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The Effects and Comparative Efficacy of Dexamethasone and Gabapentin on Nausea and Vomiting after Laparoscopic Cholecystectomy

Laparoskopik Kolesistektomi Sonrası Bulantı ve Kusmanın Önlenmesinde Deksametazon ve Gabapentinin Etkinliği ve Karşılaştırılması

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ABSTRACT

Objective: Postoperative nausea and vomiting (PONV) is a common postoperative complication. The aim of this study was to investigate the efficacy of gabapentin and dexamethasone as new treatment strategies in the treatment of PONV.

Methods: This retrospective study included a total of 136 ASA I-II patients aged 18-70 years who underwent elective cholecystectomy. Group D (n=66) received 4 mg intravenously dexamethasone after anesthesia induction and Group G (n=70) received 600 mg gabapentin oral treatment. Standard DII and V5 lead ECG, automatic non-invasive blood pressure and peripheral oxygen saturation monitoring was applied to all patients in the general operating room, anesthesia maintenance was provided with total intravenous anesthesia after orotracheal intubation and at the end of surgery, patients were transferred to the postoperative care unit. Nausea and vomiting symptoms, pain scores and the time and dose of additional antiemetic/analgesic requirements in the first 24 hours were monitored.

Results: There were no statistically significant demographic differences between the groups and the results showed that both dexamethasone and gabapentin were effective in preventing PONV. The need for rescue antiemetic therapy was similar in both groups (p=0.2). Significantly less postoperative analgesic was required in the gabapentin group than in the dexamethasone group.

Conclusion: Antiemetic drug prophylaxis should be administered to patients at high risk of PONV and treatment with different groups of antiemetic drugs should be considered. Dexamethasone and gabapentin can be considered effective drugs for the prevention of PONV.

Keywords: Postoperative nausea and vomiting, dexamethasone, gabapentin, laparoscopic surgery, laparoscopic cholecystectomy

ÖZ

Amaç: Postoperatif bulantı ve kusma (POBK) ameliyat sonrası sık görülen bir komplikasyondur. Çalışmanın amacı, POBK'de yeni tedavi stratejileri olan gabapentin ve deksametazonun etkinliğini araştırmaktı.

Yöntem: Bu retrospektif çalışmaya elektif kolesistektomi yapılan 18-70 yaş arası toplam 136 ASA I-II hasta dahil edildi. Grup D (n=66) anestezi indüksiyonundan sonra 4 mg intravenöz deksametazon ve Grup G (n=70) 600 mg gabapentin oral tedavi aldı. Tüm hastalara genel ameliyathanede standart DII ve V5 derivasyonlu EKG, otomatik non-invaziv kan basıncı ve periferik oksijen satürasyonu monitörizasyonu uygulandı, orotrakeal entübasyon sonrası total intravenöz anestezi yöntemi ile anestezi idamesi sağlandı ve ameliyat sonunda hastalar postoperatif bakım ünitesine transfer edildi. Bulantı ve kusma semptomları, ağrı skorları ve ilk 24 saat içinde ek antiemetik/analjezik gereksinimlerinin zamanı ve dozu izlendi.

Bulgular: Gruplar arasında istatistiksel olarak anlamlı demografik farklılıklar yoktu ve sonuçlar hem deksametazon hem de gabapentinin ameliyat sonrası bulantı ve kusmayı önlemede etkili olduğunu gösterdi. Kurtarıcı antiemetik tedavi ihtiyacı her iki grupta da benzerdi (p=0.2). Gabapentin grubunda deksametazon grubuna kıyasla anlamlı ölçüde daha az postoperatif analjezik gereksinimi olduğu görüldü.

Sonuç: Ameliyat sonrası bulantı ve kusma riski yüksek olan hastalara antiemetik ilaç profilaksisi uygulanmalı ve farklı antiemetik ilaç grupları ile tedavi düşünülmelidir. Deksametazon ve gabapentin POBK'nin önlenmesinde etkili ilaçlar olarak kabul edilebilir.

Anahtar sözcükler: Postoperatif bulantı ve kusma, deksametazon, gabapentin, laparoskopik cerrahi, laparoskopik kolesistektomi

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INTRODUCTION

Postoperative nausea and vomiting (PONV) are common symptoms that affect patient comfort. The etiology of PONV is multifactorial and can be caused by the type of surgery and anesthesia, multiple drug administration and environmental factors (1). The incidence of vomiting after general anesthesia is approximately 30%, the incidence of nausea is approximately 50%, and for patients at high risk for PONV, this rate is 80%. Nausea and vomiting in the postoperative period cause prolonged hospitalization and can increase patient dissatisfaction (2).

Postoperative nausea and vomiting may cause dehydration and electrolyte imbalance, increased risk of pulmonary aspiration, trauma to the surgical wound due to increased intra-abdominal pressure caused by vomiting, and delays in wound healing (3). It also causes increases in medical costs by prolonging nursing care times and post-anesthesia care unit (PACU) length of stay. Pain and PONV are the most common causes of prolonged hospitalization and patient dissatisfaction due to anesthesia (4-7).

Dexamethasone is used for antiemetic treatment. The antiemetic effect is mediated by the suppression of prostaglandin synthesis through action in the chemoreceptor trigger zone. Many studies in the literature have reported effective use of dexamethasone in antiemetic treatment (8,9).

Gabapentin used orally in the preoperative period has been observed to be effective in reducing PONV (10). It is thought that the mechanism of action of gabapentin in the treatment of PONV is due to the reduction of calcium currents by binding to voltage-gated Ca^{+2} channel alpha-2/delta subunits regulated in central nervous system-related regions such as the area postrema. Gabapentin has been reported to reduce nausea and vomiting in different studies (11,12).

The aim of this study was to investigate the effects of dexamethasone and gabapentin on PONV in laparoscopic cholecystectomy patients.

MATERIALS and METHODS

Approval for the study was granted by the local ethics committee (23.12.2015, 51). All the study procedures complied with the Helsinki Declaration.

The study included patients who underwent laparoscopic cholecystectomy between 01.05.2015 and 31.08.2015. Exclusion criteria were defined as the presence of drug allergy, active or latent peptic ulcer, esophagitis, ulcerative colitis, diverticulitis (hemorrhage perforation hazard), recent intestinal anastomosis operation, systemic fungal infections, glaucoma, uncontrolled diabetes mellitus, viral or bacterial infections, pregnancy or lactation.

The study sample comprised a total of 136 ASA I-II patients aged 18-70 years who received dexamethasone or gabapentin (Figure 1). The groups were evaluated as Group D, the dexamethasone-treated group and Group G, the gabapentin-treated group. The Apfel score was used to determine the risk factors and incidence because of the ease-of-use and high predictive value. The Apfel simplified risk score includes four basic risk factors of female gender, non-smoker, history of PONV or motion sickness, and plan to use opioids for postoperative analgesia. Each factor is scored with 1 point if present, giving a total score of 0 – 4, evaluated as the percentage risk for PONV as 10%, 20%, 40%, 60%, and 80%, respectively.

Written informed consent for anesthesia was obtained from all the patients at the preoperative outpatient assessment. Group G patients were given gabapentin 600 mg tablet orally with 100 cc drinking water 2 hours before being admitted to the operation room.

After standard triple monitoring, 0.5-2 µg kg^{-1} fentanyl, 40 mg lidocaine, and 2 mg kg^{-1} propofol were administered for induction of anesthesia. Muscle relaxation was achieved with 0.6 mg kg^{-1} dose of rocuronium and orotracheal intubation was performed 2 minutes later. Following induction in Group D, 50 mg ranitidine and 4 mg dexamethasone were diluted with 5 ml isotonic and administered separately before rocuronium. Group G received only 50 mg ranitidine following induction.

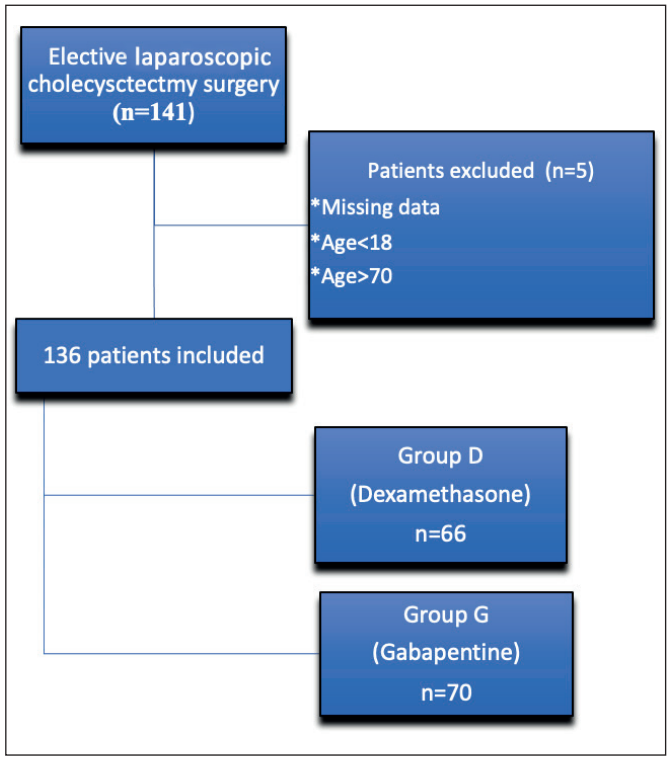

Figure 1: Flowchart of the study.

Anesthesia maintenance was achieved with 0.1-2 µg kg^{-1} remifentanil and 2-6 mg kg^{-1} h^{-1} propofol infusion. Anesthesia maintenance drug doses were similar in the two groups. Patients were monitored with 50% O_2, 50% air mixture and 3 L min^{-1} flow. Inhalation anesthesia and nitrous oxide were not used for the maintenance of anesthesia. Each patient was administered 50 mg dexketoprofen intravenously (iv) 30 minutes before the end of the operation. The neuromuscular block effect was eliminated with 1 mg kg^{-1} sugammadex. When an Aldrete Score of 9 was recorded, the patients were admitted to the ward. At 4, 12, and 24 hours of ward follow-up, patients were re-evaluated in terms of PONV as no complaint, mild nausea, severe nausea, frequent vomiting (4 times), or severe vomiting (continuous). In the severe nausea group, ondansetron 4 mg iv was administered as a rescue dose to patients with 2 or more vomiting episodes, and to patients with frequent vomiting and severe vomiting. Postoperative pain was evaluated using the numerical rating scale (NRS). Patients were asked to rate the severity of pain on a scale of 0 to 10, with 0 meaning "no pain" and 10 meaning "the worst pain imaginable". For patients who indicated pain at ≥7 on the NRS, 100 mg tramadol was administered.

Statistical Analysis

Post-hoc power analysis showed that the study had high accuracy (beta=0.16). Data obtained in the study were analyzed statistically using IBM Statistical Package for Social Sciences (SPSS) for MAC 21.0 software. Descriptive statistical methods, with results stated as mean ± standard deviation values, number and percentage, and the Chi-square test were used to analyze frequency differences between groups. The Z test was used to compare percentage values. All analyses were two-tailed, with a value of $p<0.05$ considered statistically significant.

RESULTS

No difference was determined between the groups in terms of age, gender, history of PONV/ motion sickness, and smoking. The age distribution was similar in both groups with mean age of 47.08 ± 12.04 years in Group D and 47.53 ± 10.95 years in Group G.

According to the Z test analysis, PONV was more common in females than in males (Z=3.72, p=0.0002).

There was no significant difference between the groups in terms of rates of active smokers (p=0.560).

A history of PONV or motion sickness was present in 3 patients in Group D, with no statistically significant difference determined between the groups (p=0.223) (Table I).

The mean NRS scores at 0, 4, 12, and 24 hours were similar in both groups, although a greater number of Group D patients recorded NRS scores >7. The Chi-square test results showed a difference between the two groups in terms of postoperative opioid use (χ 2 (1, N=136) = 4.04). Postoperative opioids were used more in the dexamethasone group than in the gabapentin group (p=0.044) (Table II).

The Chi-square test results demonstrated no difference between the groups in respect of the classifications of no complaint, mild nausea, severe nausea, frequent vomiting and severe vomiting. There was no difference between the

Table I: Demographic Data

	Group D		Group G		p
Age (years)	47.08 ± 12.04		47.53 ± 10.95		
Gender	**Female**	**Male**	**Female**	**Male**	
	51 (77.2%)	15 (22.7%)	57 (81.4%)	13 (18.6%)	0.699
Smoking	15 (22.7%)		20 (28.6%)		0.560
History of motion sickness, PONV	3 (4.5%)		0		0.223

PONV: Postoperative nausea and vomiting, $p<0.05$ was considered significant.

Table II: Pain Scores and Analgesic Dose Requirements

	Group D	Group G	p
NRS 0	3.35 ± 0.98	3.34 ± 0.99	0.974
NRS 4	4.27 ± 2.52	4.04 ± 1.91	0.553
NRS 12	3.5 ± 0.74	3.46 ± 0.84	0.755
NRS 24	2.41 ± 0.49	2.5 ± 0.5	0.291
Analgesic dose requirement (n)	7	15	0.044

NRS: Numeric Rating Scale, $p<0.05$ was considered significant.

groups in respect of the nausea and vomiting values between 0-4 hours, 4-12 hours, and 12-24 hours (p=0.346, p=0.546, p=0.151, respectively). Severe vomiting was observed in only one Group D patient in the postoperative 0-4 hours evaluation.

Of the Group D patients who described severe nausea at 0-4 hours postoperatively, 3 patients had 2 or more vomiting episodes, 3 had frequent vomiting and 1 had severe vomiting. All were treated with ondansetron. In the Group G, 2 patients with severe nausea, and 4 patients with frequent vomiting received ondansetron at 0-4 hours. No significant difference was determined between the groups (p=0.347).

The Group D patients who received a rescue dose of ondansetron for PONV were mostly seen between 4-12 hours. No statistically significant difference was determined between Group D and Group G in respect of the time to the first dose of rescue therapy. No rescue dose was needed at 12-24 hours postoperatively in either group. The need for rescue ondansetron postoperatively at 0-4 hours, 4-12 hours, and 12-24 hours was similar in Group D and Group G (p=0.303). This means that clinically, both dexamethasone and gabapentin have similar efficacy in the treatment of PONV (Table III).

DISCUSSION

In this study, in which the effect of dexamethasone and gabapentin on PONV in patients undergoing laparoscopic cholecystectomy was investigated, both drugs were observed to be effective in the prevention of PONV. While there was no difference between the two groups in terms of PONV, pain scores and additional antiemetic use, the use of gabapentin resulted in a lower rate of postoperative opioid consumption.

Despite recent innovations in the fields of surgery and anesthesia, PONV and pain are the most common postoperative complications. A multimodal approach and prophylaxis are recommended instead of treatment with a single drug (13). In the current study, dexamethasone and gabapentin were used as prophylaxis for PONV, and ondansetron was administered as a rescue antiemetic agent.

Female gender is the risk factor held most responsible in the etiology of PONV, followed by non-smoking and a history of PONV (14). The type of surgery is also an important factor affecting the incidence of PONV and has been reported to be higher in laparoscopic cholecystectomy (15).

Dexamethasone 4-5 mg is recommended for induction of anesthesia in patients at high risk of PONV (16). Many studies in the literature, have stated use of dexamethasone in a dose range between 4-10 mg. No difference has been shown in the antiemetic efficacy of 4, 5, 8, or 10 mg dexamethasone used in PONV prophylaxis (14). The efficacy of 4 mg dexamethasone as prophylaxis for PONV has been found to be similar to ondansetron 4 mg (17). Recent studies have suggested the use of 4 - 5 mg dexamethasone as an effective dose rather than high doses (18). In the current study, 4 mg dexamethasone was used in accordance with the literature and this was seen to be effective in reducing the incidence of PONV.

Dexamethasone has been reported to reduce postoperative opioid requirement, Visual Analog Scale (VAS) scores, and antiemetic and analgesic use by 50%, by reducing acute phase reactants (19-21). In this study, postoperative opioid use in the dexamethasone group was at the rate of 22%. Consistent with the literature, a decrease in opioid consumption was observed with dexamethasone use.

Dexamethasone side-effects such as glucose intolerance, increased risk of infection, gastric mucosal damage, adrenal suppression, and delayed bowel movements can occur after long-term use. No increased risk of infection has been reported in studies using dexamethasone for PONV postoperatively (6). Dexamethasone for PONV has been reported to be safe for use in diabetic patients (20). It has also been reported that blood glucose regulation was not impaired in patients receiving 8 mg dexamethasone (21). In the current study, no adverse side-effects were observed with the use of 4 mg dexamethasone.

Previous studies have reported that 600 mg gabapentin used 2 hours preoperatively reduces PONV effectively and that 300 mg doses of gabapentin decreased the severity of PONV but did not change the incidence (22,23). The use of 900 and 1200 mg doses has not been shown to increase antiemetic efficacy and pain scores were found to be similar to those recorded with the use of 600 mg doses (24). Preoperative use of gabapentin is recommended for PONV and postoperative pain, especially before abdominal surgery (25,26). However, preoperative gabapentin use may have side-effects such as dizziness and sedation in the early postoperative period (27). According to meta-analyses, the side-effects of gabapentin are dose-dependent (28). In the current study, no complications were observed with 600 mg dose of gabapentin and therefore a 600 mg dose of gabapentin can be considered safe.

Several agents are used in the treatment of PONV. In the literature, various drugs including dopamine and serotonin receptor antagonists, corticosteroids, antihistamines, sedatives and anticholinergics have been used to treat this disorder (2,29,30). In the current study, in which the efficacy of gabapentin and dexamethasone used for prophylaxis of PONV was investigated, the antiemetic effects of both drugs were found to be similar. The pain scores in both groups were determined to be similar. However, the postoperative opioid

Table III: Distribution of Nausea Severity and Rescue Dose Use

		Groups		
		Group D	Group G	p
0-4 hours nausea severity	No complain	48	50	0.346
	Mild nausea	7	13	
	Severe nausea	7	3	
	Frequent vomiting	3	4	
	Severe vomiting	1	0	
4-12 hours nausea severity	No complain	53	62	0.546
	Mild nausea	4	3	
	Severe nausea	6	4	
	Frequent vomiting	3	1	
	Severe vomiting	0	0	
12 - 24 hours nausea severity	No complain	62	69	0.151
	Mild nausea	4	1	
	Severe nausea	0	0	
	Frequent vomiting	0	0	
	Severe vomiting	0	0	
Rescue dose use time	None	50	59	0.397
	0-4 hours	7	6	
	4-12 hours	9	5	
	12-24 hours	0	0	

$p<0.05$ was considered significant.

requirement was 11% in the gabapentin group and 22% in the dexamethasone group. Therefore, the prophylactic use of dexamethasone and gabapentin can be considered to have a place in the treatment of PONV and pain. As a result of post-synaptic binding to voltage-dependent calcium channels, there is a decrease in calcium entry to the nerve endings and thus the release of neurotransmitters such as noradrenaline is reduced. It is used perioperatively orally in the treatment of postoperative pain (12). That opioid consumption was lower in the gabapentin than dexamethasone group could be explanied by this mechanism.

As the limitaion of the present study, postoperative pain of the patients was evaluated at rest in this study. Patients were questioned about their pain in semi-Fowler position and no specific pain was questioned.

CONCLUSION

Postoperative nausea and vomiting are common complications that lead to patient dissatisfaction and are often neglected. The results of this study demonstrated that both of dexamethasone and gabapentin reduced the incidence of PONV and postoperative pain according to the literature. Gabapentine reduce opioids consumption better than dexamethasone. In the preoperative period, administration of dexamethasone or gabapentin to patients who are in the risk group in terms of PONV is an appropriate recommendation in accordance with the literature.

Conflict of Interest: None

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AUTHOR CONTRIBUTIONS

Conception or design of the work: NKA
Data collection: GA
Data analysis and interpretation: GA
Drafting the article: GA
Critical revision of the article: NKA
Other (study supervision, fundings, materials, etc): NKA
The author (GA, NKA) reviewed the results and approved the final version of the manuscript.

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