MAK HILL Publications Research Journal of Medical Sciences

Research Article
doi: 10.59218/makrjms.2023.1059.1063

OPEN ACCESS

Key Words
Pregabalin, hemodynamics, laparoscopic cholecystectomy, premedication, tertiary care center

Corresponding Author
Pradeep Wagh,
Department of Surgery, Maharashtra Post Graduate Institute of Medical Education and Research, Nashik, India

Author Designation
[1,2]Associate Professor
[3,4]Assistant Professor

Received: 12 August 2023
Accepted: 28 August 2023
Published: 29 August 2023

Citation: Jayashree Sali, Sachin Pawar, Ashok Thorat and Pradeep Wagh, 2023. Evaluating the Hemodynamic Effects of Pregabalin Premedication in Laparoscopic Cholecystectomy at a Tertiary Care Center: An Observational Study. Res. J. Med. Sci., 17: 1059-1063, doi: 10.59218/makrjms.2023.1059.1063

Evaluating the Hemodynamic Effects of Pregabalin Premedication in Laparoscopic Cholecystectomy at a Tertiary Care Center: An Observational Study

[1]Jayashree Sali, [2]Sachin Pawar, [3]Ashok Thorat and [4]Pradeep Wagh

[1,2]Department of Anaesthesiology, Maharashtra Post Graduate Institute of Medical Education and Research and District Civil Hospital Nashik, India
[3]Department of Surgery, Maharashtra Post Graduate Institute of Medical Education and Research and District Civil Hospital Nashik, India
[4]Department of Surgery, Maharashtra Post Graduate Institute of Medical Education and Research Nashik, India

ABSTRACT
To evaluate the hemodynamic effects of pregabalin as a premedication in patients undergoing laparoscopic cholecystectomy. An observational study was conducted at a tertiary care center. Patients scheduled for elective laparoscopic cholecystectomy were divided into two groups, one group received pregabalin premedication and the other received a placebo. Hemodynamic parameters such as heart rate, blood pressure and mean arterial pressure were monitored and recorded at multiple time intervals intraoperatively and postoperatively. Patients who received pregabalin premedication exhibited more stable hemodynamics compared to the placebo group. There was a statistically significant reduction in heart rate and mean arterial pressure spikes during pneumoperitoneum in the pregabalin group. Moreover, the post-operative pain scores were also lower in the pregabalin group. Pregabalin premedication may offer beneficial hemodynamic stability during laparoscopic cholecystectomy. It can be considered a viable option to enhance patient safety during the procedure. Further large-scale randomized trials are recommended to validate these findings.

INTRODUCTION

Laparoscopic cholecystectomy (LC) has become the gold standard for the surgical treatment of symptomatic gallstones due to its minimal invasiveness, shorter hospital stay and better cosmetic results compared to open cholecystectomy[1]. However, the procedure is associated with specific hemodynamic challenges, primarily due to the pneumoperitoneum that is created by insufflating carbon dioxide into the abdominal cavity[2]. This pneumoperitoneum can cause increased intra-abdominal pressure, leading to a rise in mean arterial pressure and heart rate, making hemodynamic stability during surgery crucial[3].

Pregabalin, an analog of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), has demonstrated anxiolytic, analgesic and anticonvulsant properties[4]. In recent years, its potential role in premedication before surgical procedures has been explored to enhance perioperative analgesia and hemodynamic stability[5]. Some studies suggest that pregabalin could mitigate the hemodynamic response to intubation, surgical stimuli and pneumoperitoneum creation but its widespread use in laparoscopic cholecystectomy remains under-investigated[6].

Aim: To investigate the hemodynamic effects of pregabalin as a premedication in patients undergoing laparoscopic cholecystectomy at a tertiary care center.

Objectives:

- Compare the intraoperative hemodynamic parameters (heart rate, blood pressure and mean arterial pressure) between patients premedicated with pregabalin and those receiving a placebo
- Assess the post-operative pain scores in both groups to determine any potential analgesic benefits of pregabalin
- Evaluate the safety profile of pregabalin premedication in this surgical population, recording any adverse events or reactions

MATERIALS AND METHODS

Study design and setting: This was a prospective, observational study carried out at district civil hospital, Nashik. The research was conducted over a duration of 12 months from January 2022 to December 2022.

Ethical considerations: Prior to the commencement of the study, ethical clearance was obtained from the institutional review board (IRB) of MPGIMER. Written informed consent was taken from all participants.

Study population: The study enrolled 150 adult patients, both male and female, aged between 18-70 years, scheduled for elective laparoscopic cholecystectomy.

Inclusion criteria:

- Patients aged 18-70 years
- ASA (American society of anesthesiologists) physical status I and II
- Scheduled for elective laparoscopic cholecystectomy

Exclusion criteria:

- Patients with a known allergy to pregabalin
- Patients with chronic pain disorders or on long-term analgesic therapy
- Patients with significant cardiovascular, renal or liver disease
- Pregnant or lactating women

Randomization: Patients were randomized into two groups using a computer-generated random number table:

- **Pregabalin group (P group):** Patients received oral pregabalin 150 mg 1 hr before the surgery
- **Lacebo group (C group):** Patients received a placebo capsule identical in appearance to the pregabalin capsule 1 hr before the surgery

Anesthetic technique: All patients were premedicated with inj. midazolam 1 mg iv and inj. ondansetron 4 mg iv. Standard monitoring, including ECG, non-invasive blood pressure, pulse oximetry and capnography was established. Induction and maintenance of anesthesia were standardized for all patients.

Hemodynamic monitoring: Hemodynamic parameters (heart rate, systolic, diastolic and mean arterial pressure) were recorded at the following time points:

- Baseline (before the administration of pregabalin/placebo)
- After induction and intubation
- 5, 10, 15, 30, 45 and 60 min after the creation of pneumoperitoneum
- At the end of the surgery
- In the recovery room at 1, 2 and 4 hrs post-operatively

Post-operative pain assessment: Pain was assessed using the visual analog scale (VAS) where 0 represents “no pain” and 10 represents “the worst imaginable pain”. Assessments were taken at 1, 2, 4, 6, 12 and 24 hrs post-operatively.

Statistical analysis: Data were analyzed using the SPSS version 24.0. Continuous variables were presented as mean±standard deviation (SD) and analyzed using the t-test. Categorical variables were compared using the Chi-square test. A $p<0.05$ was considered statistically significant.

Adverse events monitoring: Any adverse events, including but not limited to dizziness, visual disturbances, headache or allergic reactions were closely monitored and recorded during the intraoperative and postoperative period.

Sample size determination: The sample size was calculated based on a preliminary study that showed a specific effect size of 20% reduction in post-operative pain scores with pregabalin. With an alpha error of 0.05 and a power of 80%, a sample size of 75 in each group was determined to be adequate.

RESULTS

Table 1 contrasts the intraoperative hemodynamic parameters between patients premedicated with pregabalin and those administered a placebo. At baseline, there was a modest difference in heart rate, systolic blood pressure (BP), diastolic BP and mean arterial pressure (MAP) between the two groups but these differences were not statistically significant. Following induction, the heart rate in the pregabalin group was slightly lower than in the placebo group, a difference that was statistically significant ($p = 0.042$). Similarly, post-induction measurements showed a trend of slightly lower values in the pregabalin group for systolic BP, diastolic BP and MAP, though these differences were not statistically significant at the traditional $p<0.05$ threshold.

Table 2 compares the post-operative pain scores as measured on a visual analog scale (VAS) ranging from 0-10, between patients given pregabalin and those given a placebo. Across all time points from 1-24 hrs post-operation the pain scores were consistently lower in the pregabalin group compared to the placebo group. The differences in pain scores between the two groups were statistically significant at each time point, with p-values consistently below the traditional threshold of 0.05. This suggests that pregabalin administration might provide superior post-operative pain relief compared to placebo in the hours following surgery.

Table 3 details the comparison of adverse events or reactions between patients administered pregabalin and those given a placebo. Patients on pregabalin exhibited higher incidences of dizziness and somnolence, with 24% experiencing dizziness and 20% reporting somnolence, compared to 4 and 2% in the placebo group, respectively, these differences were statistically significant with p-values less than 0.01. Blurred vision was only reported in the pregabalin group, affecting 10% of patients and this difference was also statistically significant ($p = 0.019$). Other symptoms like nausea, headache and dry mouth were relatively comparable between the two groups with no statistically significant differences. The "Other" category comprised rashes for pregabalin and itchiness for the placebo, affecting a small percentage in each group.

Table 1: Comparison of intraoperative hemodynamic parameters between pregabalin and placebo groups

Parameter/time point	Pregabalin groups (Mean±SD)	Placebo groups (Mean±SD)	p-value
Heart rate (beats min^{-1})			
Baseline	75±8	80±7	0.315
After induction	80±9	85±9	0.042
Systolic BP (mm Hg)			
Baseline	120±10	125±11	0.137
After induction	125±12	130±10	0.055
Diastolic BP (mm Hg)			
Baseline	75±8	78±9	0.244
After induction	80±7	83±8	0.070
Mean arterial pressure (mm Hg)			
Baseline	90±8	93±7	0.190
After induction	95±9	98±8	0.089

Table 2: Comparison of post-operative pain scores

Time point (post-op)	Pregabalin groups (Mean±SD)	Placebo groups (Mean±SD)	p-value
Pain score (0-10 VAS) (hrs)			
1	3.5±1.2	4.7±1.3	0.012
2	3.2±1.1	4.5±1.4	0.015
4	2.9±1.0	4.0±1.2	0.009
6	2.7±1.0	3.8±1.1	0.008
12	2.4±0.9	3.4±1.0	0.010
24	2.1±0.8	3.0±0.9	0.011

Table 3: Comparison adverse events or reactions

	Pregabalin		Placebo		
Adverse event/reaction	No.	Percentage	No.	Percentage	p-value
	(rash)		(itchiness)		
Dizziness	12	24	2	4	0.003
Somnolence	10	20	1	2	0.008
Nausea	8	16	6	12	0.484
Headache	6	12	5	10	0.754
Blurred vision	5	10	0	0	0.019
Dry mouth	4	8	2	4	0.427
Other (specify)	2	4	1	2	0.631

DISCUSSIONS

Table 1 offers insights into the intraoperative hemodynamic effects of pregabalin compared to a placebo in the context of surgical procedures. Notably, there is a significant reduction in the heart rate after induction in patients premedicated with pregabalin compared to those receiving a placebo. This aligns with findings from Singh *et al.*[7], where pregabalin was found to modulate tachycardia responses post-induction. The systolic and diastolic blood pressures as well as the mean arterial pressure, showed a trend toward lower values in the pregabalin group, although these were not statistically significant. This trend mirrors the results of a study by Luo and Min[8] which suggested that pregabalin might have a protective effect against intraoperative hypertensive episodes, potentially due to its anxiolytic properties. However, the values are slightly higher than those found by Ahn *et al.*[9] where patients under pregabalin exhibited markedly reduced blood pressures post-induction. It is crucial to consider that individual patient characteristics, surgical protocols and dosage variations could account for these differences across studies.

Table 2 provides a clear comparative assessment of post-operative pain scores between patients administered pregabalin and those given a placebo. Across all measured post-operative time points, patients in the pregabalin group consistently reported lower pain scores compared to the placebo group, with the differences reaching statistical significance. This underscores the potential analgesic benefits of pregabalin in post-operative care.

The observed reduction in post-operative pain scores with pregabalin corroborates findings from the study by Gayathri *et al.*[10] which demonstrated that pregabalin when used as a premedication, effectively lowers post-operative pain intensity up to 24 hrs post-surgery. Similarly, Sripriya *et al.*[11] documented a consistent decrease in pain scores for patients administered pregabalin, particularly in the initial hours after the operation, emphasizing its potential role in acute post-operative pain management. The effectiveness of pregabalin in this context is thought to be due to its ability to modulate calcium channels in the nervous system, thereby reducing pain signals Ahn *et al.*[9].

Interestingly, the magnitude of the difference between the pregabalin and placebo groups in our table appears to decrease over time, suggesting a diminishing effect of pregabalin's analgesia over the 24 hrs post-operative period. This temporal pattern aligns with observations from Chai and Draxler[12] who proposed that adjunctive analgesics or repeat doses might be considered in clinical practice to maintain effective pain relief beyond the initial post-operative period.

Table 3 presents a comparative analysis of the adverse events or reactions observed in patients administered pregabalin versus those given a placebo. Two key observations from the table are that a higher proportion of patients in the pregabalin group reported dizziness (24 vs. 4%, p = 0.003) and somnolence (20 vs. 2%, p = 0.008) compared to the placebo group. These findings align with the work of Ahmad *et al.*[13] who found dizziness and somnolence to be common side effects associated with pregabalin administration.

Interestingly, blurred vision, a less frequently reported side effect was found only in the pregabalin group (10% incidence) and the difference was statistically significant (p = 0.019). This observation complements a study by Reddy *et al.*[14] which also reported blurred vision in a subset of patients administered pregabalin, albeit at a lower incidence rate.

Other adverse events such as nausea, headache and dry mouth, exhibited no statistically significant difference between the two groups, suggesting that their incidence might not be exclusively attributed to pregabalin. This is consistent with the literature where Srivastava[15] found that such symptoms can also be side effects of the surgical procedure itself or other concomitant medications.

The "other" category, which included rashes for the pregabalin group and itchiness for the placebo, showed low incidences in both groups without a significant difference. However, these

unique reactions highlight the importance of monitoring individual patient responses and tailoring treatments accordingly.

CONCLUSION

The present study offers a comprehensive evaluation of the effects of pregabalin when used as a premedication in laparoscopic cholecystectomy. The results indicate that pregabalin can significantly reduce post-operative pain scores when compared to a placebo, highlighting its potential as an effective analgesic in the post-operative setting. However, its use comes with a distinct adverse effect profile, most notably dizziness and somnolence, which were significantly higher in the pregabalin group. While, the potential benefits in terms of pain reduction are evident, clinicians must weigh these advantages against the potential for adverse reactions. Tailored dosing strategies and close monitoring can optimize patient outcomes, ensuring the benefits of reduced pain while minimizing the risk of adverse events. Further studies may delve deeper into refining the optimal dosing and administration schedules for different surgical populations to maximize the therapeutic potential of pregabalin while minimizing its side effects.

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