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Comparing efficacy of oral clonidine and gabapentin premedication for post-operative pain and analgesic requirement in patient undergoing laparoscopic cholecystectomy: A prospective, double-blind, and placebo-controlled study

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ABSTRACT

Background: Post-operative pain is an area, which has been receiving an increasing amount of attention in recent years. Pain associated with laparoscopic cholecystectomy has been an area of interest for many, various modalities have been tried for pain relief. **Aims and Objectives:** The study aimed at comparing analgesic efficacy of oral clonidine and gabapentin premedication on post-operative pain and analgesic requirement in patients undergoing laparoscopic cholecystectomy. **Materials and Methods:** Ninety patients of American Society of Anesthesiologists Status I and II, between 20 and 60 years undergoing elective laparoscopic cholecystectomy, were randomized into three groups. Group C received 150 mcg of clonidine, Group G received 600 mg of gabapentin, and Group P received placebo multivitamin tablets 2 h before surgery. The primary objective was to study the duration of post-operative analgesia and total rescue analgesic required. The secondary objective was to find out any sedation and adverse effect associated with the use of premedicant drugs. **Results:** The duration of analgesia was found to be highest in Group G (174.33 ± 85.81 min) than in Group C (77.17 ± 63.99 min) and Group P (29.33 ± 14.55 min). Total dose of tramadol consumption in 6 h was highest in Group P (91.67 ± 23.06 mg) with statistically insignificant difference between Group G (46.67 ± 12.69 mg) and Group C (48.33 ± 9.13 mg). No statistically significant adverse event was noted in post-operative period. **Conclusion:** The use of oral clonidine and gabapentin 2 h before laparoscopic cholecystectomy significantly prolongs duration of post-operative analgesia and decreases the requirement of rescue analgesics without causing any significant adverse events.

Key words: Clonidine; Gabapentin; Laparoscopic cholecystectomy; Post-operative pain; Premedication

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INTRODUCTION

Since the introduction of laparoscopic cholecystectomy in 1985 by Prof. Erich Mühe, it became apparent that laparoscopic procedures have multiple benefits when compared to open procedures. Surgical dissection and inflammation around the gallbladder bed and pneumoperitoneum are the main causes for visceral pain postoperatively.[1] Patients may develop shoulder pain due to phrenic nerve neuropraxia and increased intra-abdominal pressure leading to stretching of subdiaphragmatic fibres.[2,3]

Various analgesic techniques and drugs such as intraperitoneal infiltration of local anesthetics, port site infiltration, opioids,

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NSAIDs, gabapentin, and pregabalin are in use to mitigate this pain in post-operative period, but no any single method is superior to others in the reduction of post-operative pain. Inadequate pain control, apart from being inhumane, may result in increased morbidity and delayed hospital discharge. Good analgesia can reduce this deleterious effect. Pre-emptive analgesia is a safe and new approach for alleviating post-operative pain.

Clonidine was originally introduced as antihypertensive drug, later on found to have analgesic, sedative, and anxiolytic properties. It improves the quality of induction, maintenance, and recovery from anesthesia. By its central sympatholytic action, it tends to attenuate the hemodynamic response to any surgical nociceptive stimulus and improve overall perianesthetic cardiovascular stability.[4] It activates postsynaptic alpha-2 receptors in dorsal horn of spinal cord to produce analgesia and, thus, helps in mitigating post-operative pain.[5,6]

Gabapentin, an anticonvulsant is well known for its antinociceptive and antihyperalgesic properties.[7] Pre-emptive use of gabapentin has gained widespread attention recently due to the ease of administration, fewer side effects, and favorable results in various procedures.[8,9]

We searched the literature available on web and found that most of the studies focused on comparing hemodynamic effects of clonidine and gabapentin premedication on laryngoscopy and during pneumoperitoneum, only few studies compared the analgesic efficacy of these drugs postoperatively in laparoscopic cholecystectomy.[10,11]

Aims and objectives

The present study was designed to compare analgesic efficacy of oral clonidine and gabapentin premedication on post-operative pain and analgesic requirement in patients undergoing laparoscopic cholecystectomy.

MATERIALS AND METHODS

This prospective, randomized, controlled, and double-blind study was conducted in the Department of Anesthesiology, Indraprastha Apollo Hospital, New Delhi in 1 year period from January 2016 to December 2016 after obtaining approval from the Institutional Ethics Committee (Approval Number: ECR/5/Inst/DL/2013 dated January 9, 2016). The study was designed in accordance with consolidated standards of reporting trials 2010 guidelines and performed according to the guidelines of the Declaration of Helsinki. Well-informed written consent was obtained from the selected patients for 1 year.

Inclusion criteria

The study population included American Society of Anesthesiologists (ASA) Grade 1 and 2 adult patients of age 20–60 years, of either sex who were admitted to hospital on the day before surgery for elective laparoscopic cholecystectomy. Considering an alpha error of 0.05 and power of study as 80%, the estimated sample size comes out to be 30 patients in each group.

Exclusion criteria

ASA Grade 2 patients with hypertension, pregnant women, obese patients with BMI >30.0 kg/m^2 alcoholics, patients concomitantly using MAO-inhibitors, tricyclic antidepressants, or opioids and patients who refused to participate were excluded from the study.

Computer-generated randomization technique was followed to divide the enrolled 90 patients into three groups as below (Figure 1).

- Group C – Received 150 mcg of clonidine 2 h before surgery
- Group G – Received 600 mg of gabapentin 2 h before surgery
- Group P – Received placebo multivitamin tablets 2 h before surgery.

During the study, double-blinding was done to avoid bias. After randomization and group allocation, drug was given by the principal investigator, post-operative observation, and visual analog scale (VAS) score recording by nursing staff, and statistical analysis by the statistician. Both nursing staff and statistician were unaware of the patient's allocated group and the given premedication drug.

Patients were given the premedication drug with a sip of water. Before surgery, patients were explained about the use of ten-point VAS.

After transferring, the patient to operation theater monitors including ECG, pulse oximeter, and non-invasive B.P. cuff were attached and pre-operative vitals were noted and an 18/20 G intravenous catheter was secured for administering intravenous fluid and drugs.

After pre-oxygenation with 100% oxygen for 3 min, anesthesia was induced with a standard anesthetic protocol using fentany l 2 mcg/kg, propofol 1.5–2.5 mg/kg, and tracheal intubation with appropriate sized cuffed endotracheal tube which was facilitated by atracurium 0.5 mg/kg. Anesthesia was maintained with nitrous oxide (60%) and sevoflurane (MAC 0.8–1.2) in oxygen.

All patients received paracetamol 1% 1 g infusion and diclofenac 1.25 mg/kg for pain intraoperatively. At the end

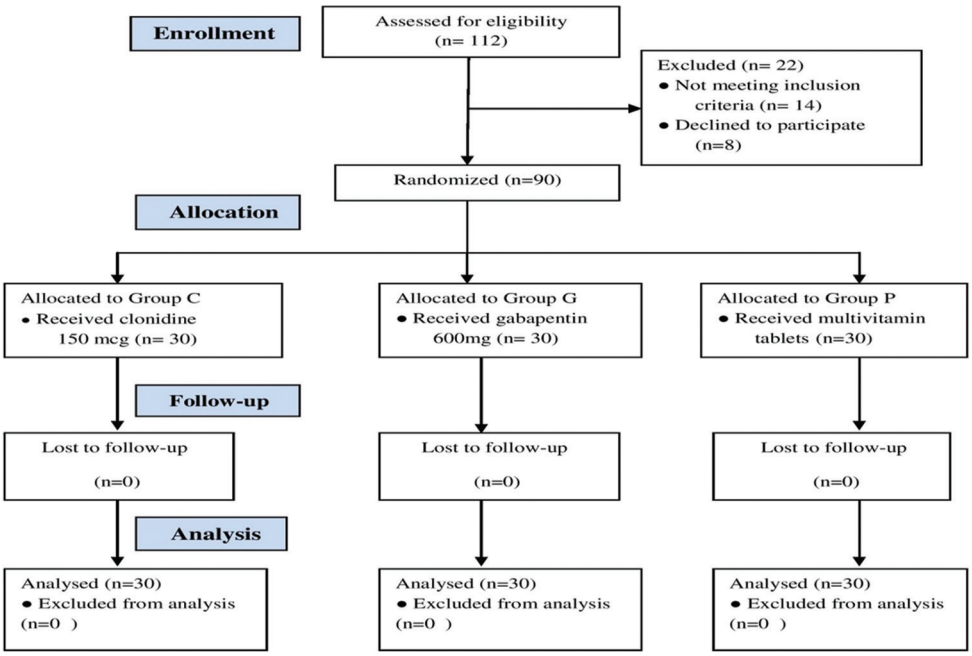

Figure 1: Consolidated standards of reporting trials flow diagram

of surgery, residual neuromuscular block was reversed using neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg intravenously and patients were extubated when respiration was sufficient and were awake to be able to follow commands.

Postoperatively, patients were transferred to the post anesthesia care unit (PACU), where they were monitored for post-operative pain, sedation, and any evidence of complications or adverse events.

Degree of sedation was assessed using sedation score from 1 to 5.

Sedation score:
1. Awake and agitated
2. Awake and comfortable
3. Asleep and arousable
4. Asleep with sluggish response to verbal commands or touch
5. No response to verbal command or touch.

VAS was used to assess pain (no pain-0 to worst possible pain-10).

Both pain and sedation were assessed at the end of surgery, 30 min, 60 min, 90 min, 2 h, 3 h, and 6 h postoperatively.

Rescue analgesia in the form of inj. tramadol 50 mg i.v. was given to the patients who complained of pain (pain score >3/10 – as per institutional protocol), at rest or at movement. Numbers of such tramadol doses were noted up to 6 h. No other analgesic or sedative was given during this period.

Any adverse effects such as nausea, vomiting, dizziness, dryness of mouth, bradycardia, hypotension, and hypertension in the recovery room were noted and treated accordingly.

Statistical analysis

The quantitative variables in all the groups are expressed as mean±SD and compared using unpaired t-test between groups and paired t-test within each group at various follow-ups. The qualitative variables are expressed as frequencies/percentages and compared using Chi-square test. $P<0.05$ was considered statistically significant. The Statistical Package for the Social sciences (SPSS) version 16.0 was used for statistical analysis.

RESULTS

The three groups were comparable with respect to their age, gender, body mass index (BMI), duration of surgery, and anesthesia without any statistically significant difference (Table 1).

The VAS score varied from 1.67±0.48 to 2.60±0.5 in Group C; from 2.0±0 to 2.60±0.5 in Group P and from 2.00±0 to 2.47±0.51 in Group G. The Group P had received rescue analgesia at mean time 29.33±14.55 min and Group C at mean time of 77.17±63.99 min which led to lower VAS at subsequent points of time.

After 6 h of surgery, VAS was significantly ($P<0.001$) lower in Group C (1.67±0.48) than in Group P (2.23±0.57) and Group G (2.00±0). Among the Groups G and P,

Group G had lower VAS than Group P which is statistically significant (P=0.028) (Table 2 and Figure 2).

The time to first rescue analgesia requirement was least in Group P (29.33±14.55 min) followed by Group C (77.17±63.99 min) followed by Group G (174.33±85.81 min). The difference between all the three pair of groups was statistically significant (P<0.001). Patients in Group P required significantly higher amount of analgesics than other Groups C and G (Table 3).

The mean sedation score varied from 2.20±0.41 to 2.83±0.38 in Group C; from 2.00±0 to 2.30±0.47 in Group P and from 2.03 to 2.57±0.5 in Group G. Patients had sedation in the early post-operative period, thereafter at 2, 3, and 6 h; after surgery, there was no significant difference in sedation score among the three groups (Table 4 and Figure 3).

The incidence of nausea was more in Group P (13.33%) as compared to Group C (6.67%) and Group G (3.33%). Vomiting was seen in one case (3.33%) in Group P. The dryness of mouth (10%) and bradycardia (10%) was seen in Group C. The incidence of dizziness was 6.67% in both Groups C and G and 3.33% in Group P. There was no statistically significant (P=0.065) distribution of adverse events among the groups (Table 5).

DISCUSSION

Laparoscopic cholecystectomy is an essence of today's surgical practice and is considered a minimally invasive procedure. The choice of anesthetic technique for the upper abdominal laparoscopic surgery is mostly limited to general anesthesia with muscle paralysis, tracheal intubation, and intermittent positive pressure ventilation.[12]

Clonidine and gabapentin are drugs under intense investigation as an adjunct to anesthesia in various forms.[13] In this series, 150 mcg clonidine tablet was administered orally, 2 h before surgery. Carabine et al. have shown that using 0.2 mg of clonidine was associated with minimal cardiovascular effects and good anxiolytic action.[14]

Similarly, gabapentin most recently has been used perioperatively for reducing stress responses in different clinical scenario. As gabapentin is already used as adjuvant for post-operative pain, we used 600 mg, 2 h before surgery based on the results of dose escalation study which concluded that 600 mg given 2 h before surgery is the optimal dose for pain.[15] Bhure et al.,[16] and Srivastava et al.,[17] also used 600 mg of oral gabapentin given 2 h before laparoscopic cholecystectomy, which provided clinically adequate analgesia. Gabapentin provides pre-operative anxiolysis, prevents chronic postsurgical pain, attenuates stress responses to noxious perioperative stimuli, and prevent post-operative delirium, nausea, and vomiting.[18]

Table 1: Demographic characteristics of patients and surgical data

Parameters	Group C N (%)	Group P N (%)	Group G N (%)	P-value
Age (in years)				0.397
<40	14 (46.67)	8 (26.67)	10 (33.33)	
40–50	6 (20)	10 (33.33)	8 (26.67)	
50–60	10 (33.33)	12 (40)	12 (40)	
Gender				
Male	14 (46.67)	13 (43.33)	14 (46.67)	0.428
Female	16 (53.33)	17 (56.67)	16 (53.33)	
BMI (in kg/m^2)				
Mean±SD	25.03±1.13	25.03±1.78	25.19±1.16	0.634
Duration of surgery (in min)				
Mean±SD	40.5±15.6	38.6±10.3	43.6±12.4	0.345
Duration of anaesthesia (in min)				
Mean±SD	61.6±10.7	65.3±12.5	63.6±11.6	0.192

Table 2: Comparison of mean VAS score between the groups

VAS score	Group C Mean±SD	Group P Mean±SD	Group G Mean±SD	P-values		
				C versus P	C versus G	P versus G
At the end of surgery	1.97±0.18	2.10±0.31	2.00±0	0.045	0.321	0.078
30 min	2.00±0	2.60±0.5	2.00±0	<0.001	-	<0.001
60 min	2.60±0.5	2.33±0.48	2.00±0	0.039	<0.001	<0.001
90 min	2.23±0.43	2.00±0	2.07±0.25	0.004	0.073	0.155
2 h	2.10±0.4	2.07±0.25	2.27±0.45	0.703	0.136	0.038
3 h	1.70±0.53	2.47±0.51	2.47±0.51	<0.001	<0.001	1.000
6 h	1.67±0.48	2.23±0.57	2.00±0	<0.001	<0.001	0.028

VAS: Visual analog scale

The patients who received clonidine or gabapentin had better post-operative pain control and needed less rescue analgesia when compared to patients who received placebo. Simultaneously, patients who received gabapentin required first rescue analgesia much later than patients who received clonidine. Similar results were shown by Shivinder Singh et al.,[19] Sung et al.,[20] with clonidine and Pandey et al.,[21] Srivastava et al.,[17] and Ho et al.,[22] with gabapentin.

Mathur et al.,[23] from their study, concluded that when given 90 min, before induction of general anesthesia oral gabapentin (300 mg) or clonidine (150 μg) preoperatively was effective in lowering post-operative VAS pain score and consumption of analgesics, it was also shown that gabapentin significantly decreases post-operative pain intensity and analgesic consumption after abdominal surgeries. Their result was in concordance with the result of our study.

In early post-operative period, the patients who received clonidine or gabapetin were more sedated than patients who received multivitamin tablets. Immediately after surgery, the patient who received clonidine were more sedated than patients who received gabapentin. As the time progressed, the sedation decreased in patients receiving clonidine or gabapentin that varied mean sedation scores between 2 (awake and comfortable) and 3 (asleep and arousable either verbally or by touch). However, the patient who received placebo had increased sedation at 90 min of surgery. This increased sedation is consistent with effect of rescue analgesic received by these patients at a mean time of 29.33±14.55 min. While, Gupta et al.,[24] and Ibrahim et al.,[25] showed that gabapentin and clonidine had more sedation than placebo in their studies, there was no statistically significant difference in sedation between the three groups for the entire period of observation other than initial 30 min in our study.

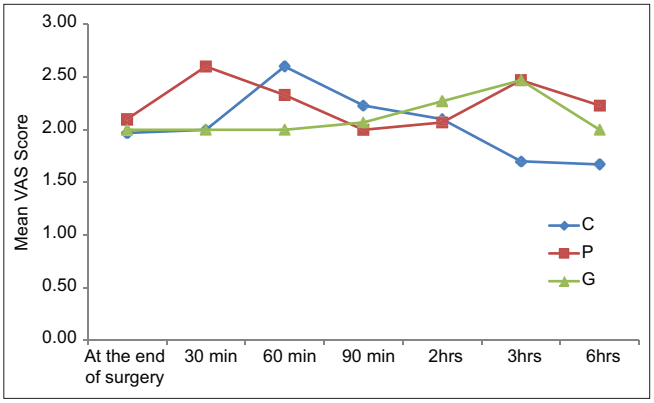

Figure 2: Comparison of mean VAS score between the groups

The adverse events such as bradycardia (10%) and dryness of mouth (10%) in the post-operative period were more in patient who received clonidine as compared to gabapentin or placebo group, but these were minor and easily controllable. About 16.67% patients who received placebo had PONV (post-operative nausea vomiting), while only 6.67% patient who received clonidine had PONV and 3.33% patients who received gabapentin had such episode. These observations were found consistent with studies of Pandey et al.,[26] and Mrinmoy et al.[27]

About 6.67% in patients who received clonidine or gabapentin had dizziness, while only 3.33% patients who received placebo had any such episode. When the adverse effects nausea, vomiting, dizziness, dryness of mouth, bradycardia put together there was no significant difference in between the groups. No incidence of hypotension or hypertension was seen in any of the group in the recovery room.

Limitations of the study

First, no measurement of stress mediators, that is, endogenous plasma catecholamines or cortisol values

Table 3: Comparison of analgesic requirements between the groups

Rescue Analgesia	Group C Mean±SD	Group P Mean±SD	Group G Mean±SD	P-values		
				C versus P	C versus G	P versus G
Time to first rescue analgesia (in min)	77.17±63.99	29.33±14.55	174.33±85.81	<0.001	<0.001	<0.001
Total analgesic requirement (in mg)	48.33±9.13	91.67±23.06	46.67±12.69	<0.001	0.561	<0.001

Table 4: Comparison of mean sedation score between the groups

Sedation Score	Group C Mean±SD	Group P Mean±SD	Group G Mean±SD	P-values		
				C versus P	C versus G	P versus G
At the end of surgery	2.83±0.38	2.00±0	2.57±0.5	<0.001	0.024	<0.001
30 min	2.30±0.47	2.00±0	2.30±0.47	<0.001	1.000	<0.001
60 min	2.20±0.41	2.17±0.38	2.30±0.47	0.744	0.380	0.229
90 min	2.27±0.45	2.30±0.47	2.03±0.18	0.779	0.011	0.005
2 h	2.27±0.45	2.23±0.43	2.10±0.31	0.770	0.098	0.171
3 h	2.47±0.51	2.27±0.45	2.47±0.51	0.112	1.000	0.112
6 h	2.23±0.57	2.13±0.35	2.27±0.45	0.414	0.802	0.203

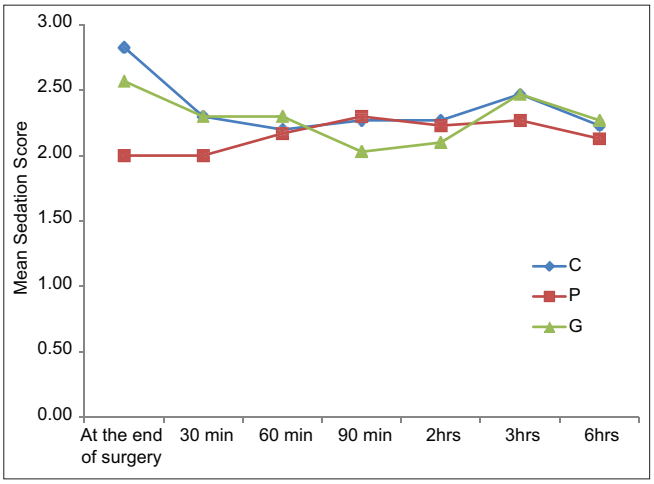

Figure 3: Comparison of mean sedation score between the groups

Table 5: Comparison of distribution of adverse events between the groups

Adverse events	Group C		Group P		Group G	
	n	%	n	%	n	%
None	20	66.67	24	80.00	27	90.00
Nausea	2	6.67	4	13.33	1	3.33
Vomiting	0	0.00	1	3.33	0	0.00
Dizziness	2	6.67	1	3.33	2	6.67
Dryness of mouth	3	10.00	0	0.00	0	0.00
Bradycardia	3	10.00	0	0.00	0	0.00
Total	30	100	30	100	30	100

perioperatively. Second, the study did not included elderly population. Third, the post-operative pain which is a subjective experience and can be difficult to quantify objectively. These limitations need to be addressed, and further multicenter studies with a large sample size may help provide data to overcome these shortcomings.

CONCLUSION

We conclude that during routine laparoscopic cholecystectomy both clonidine and gabapentin are effective premedicants, both being superior to placebo. The use of oral clonidine and gabapentin 2 h before laparoscopic cholecystectomy significantly prolongs duration of post-operative analgesia and decreases the requirement of rescue analgesics without causing any significant adverse events, but gabapentin is superior to clonidine.

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Authors Contribution:
RP- Participated in the concept of study design, conduct of study, data collection, and writing of first draft; **AD-** Prepared first draft of manuscript, interpreted the results, reviewed the literature and revision of the manuscript; **KKP-** Helped in concept of study, statistical analysis of data and logical conclusion of analyzed result, helped RP during first draft and subsequent revision of first draft; **AM-** Participated in the concept of the study, daily guidance regarding the conduct of the study, helped in data analysis and to arrive at logical conclusion, review of the literature, extensive revision of the first draft.

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