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Original Research Article

Comparing the Efficacy of Oral Pregabalin Premedication with Placebo on Stress Response in Patients Undergoing Laparoscopic Cholecystectomy After Creation of Pneumoperitoneum

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Abstract: *Hemodynamic fluctuations following pneumoperitoneum creation during laparoscopic cholecystectomy pose a challenge in anaesthesia management. Pregabalin, a gabapentinoid, has shown potential in attenuating this stress response.* ***Objective:*** *To compare the effects of oral pregabalin premedication with placebo on heart rate (HR) and mean arterial pressure (MAP) in patients undergoing laparoscopic cholecystectomy.* ***Methodology:*** *This prospective study was conducted at the Department of Anesthesiology, Nishtar Medical University and Hospital, Multan, from June 23, 2023, to December 22, 2023. Sixty patients were randomly assigned to two groups: Group A received 150 mg of oral pregabalin one hour before general anaesthesia, while Group B received a placebo. Standard intraoperative monitoring was used, and HR, systolic blood pressure (SBP), diastolic blood pressure (DBP), and MAP were recorded. Data were analysed using SPSS version 27, and an independent sample t-test was used to compare hemodynamic parameters between the two groups, with a significance level of p<0.05.* ***Results:*** *After five minutes of pneumoperitoneum creation, Group A had significantly lower HR (78.23 ± 5.03 bpm vs. 87.50 ± 5.73 bpm, p<0.001), MAP (91.73 ± 5.06 mmHg vs. 100.79 ± 5.33 mmHg, p<0.001), SBP (121.20 ± 8.34 mmHg vs. 131.57 ± 8.59 mmHg, p<0.001), and DBP (77.00 ± 5.64 mmHg vs. 85.40 ± 5.33 mmHg, p<0.001) compared to Group B.* ***Conclusion:*** *Oral pregabalin premedication effectively attenuates the hemodynamic stress response following pneumoperitoneum creation in laparoscopic cholecystectomy. Its use as a premedication can enhance perioperative hemodynamic stability.*

Keywords: Pregabalin, Hemodynamics, Pneumoperitoneum

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Introduction

Laparoscopic cholecystectomy has emerged as a widely accepted substitute to open surgery, mainly due to its advantages, which include shorter procedure time, improved cosmetic outcomes, and quicker hospital discharge. This technique necessitates the creation of a pneumoperitoneum, which enhances visibility and facilitates the surgeon in instrument handling within the abdominal cavity. However, pneumoperitoneum can also have an impact on the hemodynamic responses. (1) Carbon dioxide (CO2) is commonly used to create pneumoperitoneum during laparoscopic procedures. Still, its insufflation is related to hostile cardiovascular events, such as increased heart rate, blood pressure and systemic vascular resistance (SVR). These effects are attributed to the elevated levels of vasopressin and catecholamines (2) and increased intra-abdominal pressure.

Various approaches have been adopted to alleviate the hemodynamic stress responses caused by pneumoperitoneum, including low-pressure pneumoperitoneum (3) and the use of medications like gabapentin, (2) magnesium sulfate, (4) clonidine, (5) and dexmedetomidine. (6) Pregabalin is another effective option for reducing this response via its inhibitory action on the voltage-gated calcium channels. Pregabalin binds selectively with high affinity to the α-2-delta subunit of the hyperactive calcium channels, reducing neurotransmitters such as noradrenaline, substance P and glutamate. (3)

A study was conducted involving 64 adult patients aged 30–60 and divided into two equal groups: A(pregabalin) and B (placebo). The results of the study showed that at 3 minutes after the creation of the pneumoperitoneum, MAP was significantly lower in Group A (93.37 ± 3.66 mmHg) as compared to Group B (99.81 ± 2.40 mmHg) (p <0.001). Similarly, heart rate (HR) was also significantly lower in Group A (79.43 ± 5.28 bpm) as compared to Group B (105.96 ± 7.82 bpm), with a p-value of <0.001. (7)

Another study (8) was conducted in India, which comprised 60 patients 18–65 years of age and of either gender. The findings of that study revealed that, at 3 minutes post-laryngoscopy, SBP was significantly lower in the group which took pregabalin (116.1 ± 23.24 mmHg) as compared to the control group (133.23 ± 6.86 mmHg), with a p-value of 0.0003. That study determined that pregabalin effectively controls hemodynamic stress responses associated with laryngoscopy, tracheal intubation, and extubation.

Previous studies have reported that premedication with pregabalin attenuates the stress response on tracheal intubation, extubation and CO2 insufflation (7-9). however, more data must be collected on hemodynamic changes during laparoscopic cholecystectomy after creating pneumoperitoneum. The current study was planned to evaluate the effect of oral pregabalin on hemodynamic stability, including heart rate, MAP, SBP and DBP, after creating pneumoperitoneum. This study is expected to support the anesthesiologists in maintaining better hemodynamics during laparoscopic procedures.

Methodology

This randomised controlled trial was performed in the Department of Anesthesiology, Nishtar Medical University and Hospital Multan from 23-06-2023 to 22-12-2023, after approval from the IRB. The sample size was calculated using OpenEpi software, with the mean arterial pressure of two groups from the study by Allu H et al. (9): Group A=94.60 ± 14.77, and Group B=108.62 ± 14.24. The power of the study was 80%, and the confidence interval was 95%. There were 34 of us, but we selected 60 patients using the nonprobability consecutive sampling technique.

All the patients of both male and female gender, 30-60 years of age, with ASA-I and ASA-II, and planned to undergo laparoscopic cholecystectomy were included in the study. Patients who were known cases of Hypertension (consecutive readings > 140/90) and diabetes (HbA1c > 6.5%), CCF (ejection fraction < 35%), and those taking beta-blockers, antihypertensives or oral Pregabalin for the past 3 months were excluded.

Using the lottery method, sixty adult patients were assigned randomly to the two treatment groups, A and B, with 30 patients each. Baseline data, including age, gender, weight, and residential area, were noted. Group A was given 150 mg of pregabalin orally with a few sips of water about 60 minutes before the general anaesthesia in the holding area was administered to achieve maximum therapeutic concentration during induction. Control Group B was given a placebo capsule of the same shape and size.

Standard monitoring, such as pulse, SpO2, ECG, NIBP, and etCO2, was used. All patients were given general anaesthesia using standard anaesthetic doses by a consultant anesthesiologist as per hospital protocols. HR, SBP, DBP and MAP were recorded on the proforma before induction of anaesthesia (baseline value) and just before the creation of pneumoperitoneum and thereafter at 2 min, 5 min and then at every 10 min till 45 min of pneumoperitoneum and 5 min after release of pneumoperitoneum by an anesthesiologist with at least 3 years of experience.

Data was analysed by SPSS 27. Quantitative data, i.e. hemodynamic variables, age and weight, represented by mean ± SD in tabular form. HR, SBP, DBP and MAP, after 5 minutes of creating pneumoperitoneum, were compared between 2 study groups by applying a student t-test and a P-value of 0.05 was taken as significant. Effect modifiers like age, gender, residential area and weight were controlled through stratification. Post-stratification student t-test was used for comparison, and P <0.05 was significant.

Results

The study sample had 60 patients and was divided into two groups. Both experimental and control groups were comparable in terms of mean age, wean weight, gender, and residential area distribution (p values 0.468, 0.166, 0.573, and 0.405, respectively). Table-I

After 5 minutes of pneumoperitoneum creation, mean HR was 78.23 ± 5.03 bpm and 87.50 ± 5.73, mean MAP was 91.73 ± 5.06 mmHg and 100.79 ± 5.33 mmHg, mean SBP was 121.20 ± 8.34 mmHg and 131.57 ± 8.59 mmHg, and mean DBP was 77.00 ± 5.64 mmHg and 85.40 ± 5.33 mmHg in group A and group B, respectively($p<0.001$). Table-2

After stratification of outcome data based on age, gender, residential area and weight of the patients, the observed differences in the outcome variables were also significant ($p<0.05$). Table-III experienced burnout, which was associated with stress experienced at work. However, patient satisfaction was not associated with burnout or stress levels of nurses. Duration of patient stay was inversely related to stress score in nurses; the longer the hospital stay, the lower the stress (r= -0.40, $p<0.01$). Similarly, the longer the hospital stay, the lower the cynicism score among nurses (r= -0.36, $p<0.01$) Table 3.

Table 1: Demographic data

Variable	Group A (N=30)	Group B (N=30)	*P* value
Age, years	47.30 ± 8.64	48.83 ± 7.57	0.468
Weight, kg	63.47 ±13.29	58.83 ± 12.29	0.166
Gender, N (%)			
Male	10 (33.3 %)	8 (26.7 %)	0.573
Female	20 (66.7 %)	22 (73.3 %)	
Residencial status, N (%)			
Urban	22 (73.3 %)	19 (63.3 %)	0.405
Rural	8 (26.7 %)	11 (36.7 %)	

Data is entered as mean ± S.D. unless mentioned otherwise.

Table 2: Hemodynamic variables after 5 minutes of pneumoperitoneum creation

Variable	Group A (N=30)	Group A (N=30)	*P* value
HR	78.23 ± 5.03	87.50 ± 5.73	<0.001
MAP	91.73 ± 5.06	100.79 ± 5.33	<0.001
SBP	121.20 ± 8.34	131.57 ± 8.59	<0.001
DBP	77.00 ± 5.64	85.40 ± 5.33	<0.001

Data is entered as mean ± S.D.

Table 3: Assessment of hemodynamic responses after stratification of data

Effect modifier	Subgroup	Variable	Group A (N=30)	Group B (N=30)	*P* value
Age, years	30-45	HR	76.67±5.12	86.91±4.74	<0.001
		MAP	92.15±5.40	100.63±4.96	<0.001
		SBP	122.20±8.74	130.63±9.75	0.029
		DBP	77.13±5.72	85.64±4.80	<0.001
	45-60	HR	79.80±4.58	87.84±6.33	<0.001
		MAP	91.31±4.85	100.88±5.66	<0.001
		SBP	120.20±8.11	132.11±8.08	<0.001
		DBP	76.87±5.75	85.26±5.73	<0.001
Gender Gender	Male	HR	77.90±4.95	85.25±2.49	0.002
		MAP	90.03±5.11	100.87±4.96	<0.001
		SBP	117.30±7.80	131.12±7.26	0.001

		DBP	76.40±6.45	85.75±5.55	0.005
	Female	HR	78.40±5.19	88.32±6.38	<0.001
		MAP	92.58±4.94	100.76±5.57	<0.001
		SBP	123.15±8.09	131.73±9.18	0.003
		DBP	77.30±5.34	85.27±5.37	<0.001
Residence	Urban	HR	78.22±5.24	86.84±5.65	<0.001
		MAP	90.95±5.15	102.24±5.27	<0.001
		SBP	119.68±8.43	134.00±8.33	<0.001
		DBP	76.59±5.63	86.37±5.52	<0.001
	Rural	HR	78.25±4.77	88.64±5.97	<0.001
		MAP	93.87±4.41	98.27±4.62	0.052
		SBP	125.37±6.95	127.36±7.64	0.569
		DBP	78.12±5.89	83.73±4.75	0.035
Weight, kg	≤55	HR	78.83±5.15	86.56±5.74	0.001
		MAP	91.63±6.04	99.25±5.15	0.001
		SBP	120.42±10.33	129.62±8.06	0.013
		DBP	77.25±6.07	84.06±5.37	0.005
	>55	HR	77.83±5.07	88.57±5.75	<0.001
		MAP	91.79±4.48	102.55±5.14	<0.001
		SBP	121.72±7.01	133.78±8.93	<0.001
		DBP	76.83±5.50	86.93±5.03	<0.001

Data is entered as mean ± S.D.

Discussion

Preoperative medication and psychological preparation are essential components of anaesthetic management. A modified approach tailored to each patient has replaced the routine use of identical drugs for all patients. Premedication serves multiple purposes, including the alleviation of anxiety, promoting sedation, controlling the autonomic stress responses, reducing postoperative nausea and vomiting as well as shivering, lowering anaesthetic dose requirements, and minimising gastric secretions. Ongoing research aims to identify an ideal premedication agent to help achieve these goals with the least adverse effects. To mitigate the hemodynamic disturbances caused by laryngoscopy, endotracheal intubation, and pneumoperitoneum during laparoscopic cholecystectomy, various strategies have been explored, which include deepening the anaesthesia plane and employing a range of drugs as premedication, with varying degrees of success. (5, 10-13)

The current study observed that after 5 minutes of pneumoperitoneum creation, mean HR, MAP, SBP, and DBP were 78.23 ± 5.03 bpm, 91.73 ± 5.06 mmHg, 121.20 ± 8.34 mmHg and 77.00 ± 5.64 mmHg in pregabalin group as compared to 87.50 ± 5.73 bpm, 100.79 ± 5.33 mmHg, 131.57 ± 8.59 mmHg and 85.40 ± 5.33 mmHg in the placebo group, respectively, with statistically significant difference (p<0.001). A study involved 64 adult patients aged 30–60 and divided into two equal groups. The results of the study showed that at 3 minutes after the creation of pneumoperitoneum, MAP was significantly lower in the pregabalin group (93.37 ± 3.66 mmHg) as compared to the placebo group (99.81 ± 2.40 mmHg) (p <0.001). Similarly, HR was also significantly lower in the pregabalin group (79.43 ± 5.28 bpm) as compared to the placebo group (105.96 ± 7.82 bpm), with a p-value of <0.001. (7)Allu et al. (9), in their study, observed that 5 minutes after pneumoperitoneum creation, the control group showed a percentage increase in HR and MAP of +24% and +26%, respectively, compared to +4% and +0.8% in the pregabalin group, (p <0.05).

Pregabalin effects have also been compared with those of clonidine and control groups. In the study by Jain Met al. (14), the findings showed a significant increase in HR, SBP, DBP, and MAP in the control group as compared to the pregabalin and clonidine groups. HR was significantly lower in the clonidine group following extubation than in the control and pregabalin groups. Although clonidine demonstrated superior hemodynamic stability, pregabalin (150 mg) effectively controlled hemodynamic parameters during laparoscopic cholecystectomy.

Suryawanshi C et al. (15) also compared pregabalin with clonidine. Their study showed that HR, SBP, DBP and Map were 68.13±2.9 bpm, 110.1±3.14 mmHg, 74.6 ±3.7 mmHg and 82.7±2.7 mmHg in the clonidine group while 71.3±4.63bpm (p =0.002),108.7±5.91 mmHg (p <0.001), 69.07 ±3.4 mmHg (p <0.001) and 80.1±2.7 mmHg (p <0.001) in the pregabalin group, after 3 minutes of CO2 insufflation. Although oral pregabalin and oral clonidine effectively promoted intraoperative hemodynamic stability by controlling the stress response to laryngoscopy, intubation, and pneumoperitoneum, pregabalin demonstrated superior hemodynamic control.

Pal RK et al. (16) also compared clonidine vs pregabalin, but their observed results showed no noteworthy differences in the hemodynamic parameters after 5 minutes of pneumoperitoneum creation. Their results were HR (85.8 ± 10.5 bpm vs. 84.3 ± 9.6 bpm, p = 0.51), MAP (86.4 ± 6.4 mmHg vs. 87.9 ± 5.9 mmHg, p = 0.32), SBP (120.3 ± 8.2 mmHg vs. 124.0 ± 8.6 mmHg, p = 0.08), and DBP (69.3 ± 5.9 mmHg vs. 69.8 ± 5.2 mmHg, p = 0.71) in the clonidine and pregabalin groups, respectively.

Patodi V et al. (17) compared two doses of pregabalin, i.e., 75mg and 150 mg. They observed that the reduction in mean HR was similar between the two groups (p >0.05). In contrast, a significant decrease was observed in SBP, DBP and MAP between the groups (p < 0.05). Oral pregabalin at 150 mg was significantly more effective than the 75 mg dose in controlling the hemodynamic stress responses to laryngoscopy and endotracheal intubation.

Rathore et al. (18) also led a study to evaluate the effectiveness of oral pregabalin (75 mg) and oral clonidine (300 µg) as premedication for controlling the stress response to laryngoscopy and endotracheal intubation. Medicine was administered 2 hours before surgery. Their study found a significant increase in HR and MAP in the pregabalin group post-laryngoscopy and tracheal intubation compared to the clonidine group. Clonidine proved to be more efficacious than pregabalin in suppressing the pressure response. Their contradictory findings can be attributed to the time of drug administration and the lower dose of pregabalin used.

Conclusion

Pregabalin is an effective option for controlling hemodynamic stress response observed after the creation of pneumoperitoneum.

Declarations

Data Availability statement
All data generated or analysed during the study are included in the manuscript.
Ethics approval and consent to participate
Approved by the department concerned. (IRBEC-MMNCS-0331d-24)
Consent for publication
Approved
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Not applicable

Conflict of interest

The authors declared the absence of a conflict of interest.

Author Contribution

IA (PGR), MAF (Associate Professor),
Manuscript drafting, Study Design,
MUM (Associate Professor)
Review of Literature, Data entry, Data analysis, and drafting article.
MKS (Associate Professor), *Conception of Study, Development of Research Methodology Design,*
AS (SR), MA (Associate Professor)
Study Design, manuscript review, critical input.

All authors reviewed the results and approved the final version of the manuscript. They are also accountable for the integrity of the study.

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