. 01$).

Time of first analgesic values in Group P were significantly longer than Group C ($p<0.01$) (Table 6).

TABLO 4: Distribution of ramsay sedation scale results.

		Group C		Group P		
		n	%	n	%	p
RSS 15.min	Fully awake and cooperative	14	46.7	8	26.7	0.108
	Tranquil, responds immediately to verbal stimuli, cooperative	16	53.3	22	73.3	
RSS 30.min	Fully awake and cooperative	22	73.3	10	33.3	0.002*
	Tranquil, responds immediately to verbal stimuli, cooperative	8	26.7	20	66.7	
RSS 45.min	Fully awake and cooperative	27	90.0	16	53.3	0.002*
	Tranquil, responds immediately to verbal stimuli, cooperative	3	10.0	14	46.7	

*p<0.01.
Group C: Control group, Group P: Pregabalin group, RSS: Ramsay sedation scale.

Total analgesic doses (Pethidine mg) values in Group P were significantly lower than in Group C (p<0.01) (Table 6).

1st, 4th, 8th, 12th and 24th h VAS values were statistically significantly lower in pregabalin group-compared to placebo group (p<0.01) (Table 7).

The overall incidence of side effects is summarized in Table 8. The incidence of nausea was significantly less in patients receiving pregabalin compared to placebo (p<0.01). Other side effects, such as vomiting, feeling light-headed or dizzy, respiratory depression, visual disturbances, feeling of general fatigue were similar in two groups.

DISCUSSION

Rapid recovery and regaining full consciousness shortly after anesthesia are desirable features of anesthesia techniques. Quick recovery of consciousness after extubation, the adequacy of spontaneous respiration, an open airway and sufficient protective airway reflexes during early recovery minimize negative side effects of respiratory system origin.[27,28] Preoperative alcohol consumption, drug use or premedication, sedative analgesic and anesthetic overdose may affect recovery.

Postoperative pain mechanism is complex. The purpose of preemptive drug application is to achieve a better quality of analgesia postoperatively.[16-19] It is thought that the postoperative pain has a temporary neuropathic component and both gabapentin and pregabalin are beneficial in reducing the central neuronal sensitization in postoperative pain.[6]

TABLE 5: Distribution of mini mental test results.

	Group C		Group P		
	mean ±	SD	mean ±	SD	p
MMT (Preoperative)	27.000	1.114	27.100	1.125	0.620
MMT (1.hr)	26.933	1.143	26.800	0.961	0.573
MMT (6.hr)	27.267	1.143	27.367	1.217	0.906

Group C: Control group; Group P: Pregabalin group; MMT: Mini mental test.

TABLE 6: Distribution of time of first analgesic and total analgesic doses.

	Group C		Group P		
	mean ±	SD	mean ±	SD	p
Time to first analgesic dose (min)	82.667	30.531	275.433	51.685	0.000*
Total analgesic doses (Pethidine mg)	198.333	30.409	131.000	25.811	0.000*

*p<0.01.
Group C: Control group; Group P: Pregabalin group.

TABLE 7: Distribution of visual analog scale results.

	Group C		Group P		
	mean ±	SD	mean ±	SD	p
VAS 1.hr	4.333	1.213	1.700	0.466	0.000*
VAS 4.hr	4.967	0.669	1.733	0.521	0.000*
VAS 8.hr	4.333	0.758	1.800	0.484	0.000*
VAS 12.hr	3.233	0.858	1.933	0.583	0.000*
VAS 24.hr	2.133	0.776	1.600	0.498	0.005*

*p<0.01.
Group C: Control group; Group P: Pregabalin group; VAS: Visual analog scale.

TABLE 8: Side effects.

	Group C		Group P		
	n	%	n	%	p
Nausea	9	30	0	0	0,000*
Vomiting	1	3	0	0	0.313
Feeling light-headed or dizzy	2	7	1	3	0.554
Respiratory depression	1	3	0	0	0313
Headache	0	0	0	0	-
Visual disturbances	4	13	3	10	0.688
Hypoxemia	0	0	0	0	-
Hypotension	0	0	0	0	-
Feeling of general fatigue	2	7	4	13	0.389

* p<0. 01.
Group C: Control group; Group P: Pregabalin group.

Dirks et al, Eckhardt et al. and Hurley et al. demonstrated that gabapentin and pregabalin can increase the analgesic effects of morphine, nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors.[29-31]

NSAIDs are the most commonly prescribed analgesic medications worldwide, and their efficacy for treating acute pain has been well demonstrated. Diclofenac is a benzene-acetic acid derivative that acts, like other NSAIDs, by inhibiting cyclo-oxygenase isoforms that mediate the body's production of the prostaglandins implicated in pain and inflammation.[32]

In this study, a multimodal analgesia technique was preferred and one group received preemptive pregabalin and the other received diclofenac sodium at the end of the operation, extra dose analgesic requirement was provided with low dose pethidine.

There was no statistically significant difference among the groups with regard to extubation time (min), but time to eye opening (min) and time to respond to commands (min) were longer in pregabalin group compared to the control group (p=0.000). We used ARS and RSS to evaluate recovery. There was no significant difference for ARS between the groups (p>0.05). In other studies, patients given pregabalin were found to be more sedated in the postoperative period.[33-35] In our study, similar to other studies, patients in Group P were more sedated.

Effective postoperative analgesia prevents many negative impacts of pain; for example it provides a comfortable breathing, reduces the workload of the cardiovascular system, prevents the development of thromboembolic events with early mobilization, and prevents the increase of stress response which happens via neuroendocrine and sympathetic nervous system activation.

Studies reported that pregabalin has a significant analgesic effect in acute postoperative pain.[36-38]

The present study has demonstrated significant analgesic effect of the pre-emptive use of 300 mg pregabalin after laparoscopic cholecystectomy. A decrease in total analgesic consumption along with a significant decrease in VAS pain scores were found in patients who received pregabalin one hour before surgery (p<0.01). This study also demonstrated that a single postoperative dose of diclofenac sodium does not reduce the incidence of postoperative pain and analgesic consumption in patients undergoing laparoscopic cholecystectomy.

Postoperative nausea and vomiting (PONV) are common complications following anesthesia and surgery. The etiology of PONV is complex and depends on a variety of factors, including the technique of anesthesia, patient demographics, and type and site of surgery.[39] One of the most important class of drugs used to treat pain is opioids but their use is limited due to side effects such as sedation, dizziness, miosis, respiratory depression, nausea and vomiting.[40] In this study, the incidence of postoperative nausea was significantly lower with the use of pregabalin (p<0.01). This might be related to the decreased use of opioids after surgery and the consequent decrease in opioid-related adverse effects.

Pregabalin is a well-tolerated drug which has low incidence of side effects and less interaction with other drugs. Side effects such as somnolence, dizziness, confusion, headache, ataxia, and weight gain have been reported. Although most of these side effects were reported with chronic use of pregabalin, the most common side effects due postoperative use of pregabalin are dizziness, somnolence and sedation.[41]

Chang et al. and Jokela et al. found side effect as dizziness and headache and visual disturbances in their studies with pregabalin.[32,42] In our study, side effects such as postoperative dizziness, headache and visual disturbances were seen in both groups but no statistically significant differences were found between the groups ($p>0.05$).

The incidence of postoperative sedation was significantly higher in the pregabalin group.[33,34] This effect may also influence the use of opioids. It is possible that the more sedated patients in the pregabalin group would use less opioids. In our study, sedation in the postoperative period was statistically significantly higher ($p<0.01$) in pregabalin group compared to the control group.

The objective of postoperative cognitive function assessment is either to determine the level of recovery with determining residual effects or to investigate the mental changes caused by surgery and anesthesia. Besides the effects of agents on the respiratory and circulatory systems, the effects on memory, other cognitive functions and psychomotor capabilities are also important in determination of the duration of post-anesthetic effect.[42]

Bedside cognitive function tests are very useful in determining the mental changes. These tests evaluate orientation, short-term memory, language, perception and some motor functions. Due to being short and easy to practice, MMT is a frequently applied bedside test.

MMT postoperative 1 h values were significantly lower than preoperative values in a study with inhalation agents by Chen et al.[43] Larsen et al. analyzed cognitive function and recovery in their study with propofol, desflurane and sevoflurane.[44] They reported that more rapid awakening and recovery of patients in propofol group.

In this study, we preferred propofol, an IV anesthetic agent, instead of inhalation agents; especially due to lesser effect of propofol on cognitive functions, rapid anesthesia induction and recovery, and remifentanil was used for its early starting, short-lasting anesthetic effect allowing a more rapid recovery.

The decrease in the value of 1st h MMT regarding to preoperative value was not found statistically significant in Group C, whereas it was found statistically significant in Group P ($p<0.05$). However, the difference between preoperative 1st h and 6th h MMT values of Group C and Group P was not statistically significant ($p>0.05$).

CONCLUSION

We concluded that preemptive pregabalin administration does not delay postoperative recovery, reduces opioid requirements and the incidence of opioid-related side effects, decreases postoperative VAS scores and does not impair postoperative cognitive functions in patients who undergo laparoscopic cholecystectomy with TIVA.

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