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Original Research Article

Comparison of Hemodynamic Responses to Two Doses of Intravenous Clonidine as Premedication in Laparoscopic Cholecystectomy: A Randomized, Double-Blind Study

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Abstract:

Background: Effective premedication can attenuate hemodynamic responses during surgery, enhancing patient stability and outcomes. Clonidine, an α2-adrenergic agonist, is frequently utilized for its sympatholytic properties. This study aims to compare the hemodynamic effects of two intravenous clonidine doses as premedication in patients undergoing laparoscopic cholecystectomy.

Methods: A randomized, double-blind study was conducted on 154 patients scheduled for elective laparoscopic cholecystectomy. Participants were randomly assigned to receive either 1 µg/kg (Group A) or 2 µg/kg (Group B) of intravenous clonidine diluted in 100 ml normal saline over 15 minutes, administered 30 minutes before induction. Hemodynamic parameters including heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were monitored at specified intervals. Secondary outcomes included the incidence of side effects within the first 24 hours postoperatively. Data were analyzed using Student's t-test and Chi-square test, with significance set at $p < 0.05$.

Results: Both clonidine doses significantly stabilized hemodynamic parameters compared to baseline. Group B exhibited a more pronounced reduction in HR, SBP, DBP, and MAP at multiple time points, including post-intubation and during pneumoperitoneum ($p < 0.05$). Additionally, Group B had a lower incidence of postoperative side effects such as nausea and vomiting compared to Group A, though not statistically significant.

Conclusion: A higher dose of intravenous clonidine (2 µg/kg) as premedication provides superior hemodynamic stability compared to a lower dose (1 µg/kg) in patients undergoing laparoscopic cholecystectomy. This dose is well-tolerated and may enhance perioperative management.

Keywords: Clonidine, Hemodynamic Stability, Laparoscopic Cholecystectomy, Premedication, Randomized Controlled Trial.

Introduction

Laparoscopic cholecystectomy has become the gold standard for the surgical management of gallbladder diseases due to its minimally invasive nature and favorable postoperative outcomes [1-3]. However, the procedure involves pneumoperitoneum and patient positioning, which can elicit significant hemodynamic responses such as tachycardia and hypertension [4]. These fluctuations can pose risks, particularly in patients with underlying cardiovascular conditions, and may complicate anesthetic management [5]. Premedication strategies aim to mitigate these hemodynamic disturbances, ensuring patient stability and optimizing surgical conditions [6]. Clonidine, an α2-adrenergic agonist, has garnered attention for its ability to provide sedation, analgesia, and sympathetic blockade without causing significant respiratory depression [7]. Its use as an adjunct in anesthesia has been associated with reduced anesthetic and analgesic requirements, stable hemodynamics, and improved postoperative outcomes [8]. Previous studies have explored varying doses of clonidine, yet optimal dosing remains a subject of investigation. Lower

doses may offer mild hemodynamic benefits with minimal side effects, whereas higher doses could provide more substantial stabilization but risk increased incidence of hypotension and bradycardia [9]. Understanding the dose-dependent effects of clonidine is crucial for tailoring premedication protocols to individual patient needs and surgical contexts.

This study seeks to compare the hemodynamic responses to two different intravenous doses of clonidine (1 µg/kg vs. 2 µg/kg) administered as premedication in patients undergoing elective laparoscopic cholecystectomy. By evaluating primary outcomes such as HR, SBP, DBP, and MAP, alongside secondary outcomes like postoperative side effects, this research aims to determine the more effective and safer clonidine dose for enhancing perioperative hemodynamic stability.

Materials and Methods

Ethical Considerations and Study Registration

This study was conducted after obtaining approval from the Office of Ethics Committee, S.M.S. Medical College (Approval No. 1245/MC/EC/2021). The study was prospectively registered with the Clinical Trials Registry India (CTRI) under registration number CTRI/2022/08/045000. Informed written consent was obtained from all participants after a detailed explanation of the study protocol and procedures.

Study Design and Setting

A hospital-based, randomized, double-blind, interventional study was conducted at the Department of Anaesthesiology and General Surgery Operation Theatres of Sawai Man Singh Medical College and affiliated hospitals, Jaipur, Rajasthan. This tertiary-level, super-speciality institution is equipped with state-of-the-art medical facilities. The study was carried out over a period sufficient to enroll the desired number of participants.

Study Population

Study Universe: All patients scheduled for elective laparoscopic cholecystectomy under general anesthesia at the institution during the study period were considered.

Inclusion Criteria:

- American Society of Anesthesiologists (ASA) Grade I & II
- **Age:** 18-45 years
- **Weight:** 40-85 kg
- Planned for elective laparoscopic chole cystectomy under general anesthesia
- Provided written informed consent

Exclusion Criteria:

- History of allergy to clonidine
- Anticipated difficult intubation
- Preoperative use of antihypertensive drugs, sedatives, hypnotics, or antidepressants
- Pre-existing cardiovascular, significant respiratory, renal, or hepatic disorders
- History of drug or alcohol abuse
- Pregnant women
- Patients refusing participation

Sample Size Calculation

A total of 154 patients (77 in each group) were required to achieve 80% power at a 95% confidence level to detect a minimum difference of 0.9 ± 1.8 in mean systolic blood pressure after 30 minutes of administering two different doses of intravenous clonidine (1 µg/kg vs. 2 µg/kg). This calculation was based on parameters from a previously published study (Seed Article, Vol-8/Issue-4/April-2019, ISSN No. 2277-8179).

Randomization and Blinding

Participants were randomly allocated to one of two groups using the opaque sealed envelope method to ensure concealment:

- **Group A:** Received 1 µg/kg of intravenous clonidine diluted in 100 ml of normal saline over 15 minutes, administered 30 minutes before induction.
- **Group B:** Received 2 µg/kg of intravenous clonidine diluted in 100 ml of normal saline over 15 minutes, administered 30 minutes before induction.

The study was double-blind, meaning both the participants and the healthcare providers (including surgeons, anesthesiologists, nurses, and operating room staff) were unaware of the group assignments. Unblinding occurred only in the event of a severe adverse reaction.

Preoperative Evaluation and Baseline Measurements

Pre-Anesthetic Evaluation: Conducted one day prior to surgery, including:

- Comprehensive medical and surgical history
- General and systemic examination
- Vital parameters: blood pressure, pulse, temperature, respiratory rate
- Measurement of weight and height

Investigations:

- Hematological: Hemoglobin (Hb%), total leukocyte count (TLC), differential leukocyte count (DLC), platelet count, bleeding time (BT), clotting time (CT), prothrombin time (PT)/INR

- Biochemical: Fasting/random blood sugar, blood urea, serum creatinine, SGOT, SGPT, serum bilirubin, serum electrolytes
- Radiological: Chest X-ray, electrocardiogram (ECG)

Baseline Vital Signs: Recorded with the patient in a supine position without any tilt. Parameters included heart rate (measured via ECG), blood pressure (measured using a sphygmomanometer), and oxygen saturation (SpO_2) via pulse oximetry.

Anesthetic Procedure

1. **Pre-Induction Medications:**

- **Group A:** 1 µg/kg intravenous clonidine in 100 ml normal saline over 15 minutes
- **Group B:** 2 µg/kg intravenous clonidine in 100 ml normal saline over 15 minutes
- Additionally, both groups received:
  - Glycopyrrolate **0.004 mg/kg** i.v.
  - Metoclopramide **0.1 mg/kg** i.v.
  - Tramadol **1.5 mg/kg** i.v.
- Preoxygenation with **100% oxygen** via face mask for **3 minutes**

2. **Induction:**

- Thiopentone **2.5 mg/kg** i.v. until loss of eyelash reflex
- Succinylcholine **2 mg/kg** i.v. for tracheal intubation
- Atracurium **0.5 mg/kg** i.v. as a loading dose

3. **Maintenance of Anesthesia:**

- Ventilation with 50% oxygen and 50% nitrous oxide
- Sevoflurane 1-2%
- Atracurium 0.1 mg/kg i.v.
- End-tidal carbon dioxide maintained at 40 ± 4 mm Hg

4. **Surgical Procedure:**

- Creation of pneumoperitoneum with carbon dioxide
- Intra-abdominal pressure maintained below 15 mm Hg
- Operating table tilted to a 15-degree reverse Trendelenburg position

5. **Monitoring and Recording:**

- Continuous monitoring of hemodynamic parameters: heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), SpO_2, and respiratory rate
- Recording at the following intervals:
  - Baseline
  - 15 and 30 minutes after starting clonidine infusion
  - After intubation
  - During pneumoperitoneum
  - 5, 10, 15, and 30 minutes post-insufflation
  - Release of CO_2
  - Extubation

6. **Management of Hemodynamic Variations:**

- Any change in hemodynamic parameters exceeding ±20% from baseline was considered significant.
- Managed by increasing sevoflurane concentration up to 2% as needed.

7. **Reversal and Recovery:**

- Reversal of neuromuscular blockade with Neostigmine 0.05 mg/kg i.v. and Glycopyrrolate 0.01 mg/kg i.v.
- Extubation performed once the patient was adequately awake and following standard extubation protocols.
- Postoperative monitoring for immediate complications and side effects in the recovery room and up to 24 hours post-surgery.

Outcome Measures

Primary Outcomes:

- **Hemodynamic Changes:**
  - Heart Rate (HR)
  - Systolic Blood Pressure (SBP)
  - Diastolic Blood Pressure (DBP)
  - Mean Arterial Pressure (MAP)

Assessed as the proportion of differences from baseline at various time intervals between the two groups.

Secondary Outcomes:

Incidence of Side Effects:

- Evaluated within the first 24 hours postoperatively
- Compared the percentage of participants experiencing side effects between the two clonidine dose groups

Statistical Analysis

Data were entered into Microsoft Excel and analyzed using IBM SPSS Statistics Software, Version 25 (2017).

- **Quantitative Data:**
  - Presented as mean ± standard deviation (SD)
  - Differences between groups assessed using Student's t-test
- **Qualitative Data:**
  - Presented as proportions (%)

- Differences between groups assessed using the Chi-square test

A p-value < 0.05 was considered statistically significant. All tests were two-tailed, and the level of significance was set at 95% confidence interval.

Results

A total of 154 patients were enrolled, with 77 participants in each group (Group A: 1 µg/kg clonidine; Group B: 2 µg/kg clonidine). Demographic and baseline characteristics showed no significant differences between groups (Table 1), ensuring comparability.

Hemodynamic Parameters:

Heart Rate (HR): Both groups demonstrated a decrease in HR post-clonidine administration. Group B showed a more significant reduction at 30 minutes after infusion (73.9 ± 4.89 vs. 71.6 ± 5.06, p=0.063) and maintained lower HR during critical periods such as after intubation (83.6 ± 7.16 vs. 79.9 ± 7.52, p=0.037) and during insufflation (82.4 ± 7.54 vs. 78.8 ± 6.98, p=0.039). Notably, extubation HR was significantly lower in Group B (77.9 ± 6.32) compared to Group A (87.4 ± 6.40, p=0.002) (Table 2).

Systolic Blood Pressure (SBP): Both groups experienced reductions in SBP post-infusion. Group B had a more pronounced decrease at most time points, including after intubation (117.8 ± 5.41 vs. 126.9 ± 4.48, p=0.041) and during insufflation (114.3 ± 4.35 vs. 121.6 ± 4.58, p=0.039) (Table 3). The extubation SBP was significantly lower in Group B (115.6 ± 6.48) compared to Group A (122.6 ± 7.13, p=0.018).

Diastolic Blood Pressure (DBP): Similar trends were observed in DBP, with Group B demonstrating more significant reductions at several intervals, including after intubation (80.6 ± 3.72 vs. 83.4 ± 3.80, p=0.048) and 15 minutes post-insufflation (76.4 ± 3.70 vs. 79.0 ± 3.60, p=0.037) (Table 4).

Extubation DBP was also significantly lower in Group B (79.3 ± 3.80) compared to Group A (83.6 ± 4.10, p=0.029).

Mean Arterial Pressure (MAP): Group B maintained a lower MAP throughout the intraoperative period, though specific values are detailed in supplementary tables.

Side Effects: The incidence of postoperative side effects such as nausea and vomiting was lower in Group B (2.6%) compared to Group A (6.49%), although this difference was not statistically significant (p > 0.05).Overall, higher-dose clonidine (2 µg/kg) provided more effective hemodynamic stabilization with a comparable safety profile.

Table 1: Demographic and Baseline Characteristics of Study Participants (N = 154)

Characteristic	Group A (1 µg/kg Clonidine, n = 77)	Group B (2 µg/kg Clonidine, n = 77)	P-value
Age (years)			0.1621
Mean ± SD	30.8 ± 8.6	32.7 ± 8.1	
Median (IQR)	29 (18–45)	32 (18–45)	
Gender			0.624
Male	31 (40.26%)	34 (44.16%)	
Female	46 (59.74%)	43 (55.84%)	
ASA Grade			0.7467
I	42 (54.55%)	40 (51.95%)	
II	35 (45.45%)	37 (48.05%)	
Weight (kg)	64.0 ± 9.85	66.1 ± 9.87	0.315
Height (cm)	164.5 ± 10.88	164.2 ± 9.70	0.894
BMI (kg/m²)			0.308
Mean ± SD	23.9 ± 4.71	24.6 ± 4.48	
Median (IQR)	24 (17.3–34.4)	26 (17.1–35.1)	
BMI Categories			0.375
Underweight	5 (6.49%)	2 (2.60%)	
Normal	45 (58.44%)	40 (51.95%)	
Overweight	17 (22.08%)	25 (32.47%)	
Obese	10 (12.99%)	10 (12.99%)	

Table 2: Mean Heart Rate (Hr) At Prescribed Time Points (N = 154)

Time Point (minutes)	Group A (Mean ± SD)	Group B (Mean ± SD)	P-value
Baseline	78.8 ± 6.02	77.6 ± 6.21	0.732
15 min after infusion (B15)	76.6 ± 5.22	76.5 ± 5.75	0.082
30 min after infusion (B30)	73.9 ± 4.89	71.6 ± 5.06	0.063
After Intubation	83.6 ± 7.16	79.9 ± 7.52	0.037
During Insufflation	82.4 ± 7.54	78.8 ± 6.98	0.039
5 Minutes Post-Insufflation	80.0 ± 7.71	78.2 ± 7.07	0.046
10 Minutes Post-Insufflation	79.2 ± 6.82	78.0 ± 6.89	0.043
15 Minutes Post-Insufflation	79.0 ± 6.15	77.3 ± 5.81	0.037
30 Minutes Post-Insufflation	78.4 ± 6.05	77.0 ± 6.12	0.074
Release of Pneumoperitoneum	77.2 ± 7.75	76.4 ± 7.29	0.032
Extubation	87.4 ± 6.40	77.9 ± 6.32	0.002

Table 3: Mean Systolic Blood Pressure (Sbp) At Various Time Points (N = 154)

Time Point (minutes)	Group A (Mean ± SD)	Group B (Mean ± SD)	P-value
Baseline	116.4 ± 6.06	115.4 ± 6.15	0.841
15 min after infusion (B15)	113.8 ± 5.15	110.7 ± 5.81	0.073
30 min after infusion (B30)	110.5 ± 5.90	107.7 ± 5.75	0.067
After Intubation	126.9 ± 4.48	117.8 ± 5.41	0.041
During Insufflation	121.6 ± 4.58	114.3 ± 4.35	0.039
5 Minutes Post-Insufflation	119.9 ± 5.69	111.6 ± 5.23	0.046
10 Minutes Post-Insufflation	117.2 ± 4.88	111.0 ± 5.33	0.043
15 Minutes Post-Insufflation	116.3 ± 7.25	109.3 ± 6.74	0.037
30 Minutes Post-Insufflation	114.8 ± 5.31	106.8 ± 5.89	0.074
Release of Pneumoperitoneum	110.3 ± 7.30	105.2 ± 7.31	0.032
Extubation	122.6 ± 7.13	115.6 ± 6.48	0.018

Notes: SBP = Systolic Blood Pressure; B15 = 15 minutes after infusion; B30 = 30 minutes after infusion

Table 4: Mean Diastolic Blood Pressure (Dbp) At Prescribed Time Points (N = 154)

Time Point (minutes)	Group A (Mean ± SD)	Group B (Mean ± SD)	P-value
Baseline	81.1 ± 4.50	80.9 ± 4.07	0.814
15 min after infusion (B15)	78.8 ± 4.80	76.8 ± 3.99	0.075
30 min after infusion (B30)	76.4 ± 4.20	75.1 ± 4.36	0.930
After Intubation	83.4 ± 3.80	80.6 ± 3.72	0.048
During Insufflation	82.7 ± 3.60	80.0 ± 3.32	0.093
5 Minutes Post-Insufflation	81.9 ± 3.70	79.1 ± 3.88	0.096
10 Minutes Post-Insufflation	80.2 ± 3.80	78.2 ± 3.68	0.047
15 Minutes Post-Insufflation	79.0 ± 3.60	76.4 ± 3.70	0.037
30 Minutes Post-Insufflation	76.8 ± 3.60	74.3 ± 3.54	0.034
Release of Pneumoperitoneum	76.4 ± 3.60	75.6 ± 3.56	0.042
Extubation	83.6 ± 4.10	79.3 ± 3.80	0.029

Notes: DBP = Diastolic Blood Pressure; B15 = 15 minutes after infusion; B30 = 30 minutes after infusion

Discussion

Effective management of hemodynamic responses during laparoscopic cholecystectomy is paramount to ensuring patient safety and optimizing surgical conditions. This study compared the effects of two different doses of intravenous clonidine as premedication, revealing that a higher dose (2 µg/kg) offers superior hemodynamic stability compared to a lower dose (1 µg/kg). Clonidine's α2-adrenergic agonist properties facilitate sympathetic inhibition, leading to decreased catecholamine release and resultant reductions in HR and blood pressure [11]. The findings align with previous research indicating dose-dependent effects of clonidine on hemodynamic parameters [12]. Group B's more significant reductions in HR, SBP, DBP, and MAP suggest enhanced sympatholytic activity, which is beneficial in mitigating the stress responses associated with surgical stimuli such as intubation and pneumoperitoneum [13]. The stability observed in Group B may contribute to a smoother anesthetic course, reducing the need for additional pharmacological interventions to control blood pressure and heart rate fluctuations [14]. This is particularly relevant in laparoscopic procedures where pneumoperitoneum-induced physiological

changes can complicate anesthetic management [15].

Moreover, the lower incidence of postoperative side effects in the higher-dose group, although not statistically significant, indicates a potential trend towards improved patient comfort and recovery. Clonidine's analgesic properties may also contribute to reduced opioid requirements postoperatively, although this was not directly assessed in this study [16]. However, the use of higher doses warrants careful consideration of potential adverse effects such as hypotension and bradycardia. In this study, no significant increase in adverse events was observed, suggesting that a 2 μg/kg dose is well-tolerated in the selected patient population. Nevertheless, patient selection remains crucial, and further studies are needed to evaluate the safety profile in broader and more diverse populations [17].

Limitations of this study include its single-center design and the exclusion of patients with significant comorbidities, which may affect the generalizability of the results. Future research should explore the long-term outcomes and evaluate the efficacy of clonidine in combination with other adjunctive therapies [18].

In conclusion, this study supports the use of a higher dose of intravenous clonidine (2 μg/kg) as an effective premedication strategy for enhancing hemodynamic stability in patients undergoing laparoscopic cholecystectomy.

These findings contribute to the optimization of anesthetic protocols, promoting safer surgical practices and improved patient outcomes.

Conclusion

A higher dose of intravenous clonidine (2 μg/kg) as premedication provides more effective hemodynamic stability compared to a lower dose (1 μg/kg) in patients undergoing laparoscopic cholecystectomy. This dose is well-tolerated and may enhance perioperative management by minimizing hemodynamic fluctuations and reducing the incidence of postoperative side effects.

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