ORIGINAL ARTICLE

The Effect of Gabapentin on Postoperative Pain, Morphine Sparing Effect and Preoperative Anxiety in Patients Going for Sleeve Gastrectomy Surgical Procedure

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Abstract

Objective: To determine the effectiveness of preoperative administration of gabapentin in reduction of acute postoperative pain, morphine consumption and preoperative anxiety and sedation in obese patients undergoing laparoscopic sleeve gastrectomy.

Study Design: Double-blinded randomised control trial.

Place and Duration of Study: King Khalid University Hospital, King Saud University Riyadh, Saudi Arabia, from July 2014 to January 2017.

Methodology: Fifty patients undergoing sleeve gastrectomy were enrolled in the study. The subjects received either 1200 mg gabapentin or placebo 2 hours before surgery. The amount of morphine consumption and postoperative pain at 4, 8,12,16, 20 and 24 hours of surgery were measured. Preoperative anxiety and sedation were recorded at 2 hours interval after the drug administration.

Results: There was no significant difference in patient characteristics in both groups. 24 hours PCA morphine consumption was significantly lower in gabapentin group than in the placebo group, 15.08 ±4.55 *vs.* 27.80 ±2.51 (p=0.001). Preoperative VAS anxiety, pre- *verses* post-drug, was significantly lower in gabapentin group 5.80 ±1.11 vs. 3.52 ±1.00 (p=0.001) than in placebo group 6.08 1.28 vs. 6.28 1.24 (p=0.635). Preoperative sedation score was not different in both groups.

Conclusion: Preoperative oral gabapentin was effective in reducing the postoperative pain, morphine consumption and preoperative anxiety in morbid obese patients undergone laparoscopic sleeve gastrectomy.

Key Words: *Obesity-morbid, Gabapentin, Postoperative pain, Analgesic opioid, Preoperative anxiety, Laparoscopic sleeve gastrectomy.*

INTRODUCTION

Morbid obese patients have different pharmacodynamic and pharmacokinetic as compared to normal weight individuals.[1] These patients have low pain threshold.[2] Management of postoperative pain in obese patients is always a challenge. Laparoscopic sleeve gastrectomy is an effective surgical procedure in facilitating the patient weight loss and preventing the serious future health complications. Laparoscopic sleeve gastrectomy causes moderate to severe postoperative pain.[3] Caution is always warranted when analgesics, opioids, are used in obese patients, especially in the postoperative period. Different types of surgeries cause different types and severity of pain and postoperative analgesic requirement.[4] Multiple modal analgesia is recommended in obese patients for the reduction of opioid consumption and its side effects.[5]

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Gabapentin as a multimodal analgesic and pain modulator has been extensively studied for many surgical procedures and found to be having post-operative opioid sparing effect and improved pain scores.[6] Gabapentin inhibits the calcium influx to Aδ and C neurons reducing excitatory neurotransmitter release from the dorsal horn and thereby inhibiting nociception.[5] However, in literature the effectiveness of preoperative administration of gabapentin for postoperative pain and opioid sparing effect showed varying results in different types of surgeries. The effectiveness of gabapentin in a particular surgical intervention is difficult to predict. The evidence regarding the effect of gabapentin on post-operative pain and opioid sparing effect in morbidly obese patients is sparse. Gabapentin is also known to be effective for the treatment of generalised anxiety disorders. However, in literature mixed results were reported regarding its effectiveness for the reduction of preoperative anxiety. It was hypothesised that pre-operative administration of an anticonvulsant drug, gabapentin, could be helpful to optimise the post-operative pain, opioid requirement and preoperative anxiety in obese patients undergoing laparoscopic sleeve gastrectomy.

The objective of this study was to determine the effective-ness of gabapentin for the reduction of acute post-operative pain, morphine consumption and preoperative

anxiety in obese patients undergoing laparoscopic sleeve gastrectomy.

METHODOLOGY

This double-blind randomised control trial was approved by the Independent Review Board, King Saud University, Riyadh (E- 13902, date of approval 2-06-2014) and was registered at http://Clinicaltrials.gov (NCT03023501). The study was conducted from July 2014 to January 2017 at King Khalid University Hospital, King Saud University, Riyadh. After obtaining written informed consents from the patients, 50 obese patients (BMI >35-50 Kg/m^2) scheduled for sleeve gastrectomy of either gender, age ranges in between 18-50 years and American society of anesthesia physical status (ASA) 1 and 2 were included in the study. Patients taking any sedative, tranquillisers, contraindications to gabapentin and history of sleep apnea using CPAP were excluded from the study. Randomisation was performed using computer generated table and the investigational pharmacy was responsible for the blinding and dispensing of medication. Sample size was calculated based on the Clarke and Spreng studies.[7,8] In order to calculate the necessary sample size, it was considered that a 20% decrease in postoperative pain, morphine consumption and preoperative anxiety after administration of the study drug would be successful. For results to be statistically significant with α=0.05 and potency of 80%, it was necessary to recruit 25 patients in each experimental group.

Patients were taught about the use of anxiety visual analog scale (VAS, 0 = no anxiety to 10 = worst imaginable anxiety),[7] pain VAS (0 = no pain to 10 = worst imaginable pain)[7] and use of patient control analgesia (PCA) device. The duration of study was 24 hours postoperative period. No Pre-anesthetic medications were prescribed, and all patients were fasted midnight prior to surgical procedure. Patients were randomly divided into two groups of 25 each, Group-P (Placebo) and Group-G (Gabapentin). Patients received either gabapentin (Neurontin 400mg capsule, Pfizer, Goedecke GmbH, Germany) 1200 milligram (Group-G) or placebo drug, orally 2 hours before calling the patient to operating room. The study agents were provided by the hospital pharmacy. Randomisation and blinding were the responsibility of the hospital pharmacy. The staff involved in data collection and patient management were unaware of the group assignment.

In operating room, all ASA standard monitors and nerve stimulator to the ulnar nerve of one of the upper limbs were attached. A 18-gauge intravenous (IV) catheter was inserted on one of the upper limbs vein. Ringers lactate solution was initiated at the rate of 120 ml per hour. All drug dosages were calculated according to the ideal body weight. General anesthesia was standardised and all patients were induced with intravenous propofol 1.5 - 2 mg/kg, fentanyl 2 - μg/kg. IV remifentanil infusion at the rate of 0.05 μg/kg/min was initiated after induction of anesthesia. IV rocuronium 0.5 mg/kg was given as muscle relaxant for facilitation of endotracheal intubation and intraoperative maintenance of muscle relaxation. General anesthesia was maintained with desflurane and 50% oxygen in air, maintaining MAC at 0.7-1. Controlled ventilation was adjusted while keeping the EtCo2 in between 35-40 mm Hg. Thirty minutes before the anticipated end of surgery, 0.08 mg/kg IV bolus of morphine was given. Desflurane and remifentanil were discontinued at skin closure. At the end of surgery neuromuscular blockade was reversed at three train of four with IV sugamadex 2-mg/kg of the ideal body weight. After extubation, patients were transferred to the post-anesthesia care unit (PACU). Patients were discharged to the ward when they achieved the modified Aldrete score of nine on two sequential measurements at 10-minute intervals. PCA morphine access was provided immediately in PACU. The device was set to deliver 1-mg boluses of intravenous morphine with a lockout period of 5 minutes and no background infusion. This PCA regimen was continued for 24 hours and Perfaglan (paracetamol) 1-gram IV was given every 8-hourly for 24 hours. On patient demand, supplemental 1-mg morphine was given in between the PCA lockout time. Blood pressure, heart rate and oxygen saturation percentage were recorded as baseline and at 2 hours interval of study drug administration.

Postoperative VAS pain and morphine consumption were recorded in PACU and at 4, 8, 12, 16, 20 and 24 hours. Preoperative VAS anxiety was recorded before administration of study drug and then at two hours interval in the waiting area of the operating suit. Preoperatively sedation score was recorded, using Pasero Opioid-induced Sedation Scale,[9] (POSS), 2 hours after the administration of study drug in the operating suit waiting area. Postoperatively potential side effects of gabapentin, dizziness, nausea and vomiting (requiring treatment) were recorded. Nausea and vomiting was treated with IV 10 mg metoclopramide and/or 2 mg ondansetron.

All data were collected in a predesigned form and IBM statistical analysis SPSS USA version 21 was used for data entry and analysis. Frequency for qualitative variables and means and standard deviation (SD) for quantitative variables were calculated. Qualitative data analysis was performed using Chi-square or Fisher exact test. Quantitative data analysis was performed using Students t-test. Paired independent sample t-test was applied for anxiety before and after giving the study drug. P-value <0.05 was considered significant in all statistics.

RESULTS

Fifty patients fulfilled the eligibility criteria and were included in the study. No significant difference in age, gender, weight, height, BMI, ASA status, duration of anesthesia and duration of stay in PACU were observed between the groups (Table I). The overall 24-hour morphine consumption was significantly higher in Group-P as compared to Group-G (p=0.001). The post-operative morphine consumption and VAS pain was significantly higher in Group-P as compared to Group-G in PACU and at 4-12 hours postoperatively (Table II).

Baseline anxiety VAS in Group-G and Group-P was 5.80 ±1.11 vs. 6.08 ±1.08 (p=0.416). The VAS anxiety, 2-hour after drug administration in Group -G and Group-P was 3.52 ±1.00 *vs*. 6.28 ±1.24 (P=0.001). The difference in VAS anxiety before and after the drug administration in Group- G was 5.80 ±1.26 *vs.* 3.52 ±1.00 (p=0.001) and in Group-P was 6.08 ±1.08 *vs*. 6.28 ±1.24 (p=0.635, Table III). The preoperative sedation score (POSS), was comparable in both groups and difference was non-significant (Table III).

Table I: Patient characteristics, duration of anesthesia and duration of stay in PACU in Group-G (Gabapentin) and Group-P (Placebo). The data is presented as means ±SD and frequencies and percentages as appropriate. P-value of less than 0.05 ($p \leq 0.05$) is considered as significant.

Items	Group-G	Group-P	p-value
Age	30.48 ±9.50	32.36 ±9.10	0.508
Gender M : F	15 : 10	13 : 12	0.569
	60% / 40%	52% / 48%	
Weight	115.32 ±10.69	116.48 ±14.95	0.597
Height	155.16 ±9.27	156.24 ±10.98	0.772
BMI	47 ±4.14	46.88 ±3.11	0.905
ASA status 1/2	5/20	8/17	0.333
	20% / 80%	32% / 68%	
Duration of anesthesia (min)	99.40 ±6.67	99.28 ±7.70	0.957
Duration of stay PACU (min)	76.80 ±17.07	78.20 ±16.82	0.996

Table II: Patients postoperative pain VAS and postoperative morphine consumption in Group-G (Gabapentin) and Group-P (Placebo). The data is presented as means ± SD. P-value of less than 0.05 ($p \leq 0.05$) is considered as significant.

Items	Group-G	Group-P	p-value
Postoperative pain VAS scores			
PACU	4.64 ±1.93	6.40 ±1.11	0.001
4 -Hours	3.32 ±1.60	6.20 ±1.08	0.001
8-Hours	2.52 ±1.19	4.96 ±1.45	0.001
12- Hours	2.16 ±1.06	4.20 ±1.73	0.001
16 Hours	1.72 ±0.89	1.84 ±0.94	0.646
20 Hours	1.72 ±0.97	1.80 ±1.04	0.781
24- Hours	1.60 ±0.76	1.72 ±0.89	0.611
Postoperative morphine consumption			
PACU	5.00 ±1.32	7.64 ±1.49	0.001
4 -Hour	4.72 ±1.62	7.28 ±0.93	0.001
8-Hour	3.52 ±1.80	5.92 ±1.44	0.001
12- Hour	2.08 ±1.03	4.36 ±1.80	0.001
16-Hour	1.84 ±0.98	2.08 ±0.75	0.313
20-Hour	1.168 ±0.85	1.40 ±0.50	0.163
24-Hour	1.04 ±0.61	1.24 ±0.92	0.372
Overall 24-hour morphine consumption	15.08 ±4.55	27.80 ±2.51	0.001

Table III: Patients preoperative anxiety VAS, preoperative sedation and complications in Group-G (Gabapentin) and Group-P (Placebo). The data is presented as means ± SD and frequency. P-value of less than 0.05 ($p \leq 0.05$) is considered as significant.

Items	Group-G	Group-P	p-value
Anxiety VAS			
Pre-drug	5.80 ±1.11	6.08 ±1.28	0.416
Post-drug	3.52 ±1.00	6.28 ±1.24	0.001
Within group p-value	0.001	0.635	
Preoperative sedation POSS			
S/1/2/3/4	6/3/16/0/0	4/5/16/0/0	0.638
Complication			
Dizziness (yes / no)	3/22	5/20	0.440
Nausea / vomiting (No/nausea/vomiting)	20/4/1	16/6/3	0.398

DISCUSSION

The current clinical trial demonstrated that single oral dose of 1200 mg gabapentin resulted in reduction of postoperative pain scores, overall 24-hour morphine consumption and reduction in preoperative anxiety without serious side effects in obese patients undergone laparoscopic sleeve gastrectomy.

Postoperative pain management in obese patients is always a challenge for the anesthetist. Laparoscopic sleeve gastrectomy causes moderate to severe pain postoperatively.[3] Opioids administration in these patients, already at risk of obstructive sleep apnea, can have an increased effect of respiratory depression. The use of multimodal analgesia, drugs acting on different analgesic mechanism, are becoming popular.[10] Gabapentin was introduced as an anticonvulsant drug for the treatment of refractory partial seizures. Subsequently, it was found to be effective in variety of chronic pain conditions. In anesthesia practice, the multimodal roles of gabapentin were evaluated on preoperative anxiety, postoperative analgesia, postoperative opioid sparing effect, post-operative nausea and vomiting and delirium.[11] Gabapentin, as a pain modulator, was extensively studied for the postoperative pain and postoperative analgesia.[12]

Gabapentin is effective in controlling the postoperative pain and has inhibitory effect in the development of alodynia and hyperalgesia resulting from skin sensitisation.[13] Dahl *et al*. suggested that postoperative pain might be considered as reversible and transient type of neuropathic pain.[14] The analgesic effect of gabapentin seems to be related to the surgical procedure undertaken and more procedure-specific evaluation is needed for different types of surgeries. However, conflicting results were reported regarding its efficacy. Zakkar *et al*. performed a literature search of five identical studies in which gabapentin was used for reduction of pain after thoracic surgery.[6] They concluded that there was no evidence to support the role of

preoperative single dose of gabapentin in reducing post-operative pain scores and opioid consumption. Misra *et al*. showed that gabapentin premedication had no effect in reduction of postoperative pain scores and opioid consumption after craniotomies.[15] However, Ajori *et al*. showed that gabapentin premedication for hysterectomy patients significantly decreases the postoperative pain and analgesics requirements.[12] Similar outcome were achieved in orthopedic and lumbar spine surgery.[13,16]

The evidence regarding effects of pain modulator like gabapentin on postoperative pain and analgesics requirement after sleeve gastrectomy is sparse. In these patients, there was gradual reduction in pain scores and PCA morphine requirements in both groups and continued up to 12-hour postoperatively. In gabapentin group pain scores were in mild range as compared to control group, ranges in between mild to moderate. This may be due to the fact that orally administered gabapentin is absorbed by diffusion and in part by carrier mediated transport system. After a single oral dose, the mean plasma gabapentin concentration (C max) reaches approximately in 3 hours,[17] and elimination half-life is between 5-9 hours.[18] This may explain that the post-operative reduction in pain scores and morphine requirement effects lasted for 12 hours. Intraoperative infusion of remifentanil exacerbates postoperative pain and opioid consumption.[19]

Gabapentin is an effective anti-hyperalgesic agent for the preventive treatment of remifentanil-induced transient hyperalgesia.[20] In the gabapentin group, postoperative reduction in pain VAS and morphine requirements may be due to its anti-hyperalgesic effect. Another mechanism action of gabapentin for reduction of postoperative pain and analgesia requirement could be explained by the prevention and reduction of surgical procedure-induced development of central neuronal hyper excitability.[13] In this study, preoperative oral gabapentin was effective in decreasing the postoperative pain scores and opioid requirements in the immediate postoperative period.

Gabapentin has anti-hyperalgesic effect and has been reported as an anxiolytic agent. The promising approach in surgical patients is alleviation of preoperative anxiety as an adjunct to postoperative pain. However, mixed results were reported when gabapentin was used as premedication for the treatment of preoperative anxiety.[7] Adam *et al*. reported that 1200 mg gabapentin provided preoperative anxiolysis without casing sedation and impairing preoperative memory.[21] Clark *et al*. showed that 1200 mg gabapentin premedication was effective in reducing the anxiety numerical rating score and postoperatively pain catastrophising scores.[7] Josef *et al*. did not find any significant anxiolytic effect of gabapentin as compared to alprazolam.[22] Psychological stress revealed that anxiety and pain are well correlated.[23] The promising approach in surgical patients is alleviation of preoperative anxiety as an adjunct to postoperative pain. In this study, gabapentin premedication was found to be effective in reducing the preoperative anxiety.

It should be noted that this study was not powered to investigate the side effects of gabapentin. Gabapentin is considered to be a well-tolerated and safe agent.[20] However, the reported common side effects of gabapentin are somnolence, dizziness and lightheadedness. Gabapentin is known to reduce the preoperative anxiety, postoperative nausea vomiting and pruritus, at the expense of increased sedation.[24] The potential for dizziness and drowsiness has been discussed in literature, but no serious side effects have been reported in the acute pain studies.[5] Despite the use of relatively large dose of gabapentin, no significant difference in side effects were observed in these patients. Two patients in gabapentin group and four patients in placebo group received ondasetron for nausea and vomiting but the difference did not reach to the significance level.

The limitation of this study is that preoperative anxiety was assessed by using VAS instead of more commonly used tests in psychiatry, Amsterdam Preoperative Anxiety and Information Scale (APAIS) or State Trait Anxiety Inventory (STAI). However, in literature review it was shown that there is a positive correlation between VAS and other tests (APAIS and STAI) and VAS is easy and fast to use.[24]

CONCLUSION

Gabapentin premedication was effective in reducing the postoperative pain, morphine requirement and pre-operative anxiety in obese patients undergone laparo-scopic sleeve gastrectomy.

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