Original Article

A randomized double-blind placebo-controlled clinical study on the effects of gabapentin premedication on hemodynamic stability during laparoscopic cholecystectomy

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Abstract

Background: Carbon dioxide pneumoperitoneum for laparoscopic surgery increases arterial pressures, heart rate, and systemic vascular resistance. In this randomized double-blind placebo-controlled clinical study, we investigated the efficacy of gabapentin premedication to provide perioperative hemodynamic stability in patients undergoing laparoscopic cholecystectomy.

Materials And Methods: Sixty patients, of either sex (18–65 years of age) undergoing elective laparoscopic cholecystectomy were randomly allocated to two groups of 30 patients each. Patients of group G received oral gabapentin 900 mg 2 h before induction of anesthesia, while patients in group P received placebo at the same time.

Results: Mean arterial pressure in patients of group G were significantly lower ($P < 0.05$) after tracheal intubation and pneumoperitoneum and remained lower, as compared to group P, throughout the pneumoperitoneum. Similarly, heart rate in group G was significantly lower ($P < 0.05$) after tracheal intubation and pneumoperitoneum and remained lower, in comparison to group P, throughout the peumoperitoneum. Intravenous labetalol was required, to control intraoperative hypertension, in 33.3% (10 out of 30) patients in group P. There was no significant difference in the incidence of adverse effects between the two groups.

Conclusion: Gabapentin premedication provided perioperative hemodynamic stability during laparoscopic surgery.

Key words: Gabapentin, hemodynamics, laparoscopic surgery

Introduction

For laparoscopic surgical procedures, carbon dioxide (CO_2) is commonly used to create pneumoperitoneum.[1,2] CO_2 insufflation and pneumoperitoneum cause adverse cardiovascular effects such as abrupt elevation of arterial pressure, systemic vascular resistance, and decreased cardiac output.[3,4] The hemodynamic responses are due to increased release of catecholamines, vasopressin, or both.[5,6] Severe increases in arterial pressure and heart rate (HR) can be deleterious to patients with compromised cardiac function.[7] Attenuation of circulatory response to pneumoperitoneum is usually done by opioids,[8] vasodilators,[9] beta blocking agents,[10] and alpha2 adrenergic agonists.[11]Gabapentin, a newer antiepileptic drug, is commonly used in the perioperative period to reduce opioid requirements and to decrease postoperative pain.[12] 800 mg of gabapentin, administered orally before surgery, has been found to be effective in reducing the pressor response to laryngoscopy and endotracheal intubation.[13] We hypothesized that 900 mg of gabapentin, administered orally 2 h before the induction of anesthesia, would attenuate the hemodynamic response to laparoscopic surgery.

Materials and Methods

The study protocol was approved by the Institutional Ethical Committee and informed consent was taken from each of the patients. Sixty ASA grade I and II patients, aged 18–65 years, undergoing elective laparoscopic cholecystectomy, were randomly assigned to two groups containing 30 patients

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each. The group size of 30 was determined by power analysis based on standard deviation data from previously published reports. Patients with hypertension, morbid obesity, and severe hepatic, renal, endocrine, and cardiac dysfunction were excluded from the study. Patients with a history of dizziness or frequent headaches, currently taking sedatives or anticonvulsants, were also excluded.

Using a computer-derived random number sequence, 60 patients were allocated by means of sealed opaque envelopes into one of the two groups to receive either gabapentin 900 mg (group G) or placebo (group P). Similar looking vitamin B complex capsules were arranged for the placebo group to maintain blinding. The study drug was administered orally with sips of water 2 h before the induction of anesthesia and no other premedication was given. The anesthesiologist who administered anesthesia to the patient was unaware of the nature of study drug administered.

On arrival to operation theatre, routine monitoring (electrocardiogram, pulse oxymetry, and noninvasive blood pressure) was started and baseline vital parameters like HR, mean arterial blood pressure (MAP), and arterial oxygen saturation (SpO_2) were recorded. Level of sedation (sedation score) was assessed by sedation scale: 1 - awake and agitated; 2 - awake and comfortable; 3 - asleep, but arousable; 4 - asleep with sluggish response to persistent call or touch; and 5 - no response to call or touch.

An intravenous line (IV) was placed. Anesthesia was induced with fentanyl 2 mcg/kg and propofol 2 mg/kg IV. Endotracheal intubation was facilitated by rocuronium 0.7 mg/kg IV. Anesthesia was maintained with 33% O_2 in N_2O, 0.6% isoflurane, and rocuronium. CO_2 was insufflated into the peritoneal cavity to create pneumoperitoneum. Intra-abdominal pressure was maintained to 12 mmHg throughout the laparoscopic procedure. All the patients were positioned with a head-up tilt for about 15°. The lungs were mechanically ventilated to keep end-tidal carbon dioxide ($EtCO_2$) between 35 and 40 mmHg.

In case of acute and severe hemodynamic fluctuations, the following medical interventions were taken: for bradycardia (HR < 60 beats/min), bolus dose of atropine 0.6 mg IV; for hypotension (MAP < 60 mm Hg,) increased rate of infusion of IV fluid and/or bolus dose of phenylephrine 100 mcg IV and for hypertension (MAP > 110 mm Hg), bolus dose of labetalol 5 mg IV.

At the end of the operation, ondansetron 4 mg was administered for prophylaxis against nausea and vomiting. Residual neuromuscular block was reversed by appropriate dose of neostigmine and glycopyrrolate and tracheal extubation was performed. HR and MAP were recorded at the following points of time: 1 - prior to induction; 2 - 3 min after endotracheal intubation; 3 - before pneumoperitoneum; 4 - 15 min after pneumoperitoneum; 5 - 30 min after pneumoperitoneum; 6 - 10 min after release of pneumoperitoneum; and 7 - 10 min after extubation. Patients were observed for adverse events like dizziness, somnolence, bradycardia, hypotension, and hypertension during postoperative period in postanesthesia care unit. Somnolence was graded by Epiworth scale as: 0 - I never fall asleep or the probability to fall asleep is low; 1 - slight probability to fall asleep; 2 - moderate probability to fall asleep; or 3 - high probability to fall asleep.

Comparison between groups was performed with the Kruskal–Wallis one way ANOVA by ranks or Fisher's exact *test* for small samples with a 5% risk. Mann-Whitney-Wilcoxon tests were performed when tests of normal distribution have failed. P value < 0.05 was considered to be statistically significant [Graph Pad In Stat version 3.05, Graph Pad Software, San Diego, CA]

Results

Demographic profile and preoperative vital parameters were comparable between the two groups [Tables 1 and 2]. There was no significant difference in the preoperative MAP values and MAP values before induction between the two groups [Table 3]. MAP values in group G were significantly lower ($P < 0.05$) after tracheal intubation, before pneumoperitoneum and remained lower compared to group P, throughout the period of pneumoperitoneum. MAP value in group G was significantly lower after tracheal extubation too [Table 3].

There was no significant difference in the preoperative HR and HR before induction between the two groups [Table 4]. In group G, HR was significantly lower ($P < 0.05$) after tracheal intubation, before pneumoperitoneum and remained lower comparison to group P throughout the period of peumoperitoneum. In group G, HR was significantly lower after extubation too [Table 4].

Incidence of dizziness and somnolence was observed in a very few patients of group G, but it was not statistically significant ($P > 0.05$) [Table 4]. No patient, in either group, suffered from bradycardia or hypotension. Ten patients of group P received labetalol for treatment of intraoperative hypertension, whereas no patient in group G suffered from hypertension and this difference was statistically significant [Table 5].

Discussion

In laparoscopic surgery, CO_2 is routinely used to create

pneumoperitoneum.[1,2] Elevated intra-abdominal pressure, due to pneumoperitoneum, and CO_2 insufflation have adverse effects on the cardiovascular system.[3] Plasma level of catecholamines and vasopressin are increased immediately after pneumoperitoneum. Increased catecholamine level activates the renin–angiotensin–aldosterone system (RAAS), leading to characteristic hemodynamic alterations such as decreased cardiac output, elevated arterial pressure and increased systemic/pulmonary vascular resistance.[4,5] Vasopressin release also contributes to the elevation of arterial pressure and systemic vascular resistance.[6] Patients with normal hearts can cope with these changes but patients with compromised cardiac function may not be able to tolerate the hemodynamic changes..[7] Various drugs have been used to attenuate the hemodynamic responses to pneumoperitoneum during laparoscopic surgery. Beta-adrenergic blocking agents like esmolol[10] and alpha$_2$ agonists like clonidine[11] and dexmedetomidine[14] have been used to attenuate the rise in MAP and HR. A bolus dose of 50 mg/kg magnesium sulfate was administered intravenously before pneumoperitoneum was found to attenuate the hemodynamic and endocrine responses to pneumoperitonium during laparoscopic surgery. [15]Gabapentin (1-aminomethyl cyclohexane acetic acid) is structurally related to the neurotransmitter gamma-amino butyric acid (GABA). It is a second generation antiepileptic drug used in the treatment of neuropathic pain.[12] Gabapentin has an opioid sparing action as well. Gabapentin has been found to provide preoperative anxiolysis, prevent chronic postsurgical pain, attenuate stress responses to noxious perioperative stimuli, and prevent postoperative delirium, nausea, and vomiting.[12] Several studies have investigated the effect of gabapentin on hemodynamic alteration due to pressor responses. A single dose of 800 mg of gabapentin administered orally 1 h before surgery was found to attenuate the hemodynamic responses to laryngoscopy and intubation.[13] 1600 mg of gabapentin, administered in four divided doses (started the day before surgery), was found to attenuate the elevation of blood pressure due to laryngoscopy and tracheal intubation but not the HR.[16] 1000 mg oral gabapentin, administered 1 h before operation, significantly attenuated the hemodynamic response to laryngoscopy and endotracheal intubation.[17] 900 mg gabapentin, administered 2 h before induction of anesthesia, attenuated the adverse hemodynamic response to skull pin insertion in patients undergoing craniotomy.[18] The mechanism by which gabapentin attenuates the adverse hemodynamic response is unknown. The drug may act by inhibiting voltage gated calcium channels similar to calcium channel blockers.[19] The recommended dose of gabapentin is 900 mg, administered 1–2 h before surgery[12,18] and it is generally well tolerated having no serious side effects.[20] We selected 900 mg as the dose of oral gabapentin for our study.

Table 1: Demographic profile (mean ± SD)

	Group *G* (*n* = 30)	Group *P* (*n* = 30)	*P* value
Age (years)	39.4 ± 6.24	41.4 ± 6.86	0.58
Sex (M/F)	12/18	10/20	
Weight (kg)	54.44 ± 7.14	55.48 ± 8.62	0.64
Duration of surgery (min) 45.4 ± 6.24	44.36 ± 5.26	0.54	

Table 2: Preoperative vital parameters (mean ± SD)

	Group *G* (*n* = 30)	Group *P* (*n* = 30)	*P* value
Mean arterial pressure	93.4 ± 8.6	92.4 ± 6.8	0.28
Heart rate	80.6 ± 7.3	82.24 ± 6.6	0.32
Sedation Score	1.24 ± 0.42	1.32 ± 0.53	0.07

Table 3: Changes in mean arterial pressure (mean ± SD)

	Group *G*	Group *P*	Statistical significance
Before premedication	93.4 ± 8.6	92.32 ± 6.8	*P* > 0.05; NS
Before induction	88.2 ± 6.8	91 ± 8.4	*P* > 0.05; NS
After intubation	96.4 ± 9.6	108.4 ± 11.7	*P* < 0.05; S
Before PP	92.6 ± 10.8	102 ± 11.24	*P* < 0.05; S
15 min after PP	95.4 ± 10.4	109 ± 12.7	*P* < 0.05; S
30 min after PP	96.6 ± 11.6	108 ± 12.6	*P* < 0.05: S
10 min after release of PP	91.4 ± 9.2	104.8 ± 11.4	*P* < 0.05; S

P values were determined by comparing Group G and Group P.
PP = Pneumoperitoneum, S = Significant, NS = Not Significant

Table 4: Changes in heart rate (mean ± SD)

	Group G	Group P	Statistical significance
Before premedication	80.6 ± 7.3	82.24 ± 6.6	*P* > 0.05; NS
Before induction	78.6 ± 8.6	84.24 ± 6.2	*P* > 0.05; NS
After intubation	87.6 ± 10.44	101.2 ± 12.6	*P* < 0.05; S
Before PP	78.6 ± 9.4	94.4 ± 10.8	*P* < 0.05; S
15 min after PP	79.2 ± 8.8	99.4 ± 11.4	*P* < 0.05; S
30 min after PP	80.4 ± 10.4	98.8 ± 11.6	*P* < 0.05; S
10 min after release of PP	78.4 ± 9.6	88.2 ± 10.4	*P* < 0.05; S

P values were determined by comparing Group G and Group P.
PP = Pneumoperitoneum, S = Significant, NS = Not Significant

Table 5: Distribution of patients according to adverse effects. Values are in number

Adverse effects	Group *G*	Group *P*	Statistical significance
Dizziness	1	0	*P* > 0.05, NS
Somnolence	2	0	*P* > 0.05, NS
Bradycardia	0	0	*P* > 0.05, NS
Hypotension	0	0	*P* > 0.05, NS

S = Significant, NS = Not significant

In our study, baseline MAP and MAP before induction of anesthesia was comparable between the two groups. After

endotracheal intubation, MAP was significantly less in group G in comparison to group *P*. MAP were significantly lower throughout the period of CO_2 pneumoperitonium and after tracheal extubation in patients of group G compared to patients of group *P*. We observed similar finding in case of HR too. There was no significant difference in baseline HR and HR before induction between the two groups. In group G, HR was significantly lower after tracheal intubation and remained less throughout the period of pneumoperitonium and also after extubation.

A rise in intra-abdominal pressure (IAP) to 40 mmHg causes a 35% decrease in cardiac output in dogs.[21] Hemodynamic alterations were much less at 12 mmHg of IAP[22] and we kept the IAP 12 mmHg. Despite maintaining normocapnia and keeping IAP 12 mmHg, there was significant rise of MAP and HR after pneumoperitoneum in patients of group *P*. In group G, hemodynamic responses to pneumoperitoneum were effectively blunted and both MAP and HR remained at a significantly lower level compared to group *P*.

No patient of either group suffered from bradycardia and hypotension in our study. Hypertension occurred in 10 patients of group *P*, which was treated with labetalol but no patient of group G suffered from hypertension. There is no significant difference in the incidence of dizziness and somnolence between the two groups.

One limitation of our study was that it was conducted in normotensive ASA grade I and II patients without cardiac dysfunction and so the findings of the study are applicable to patients with no risk factors.

To conclude, we found that oral gabapentin attenuates the elevation of MAP and HR during and after pneumoperitoneum and thereby providing hemodynamic stability during laparoscopic surgery. As the results of this study are encouraging, we propose conducting a similar study with oral gabapentin in hypertensive patients and in patients with compromised cardiac function in future.

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