Original Research Article

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# Comparison between Oral Clonidine and Oral Gabapentin as Pre-Emptive Analgesic on Reducing Post Operative Analgesic Requirement in Laparoscopic Cholecystectomy

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## ABSTRACT

**Introduction:** Laparoscopic cholecystectomy is commonly associated with significant postoperative pain, which requires effective analgesic strategies to enhance patient comfort and recovery. Multimodal preemptive analgesia using adjuvant drugs such as clonidine and gabapentin has gained increasing attention for improving postoperative pain control and reducing opioid consumption. Therefore, this study was designed to compare the efficacy of oral clonidine and oral gabapentin in attenuating postoperative pain and analgesic requirements in patients undergoing elective laparoscopic cholecystectomy under general anaesthesia.

**Methods:** This randomized controlled, double-blind investigation was carried out in the Department of Anesthesiology at Bangladesh Medical College Hospital (BMCH) in Dhaka, from April 2022 to September 2022. A total of 60 individuals diagnosed with cholelithiasis scheduled for elective laparoscopic cholecystectomy under general anesthesia were randomly divided into two equal cohorts ($n = 30$ each): Group C was administered oral clonidine at a dosage of 100 µg, whereas Group G was given oral gabapentin at a dosage of 600 mg.

**Result:** Baseline characteristics including age (34.5 ± 4.43 vs 35.4 ± 5.02 years, $P = 0.72$), sex ($P = 0.41$), weight (70.87 ± 12.66 vs 72.67 ± 14.01 kg, $P = 0.44$), and ASA status ($P = 0.83$) were comparable between Group C (clonidine) and Group G (gabapentin). Postoperative VAS scores were significantly lower in Group G at 8 hours and higher in Group C at 12 hours, with no differences at 4 and 24 hours. Gabapentin significantly prolonged the time to first analgesic requirement and reduced total analgesic consumption compared to clonidine ($P = 0.03$ and $P = 0.04$, respectively).

**Conclusion:** The paper at hand shows that pre-emptive Gabapentin enhances and extends the duration of analgesia after surgery by postponing the time of the first dose of analgesic and lowering the amount of analgesic taken, without any harmful changes in haemodynamic status and no side effects against Clonidine, when administered 1 hour before the surgery.

**Keywords:** Clonidine, gabapentin, laparoscopic cholecystectomy

## Introduction

Laparoscopic cholecystectomy as a significant achievement in contemporary surgical treatment. It has also evolved into a crucial element of outpatient and same-day surgeries; therefore, it necessitates a balanced anesthetic approach to provide a seamless post-operative recovery.[1] Post-laparoscopic cholecystectomy, pain remains a significant concern.[2] The bodily trauma resulting from surgery elicits a multifaceted stress reaction that exacerbates the sensation of postoperative discomfort.[3] Opioids continue to be the cornerstone of postoperative pain management; still, their adverse effects, including respiratory depression, nausea, vomiting, pruritus, and prolonged recovery of bladder and stool function, are unfavorable. Alternative approaches, including Nonsteroidal anti-inflammatory medicines (NSAIDs), are employed for postoperative pain relief, although they may lead to gastrointestinal mucosal injury, hemorrhage, renal toxicity, allergic responses, and cardiac failure. Selective cyclooxygenase-2 nonsteroidal anti-inflammatory drugs has pro-thrombotic characteristics and elevate the likelihood of stroke and myocardial ischemia. A comprehensive strategy is suggested to alleviate postoperative discomfort and minimize medication-related adverse effects. Given that surgical stimulation correlates with both peripheral and central sensitization, anti-hyperalgesic medications can alleviate postoperative pain by inhibiting hypersensitivity within the central nervous system.[4] Clonidine, as a primary alpha-2 agonist, is proficient in managing hypertension, anxiety disorders, headaches, alcohol withdrawal syndrome, and pain, while enhancing cardiovascular stability at the surgical site.[5] Clonidine is a lipid-soluble imidazoline derivative that is swiftly and nearly entirely absorbed following oral intake, reaching peak plasma levels within 60 to 90 minutes. Clonidine induces drowsiness and alleviates anxiety.[6] It produces a primary sympatholytic influence and possesses a half-life of 9 to 12 hours. It is a frequently utilized α2-agonist premedication that demonstrated a notable decrease in anesthetic needs.[7] Gabapentin [1-(aminomethyl) cyclohexaneacetic acid], an alkylated derivative of gamma-aminobutyric acid, was initially formulated as an anticonvulsant but is now utilized for managing chronic neuropathic pain.[8] Gabapentin is frequently utilized in the postoperative phase for numerous Enhanced Recovery After Surgery (ERAS) protocols.[9] It has been utilized successfully to alleviate pain, nausea, and vomiting during laparoscopic cholecystectomy in multiple clinical studies.[10] It possesses antinociceptive and anti-hyperalgesic characteristics, which are essential for managing postoperative hyperalgesia.[5] Following a solitary oral administration of 300 mg Gabapentin, the average peak plasma concentration is reached within 2–3 hours. The rates of absorption are contingent upon the dosage, perhaps attributable to a transport mechanism that can reach saturation. The bioavailability of 300 mg gabapentin is 60% and diminishes as the dosage increases. Excretion occurs via renal clearance and takes approximately 5–7 hours following a solitary administration of 200–400 mg. When these medications are used in conjunction with opioids or NSAIDs, they work together to diminish the hyperalgesia linked to peripheral inflammation.[8–10] Consequently, in light of the significance of managing postoperative pain and the rising frequency of laparoscopic procedures, a comparative analysis was performed between oral clonidine and oral gabapentin as preemptive analgesics to diminish postoperative analgesic needs for laparoscopic cholecystectomy.

## Methods

This randomized controlled study was conducted in the Department of Anesthesiology at Bangladesh Medical College Hospital (BMCH) in Dhaka, spanning from April 2022 to September 2022. A group of 60 patients diagnosed with cholelithiasis, set to undergo elective laparoscopic cholecystectomy under general anesthesia, was assembled and randomly allocated into two equal cohorts ($n$ = 30 each). Group C was administered 100 µg of oral clonidine, and Group G was

given 600 mg of oral gabapentin, both provided one hour before to surgery with little water intake. Inclusion criteria included participants aged 20 to 60 years of both sexes, categorized as ASA physical status I–II, slated for elective laparoscopic cholecystectomy, and capable of understanding the Visual Analog Scale (VAS). Exclusion criteria included patient nonadherence, recorded hypersensitivity to trial medications, chronic pain, inadequately managed thyroid, renal, or hepatic ailments, uncontrolled cardiovascular issues, emergency surgical procedures, pregnancy, substance abuse, and ASA classification III–IV. Postoperative pain was assessed by an investigator blind to group allocation using the VAS at 4, 8, 12, and 24 hours following the procedure. Intramuscular pethidine (1.5 mg/kg) was administered as a supplementary analgesic when the Visual Analog Scale surpassed 3 or at the patient's behest. The primary results included the time until the first analgesic request and VAS scores, whereas the secondary aim related to the total pethidine usage during a 24 hour period. Post-operative symptoms such as nausea and vomiting were recorded and managed with 10 mg of intravenous metoclopramide. Patients were discharged from postoperative care upon demonstrating minimal pain and the lack of significant nausea, vomiting, or bleeding. The examination of data was performed using SPSS version 20. Quantitative factors were expressed as mean ± standard deviation, whilst qualitative variables were indicated by frequency and percentage. Statistical analysis was performed using the Chi-square test and unpaired t-test as appropriate, with $P < 0.05$ as statistically significant, $P < 0.001$ as highly significant, and $P > 0.05$ as not significant. Ethical approval was obtained from the institutional ethics committee.

## Results

Table 1 shows the fundamental attributes of the study participants. The age distribution among the groups was similar, with the largest percentage of patients in the 30–39 years category in both Group C (30.0%) and Group G (33.3%). The average age in Group C was 34.5 ± 4.43 years, while in Group G it was 35.4 ± 5.02 years ($P = 0.72$). In both cohorts, female patients were the majority, representing 60.0% in Group C

**Table 1:** Distribution of the study patients according to baseline characteristics ($n = 60$)

| Variable | Category | Group C ($n = 30$) *n* (%) | Group G ($n = 30$) *n* (%) | *P*-value |
|---|---|---|---|---|
| Age (years) | 20–29 | 5 (16.7) | 7 (23.3) | 0.72[ns] |
| | 30–39 | 9 (30.0) | 10 (33.3) | |
| | 40–49 | 8 (26.7) | 7 (23.3) | |
| | 50–59 | 8 (26.7) | 6 (20.0) | |
| | Mean ± SD | 34.5 ± 4.43 | 35.4 ± 5.02 | – |
| Sex | Male | 12 (40.0) | 10 (33.3) | 0.41[ns] |
| | Female | 18 (60.0) | 20 (66.7) | |
| Weight (kg) | 40–49 | 1 (3.3) | 3 (10.0) | 0.44[ns] |
| | 50–59 | 7 (23.3) | 9 (30.0) | |
| | 60–69 | 7 (23.3) | 6 (20.0) | |
| | 70–79 | 7 (23.3) | 4 (13.3) | |
| | 80–89 | 6 (20.0) | 5 (16.7) | |
| | 90–99 | 2 (6.7) | 3 (10.0) | |
| | Mean ± SD | 70.87 ± 12.66 | 72.67 ± 14.01 | – |

ns = Not significant. *P*-values were obtained using the Chi-square test. Group C = Patients who received oral clonidine 100 µg. Group G = Patients who received oral gabapentin 600 mg.

and 66.7% in Group G, whereas male patients comprised 40.0% and 33.3%, respectively ($P = 0.41$). In terms of body mass, the majority of patients fell between the range of 50 to 89 kg. The average weight was 70.87 ± 12.66 kg in Group C and 72.67 ± 14.01 kg in Group G ($P = 0.44$).

Table 2 shows the allocation of study participants based on ASA physical status. In Group C, 18 patients (60.0%) were designated as ASA Grade I, while 12 patients (40.0%) were categorized as ASA Grade II. In Group G, 19 patients (63.3%) were classified as ASA Grade I, while 11 patients (36.7%) were classified as ASA Grade II. In all, 37 patients (61.7%) were ASA Grade I and 23 patients (38.3%) were ASA Grade II. The variance in ASA grade distribution between the two groups was not statistically significant ($P = 0.83$).

Table 3 shows the allocation of research participants based on the length of the surgical procedure. The average surgical length was 43.17 ± 5.38 minutes for Group C and 45.33 ± 6.68 minutes for Group G. Despite Group G exhibiting a little longer mean operating time, the disparity was not statistically significant ($P = 0.33$), suggesting that the surgical length was similar across both groups.

Table 4 shows the comparison of mean arterial pressure between the two groups at different postoperative time intervals. At the 4$^{th}$ hour after anaesthesia, the mean arterial pressure was significantly higher in Group C (66.97 ± 13.39 mmHg) compared to Group G (62.73 ± 2.88 mmHg) ($P = 0.03$). At the 8$^{th}$ hour, the mean arterial pressure was 64.70 ± 2.74 mmHg in Group C and 63.63 ± 1.16 mmHg in Group G ($P = 0.89$). At the

**Table 2:** Distribution of the study patients according to ASA physical status ($n = 60$)

| ASA Grade | Group C ($n = 30$) n (%) | Group G ($n = 30$) n (%) | Total ($n = 60$) | *P*-value |
|---|---|---|---|---|
| Grade I | 18 (60.0) | 19 (63.3) | 37 (61.7) | 0.83 |
| Grade II | 12 (40.0) | 11 (36.7) | 23 (38.3) | |
| Total | 30 (100.0) | 30 (100.0) | 60 (100.0) | |

ns = Not significant. *P*-value obtained by unpaired Student's *t*-test. Group C = Patients who received oral clonidine 100 µg. Group G = Patients who received oral gabapentin 600 mg.

**Table 3:** Distribution of the study patients according to duration of operation ($n = 60$)

| Duration of Operation (minutes) | Group C ($n = 30$) Mean ± SD | Group G ($n = 30$) Mean ± SD | *P*-value |
|---|---|---|---|
| Surgery duration | 43.17 ± 5.38 | 45.33 ± 6.68 | 0.33 |

ns = Not significant. *P*-value obtained by unpaired Student's t-test. Group C = Patients who received oral clonidine 100 µg. Group G = Patients who received oral gabapentin 600 mg.

**Table 4:** Distribution of the study patients according to mean arterial pressure after anaesthesia ($n = 60$)

| Mean Arterial Pressure (mmHg) | Group C ($n = 30$) Mean ± SD | Group G ($n = 30$) Mean ± SD | *P*-value |
|---|---|---|---|
| 4$^{th}$ hour after anaesthesia | 66.97 ± 13.39 | 62.73 ± 2.88 | 0.03 |
| 8$^{th}$ hour after anaesthesia | 64.70 ± 2.74 | 63.63 ± 1.16 | 0.89 |
| 12$^{th}$ hour after anaesthesia | 66.73 ± 2.35 | 65.37 ± 2.44 | 0.13 |
| 24$^{th}$ hour after anaesthesia | 74.43 ± 3.11 | 73.77 ± 3.71 | 0.55 |

s = Significant; ns = Not significant. *P*-values obtained by unpaired Student's *t*-test. Group C = Patients who received oral clonidine 100 µg. Group G = Patients who received oral gabapentin 600 mg.

12th hour, the corresponding values were 66.73 ± 2.35 mmHg and 65.37 ± 2.44 mmHg, respectively ($P$ = 0.13). At the 24th hour, the mean arterial pressure was 74.43 ± 3.11 mmHg in Group C and 73.77 ± 3.71 mmHg in Group G ($P$ = 0.55).

Table 5 shows the comparison of heart rates between the two cohorts at various postoperative time intervals. At the fourth hour post-anesthesia, the average heart rate in Group C (78.57 ± 8.19 beats/min) was markedly elevated compared to Group G (70.26 ± 11.59 beats/min) ($P$ = 0.03). At the eighth hour, the average heart rate was 75.26 ± 11.35 beats per minute in Group C and 69.26 ± 9.02 beats per minute in Group G ($P$ = 0.14). At the twelfth hour, the associated values were 78.26 ± 12.42 beats per minute and 70.26 ± 14.37 beats per minute, respectively ($P$ = 0.09). At the conclusion of the 24th hour post-anesthesia, the average heart rate was 66.26 ± 5.07 beats per minute in Group C and 65.37 ± 2.01 beats per minute in Group G ($P$ = 0.15). Aside from the fourth postoperative hour, no notable statistical changes in heart rate were detected between the two cohorts.

Table 6 shows the postoperative Visual Analog Scale (VAS) values between the two cohorts at various time intervals following anesthesia. At the fourth hour, the average VAS score was 1.64 ± 0.63 for Group C and 1.38 ± 0.50 for Group G, showing no statistically significant difference ($P$ = 0.66). At the eighth hour, the average VAS score was markedly elevated in Group C (3.92 ± 0.63) compared to Group G (3.21 ± 0.28) ($P$ = 0.04). At the twelfth hour, the average VAS score was 1.66 ± 0.78 for Group C and 1.92 ± 0.76 for Group G, with the difference being statistically significant ($P$ = 0.04). At the 24th hour, the average VAS score was 1.53 ± 0.51 for Group C and 1.37 ± 0.49 for Group G, showing no statistically significant difference between the groups ($P$ = 0.32).

Table 7 shows the comparison of postoperative analgesic requirements between the two groups.

**Table 5:** Distribution of the study patients according to heart rate after anaesthesia ($n$ = 60)

| Heart Rate (beats/min) | Group C ($n$ = 30) Mean ± SD | Group G ($n$ = 30) Mean ± SD | $P$-value |
|---|---|---|---|
| 4th hour after anaesthesia | 78.57 ± 8.19 | 70.26 ± 11.59 | 0.03 |
| 8th hour after anaesthesia | 75.26 ± 11.35 | 69.26 ± 9.02 | 0.14 |
| 12th hour after anaesthesia | 78.26 ± 12.42 | 70.26 ± 14.37 | 0.09 |
| 24th hour after anaesthesia | 66.26 ± 5.07 | 65.37 ± 2.01 | 0.15 |

s = Significant; ns = Not significant. $P$-values obtained by unpaired Student's t-test. Group C = Patients who received oral clonidine 100 µg. Group G = Patients who received oral gabapentin 600 mg.

**Table 6:** Distribution of the study patients according to visual analogue scale (VAS) after anaesthesia ($n$ = 60)

| VAS Score | Group C ($n$ = 30) Mean ± SD | Group G ($n$ = 30) Mean ± SD | $P$-value |
|---|---|---|---|
| 4th hour after anaesthesia | 1.64 ± 0.63 | 1.38 ± 0.50 | 0.66 |
| 8th hour after anaesthesia | 3.92 ± 0.63 | 3.21 ± 0.28 | 0.04 |
| 12th hour after anaesthesia | 1.66 ± 0.78 | 1.92 ± 0.76 | 0.04 |
| 24th hour after anaesthesia | 1.53 ± 0.51 | 1.37 ± 0.49 | 0.32 |

s = Significant; ns = Not significant. $P$-values obtained by Student's t-test. Data are presented as mean ± SD. Group C = Patients who received oral clonidine 100 µg. Group G = Patients who received oral gabapentin 600 mg.

The mean time to first analgesia requirement was significantly shorter in Group C (563.65 ± 0.98 minutes) than in Group G (650.00 ± 0.07 minutes) ($P = 0.03$), indicating a longer duration of postoperative analgesia in the gabapentin group. The mean total analgesic dose required during the postoperative period was also significantly higher in Group C (79.67 ± 22.37 mg) compared with Group G (58.67 ± 24.71 mg) ($P = 0.04$).

## Discussion

In this study 18 out of 12 patients were classified as ASA grade I/II in Group C, whereas 19 out of 11 were in Group G, with no statistically significant difference ($P > 0.05$) between the two groups. Sussan Soltani Mohammadi and colleagues demonstrated that the ASA status for the Clonidine Group was 58.1 ± 14.3, whereas the Gabapentin Group recorded 57.7 ± 13.4.[3] The disparity was not statistically significant ($P > 0.05$) between the two groups. Abbas et al. demonstrated that the ASA classification (Grade I/II) for the Gabapentin cohort was 21/9, while the placebo cohort exhibited 24/6. The disparity was not statistically meaningful ($P > 0.05$).[5] Seyed Mojtaba Marashi et al. showed that the ASA status (Grade I/II) for the Clonidine Group was 12/10 and in the Gabapentin Group was 11/11. The difference was not statistically significant ($P > 0.05$) between the two Groups. The mean length was determined to be 43.17 ± 5.39 minutes in Group C and 45.33 ± 6.68 minutes in Group G with no statistical significance ($P > 0.05$) between the two Groups. Irfan Andleeb Gul et al. they showed the mean duration of surgery for Group C was 161.00 ± 7.59 min, in Group G was 158.50 ± 6.58 min, and in Group P was 158.17 ± 5.65 min.[11] The difference was not statistically significant ($P > 0.05$) between the Groups. Abbas et al. showed that the mean duration of surgery for Group A was 63.0 ± 16.1 min, and for Group B was 65.6 ± 10.7 min.[3] The difference was not statistically significant ($P > 0.05$) between these Groups. Seyed Mojtaba Marashi et al.[12] they showed the mean duration of surgery for the Clonidine Group was 126 ± 20.5 min, in Gabapentin Group was 129 ± 20.5 min. The difference was not statistically significant ($P > 0.05$) between these Groups. In this study, mean arterial blood pressure after anaesthesia was recorded and found that MAP at the 4$^{th}$ hour was 66.97 ± 13.39 mmHg for Group C and 62.73 ± 2.89 mmHg for Group G, and was statistically significant (0.03) between these two Groups. MAP at the 8$^{th}$ hour was 64.70 ± 2.74 mmHg for Group C and 63.63 ± 1.16 mmHg for Group G, and was not statistically significant between these two Groups. MAP at the 12$^{th}$ hour was 66.73 ± 2.35 mmHg for Group C and 65.37 ± 2.44 mmHg for Group G, and was not statistically significant between these two Groups. MAP at 24$^{th}$ hour was 74.43 ± 3.11 mmHg for Group C and 73.77 ± 3.71 mmHg for Group G, and was not statistically significant between these two Groups. In this study, heart rate post-anaesthesia was recorded and found that heart rate at the 4$^{th}$ hour was 78.57 ± 8.19 for Group A and 70.26 ± 11.59 for Group G, and was statistically significant (0.03) between these two Groups. Heart rate at the 8$^{th}$ hour was 75.26 ± 11.35 for Group C and 69.26 ± 9.02 for Group G, and was not statistically significant between these two Groups. Heart rate at the

**Table 7:** Distribution of the study patients according to analgesic requirement after anaesthesia ($n = 60$)

| Analgesic Parameter | Group C ($n = 30$) Mean ± SD | Group G ($n = 30$) Mean ± SD | *P*-value |
|---|---|---|---|
| Time to first analgesia requirement (minutes) | 563.65 ± 0.98 | 650.00 ± 0.07 | 0.03 |
| Total analgesic dose required (mg) | 79.67 ± 22.37 | 58.67 ± 24.71 | 0.04 |

s = Significant. *P*-values obtained by Student's t-test. Data are presented as mean ± SD. Group C = Patients who received oral clonidine 100 µg. Group G = Patients who received oral gabapentin 600 mg.

12th hour was 78.26 ± 12.42 for Group C and 70.26 ± 14.37 for Group G, and was not statistically significant between these two Groups. Heart rate at the 24th hour was 66.26 ± 5.07 for Group C and 65.37 ± 2.01 for Group G, and was not statistically significant between these two Groups. In this study, VAS after anaesthesia was recorded and found that VAS at the 4th hour were 1.64 ± .63 for Group C and 1.38 ± .50 for Group G, and was not statistically significant (0.65) between these two Groups. VAS at the 8th hour were 3.92 ± .63 for Group C and 3.21 ± 1.28 for Group G, and was statistically significant (0.04) between these two Groups. VAS at the 12th hour was 1.66 ± .78 for Group C and 1.92 ± .76 for Group G, and was not statistically significant (0.04) between these two Groups. VAS at 24th hour was 1.53 ± .51 for Group C and 1.37 ± .49 for Group G, and was not statistically significant (0.32) between these two Groups. Irfan Andleeb Gul et al. found that in the Clonidine Group, VAS started increasing at 4 h, but the patient demanded the first dose of rescue analgesia at 8th h postoperatively.[11] This study observed that the time of first analgesic requirement was found to be 563.65 ± .98 minutes in Group C and 650.00 ± .07 minutes in Group G & was statistically significant (0.03) between the two Groups. Group C needed analgesia early as compared to Group G, which means Group G has a longer duration of analgesic coverage as compared to Group A. This study observed that the total analgesic requirement of pethidine was found to be 79.67 ± 22.37 mg in Group C up to 24 hours and 58.67 ± 24.71 mg in Group G in 34 last 24 hours & was statistically significant (0.04) between the two Groups. Seyed Mojtaba Marashi et al. found that the total rescue analgesic requirement was 47.1 ± 49.1 mg morphine for the Clonidine Group and was 18.3 ± 15.6 mg morphine for the Gabapentin Group, so the Clonidine Group needed more analgesia in the last 24 hours than the Gabapentin Group.[12] Parikh et al. showed that the rescue analgesia requirement in the gabapentin group was significantly lower than that in the placebo group.[13]

## Limitations of the Study

In terms of limitations, side effects were not investigated. The study population was recruited from one designated hospital in Dhaka city hence the result of the study may not depict the exact picture of the country. Another disadvantage of the present investigation was the small size of the sample. So, in the future, more study can be made with a greater sample.

## Conclusion

The present study demonstrates that pre-emptive Gabapentin improves and produces a longer duration of postoperative analgesia by delaying the time of the first dose of analgesic and reduces analgesic requirements with no deleterious effects on haemodynamic status and no side effects compared to Clonidine, when given 1 hour before operation.

## Recommendation

Since this study was conducted at a single center with a relatively limited sample size, the findings may not be fully generalizable to the broader population. Therefore, further multicenter studies involving a larger number of patients from multiple tertiary-level hospitals are recommended to validate the results. Such studies would provide stronger evidence and support the development of more reliable clinical guidelines and policy recommendations.

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