RESEARCH PAPER

Intrathecal Versus Intravenous Clonidine (50 µg) for Attenuation of Pneumoperitoneum-Related Hemodynamic Responses During Laparoscopic Assisted Vaginal Hysterectomy: A Prospective Randomized Comparative Study

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ABSTRACT

Background: Carbon dioxide pneumoperitoneum produces predictable sympathetic and neurohumoral activation; this combination with an increased systemic vascular resistance and increased arterial pressure complicates anesthetic management during laparoscopy. α2-agonists reduce central sympathetic outflow and may improve perioperative circulatory stability. There is good evidence for intravenous clonidine but few comparative data against intrathecal clonidine (as a sole neuraxial adjunct under general anesthesia).

Methods: In a prospective randomized comparative trial at Apollo BGS Hospital, Mysore (June 2017–May 2018), 60 ASA I–II adults (35–60 years) scheduled for elective laparoscopic assisted vaginal hysterectomy under general endotracheal anesthesia were randomized to the administration of intravenous clonidine 50 µg in 50 mL normal saline over 10 minutes, 10 minutes ahead of induction (Group IV; n=30), or intrathecal clonidine 50 µg at L3–L4 immediately before induction (Group IT; n=30). Heart rate (HR) and blood pressures were obtained under a blind observer at baseline (T0), post-intubation (T1), pre-pneumoperitoneum (T2), 5/15/30 minutes post pneumoperitoneum (T3/T4/T5), and 5 minutes post CO_2 release (T6). Ramsay Sedation Score (RSS) was administered in PACU for the evaluation of postoperative sedation.

Results: The baseline population and ASA distribution were similar. During pneumoperitoneum, Group IT had significantly reduced HR at T3–T6 (e.g., T4: 79.2±10.2 vs 87.5±10.9 bpm; p=0.004) and lower SBP/DBP/MAP from T2–T6 (all p≤0.011 at crucial intraoperative points). RSS distribution did not differ between groups (p=0.590). Hypertension episodes were fewer in Group IT (1 vs 6), while hypotension was more frequent (4 vs 1); no post-dural puncture headache occurred in Group IT

Conclusion: In this LAVH cohort, intrathecal clonidine 50 µg resulted in enhanced attenuation of pneumoperitoneum-related tachycardia and pressor responses relative to intravenous clonidine 50 µg, without increasing early postoperative sedation. The trade-off was increased hypotension, demonstrating that a careful dose and readiness for vasopressors are warranted.

Keywords: clonidine; intrathecal; intravenous; pneumoperitoneum; laparoscopy; hemodynamics; hysterectomy; anesthesia

How to cite this article: Rajath U, Nileena P, Kulkarni S, Yadhunandan S. Intrathecal Versus Intravenous Clonidine (50 µg) for Attenuation of Pneumoperitoneum-Related Hemodynamic Responses During Laparoscopic Assisted Vaginal Hysterectomy: A Prospective Randomized Comparative Study. Int J Drug Deliv Technol. 2026;16(9s): 15-21; DOI: 10.25258/ijddt.16.9s.2

INTRODUCTION

Laparoscopic surgery is preferred for decreased tissue trauma, earlier ambulation, and shorter hospital stay, but presents unique anesthetic difficulties in response to carbon dioxide pneumoperitoneum and positional adjustments. Pneumoperitoneum formation raises intra-abdominal pressure and disrupts venous return, afterload, and pulmonary mechanics; clinically, this is frequently observed as increased systemic vascular resistance and arterial pressure with variable changes in cardiac output. In classic physiologic studies, the effects of laparoscopic insufflation were demonstrably hemodynamic perturbations with comparative research suggesting that the nature of the insufflation gas also modulates cardiovascular responses. Collectively these results serve to demonstrate that “minimally invasive” is not synonymous with “physiologically minimal,” especially in the insufflation stage. [1],[2]

Even beyond mechanical effects, pneumoperitoneum provokes neurohumoral stress activation. Increased

amounts of catecholamines and vasopressin have been observed, especially at elevated intra-abdominal pressures, highlighting the importance of endocrine, rather than simply mechanical, pathways in the pressor response. Laparoscopy can induce a lower total surgical stress compared to open surgery, though the hemodynamic stress response during the intraoperative period continues to be of clinical importance, especially for patients with limited cardiovascular reserve. [4] Consequently, anesthesiologists have pursued several interventions—insufflation pressure, ventilation, anesthetic depth, pharmacologic modulation—to blunt these effects.

As pharmacologically active alternatives, α2-adrenergic agonists are attractive because they reduce central sympathetic outflow, lower circulating catecholamines, and enhance baroreflex-mediated stability. An older, more widely available α2-agonist, clonidine offers sedative and analgesic-sparing properties which tend to stabilize perioperative hemodynamics. There is evidence for the premedication with oral clonidine to enhance the perioperative hemodynamic stability and reduce anesthetic requirements in laparoscopic setting. [5] Intravenous clonidine has similarly been found in the literature, with dose comparisons indicating meaningful attenuation of pneumoperitoneum-associated stress responses, but at higher doses that higher risk of hypotension is observed.

Intrathecal clonidine, predominantly investigated as a local anesthetic adjuvant, has consistently been effective in prolonging analgesia and modifying sympathetic tone; systematic study evidence confirms that neuraxial clonidine does indeed have a meaningful effect on perioperative physiology, whilst dose-related hypotension and sedation are still key safety issues. Intrathecal clonidine can provide a direct spinal sympatholytic effect and may theoretically attenuate the pneumoperitoneum-related pressor response more potently than a low intravenous dose under a general anesthesia primary anesthetic [7]. Yet, head-to-head comparisons of intrathecal clonidine alone versus intravenous clonidine (both at low dose) to demonstrate hemodynamic attenuation of pneumoperitoneum during laparoscopic gynecologic surgery remain infrequent.

Therefore, this study compared intravenous clonidine 50 µg with intrathecal clonidine 50 µg in adults undergoing laparoscopic assisted vaginal hysterectomy under general anesthesia, focusing on attenuation of hemodynamic responses to pneumoperitoneum and on early postoperative sedation. [8]

MATERIALS AND METHODS

Study design, setting, duration

A prospective, randomized, comparative study was conducted at Apollo BGS Hospital, Mysore, India, over 12 months (June 2017 to May 2018). The Institutional Ethical Committee approved the protocol, and written informed consent was obtained from all participants.

Participants

Sixty adult patients (35–60 years), American Society of Anesthesiologists (ASA) physical status I–II, scheduled for elective laparoscopic assisted vaginal hysterectomy (LAVH) under general endotracheal anesthesia were enrolled.

Inclusion criteria: ASA I–II; age 35–60 years; elective LAVH under general anesthesia. **Exclusion criteria:** BMI >30 kg/m²; uncontrolled hypertension; cardiac disease; hepatic/renal impairment; current clonidine/methyldopa/beta-blocker/benzodiazepine/MAOI therapy; anticipated difficult intubation; clonidine allergy or dependence; contraindication to intrathecal injection.

Randomization and blinding

Patients were randomly allocated using a computer-generated random number table into two equal groups (n=30 each). The anesthesiologist performing the study intervention was not the observer. A second anesthesiologist, blinded to group assignment, induced anesthesia and recorded intraoperative variables and postoperative sedation.

Interventions

- **Group IV:** clonidine 50 µg diluted in 50 mL normal saline infused intravenously over 10 minutes, completed 10 minutes before induction.
- **Group IT:** clonidine 50 µg intrathecally (prepared by diluting 150 µg in 3 mL to yield 50 µg/mL), injected at L3–L4 with a 27G Quincke needle in the sitting position immediately before induction.

Anesthetic technique

All subjects were given fentanyl 2 µg/kg by injection and midazolam 0.03 mg/kg via injectable, then preoxygenation using 100% oxygen for 3 minutes. Induction, propofol (2 mg/kg) and vecuronium (0.1 mg/kg). Tracheal intubation with a 7.5-mm endotracheal tube was done. Mechanical ventilation was targeted for $EtCO_2$ 35–45 mmHg (tidal volume 8 mL/kg; rate ~14/min adjusted as necessary). Maintenance employed oxygen/nitrous oxide (33%/67%) and isoflurane ~0.5% with incremental vecuronium boluses (1 mg) as indicated.

Pneumoperitoneum was formed with CO_2 and intra-abdominal pressure was kept at 12–15 mmHg. The reversal was performed using neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg intravenously.

Outcomes and measurements

Continuous ECG, SpO_2, $EtCO_2$, and non-invasive blood pressure were monitored. HR, SBP, DBP, and MAP were recorded at:
T0 (baseline pre-induction before clonidine), T1 (3 minutes post-intubation), T2 (pre-pneumoperitoneum), T3 (5 minutes after pneumoperitoneum), T4 (15 minutes), T5 (30 minutes), T6 (5 minutes after CO_2 release).

Hemodynamic derangements were treated per protocol: hypertension (SBP >20% baseline) by isoflurane increments; tachycardia (HR >100/min) by fentanyl 25 µg bolus; hypotension (SBP <20% baseline) by fluids then ephedrine 6 mg if needed; bradycardia (HR <50/min with hypotension) by atropine 0.6 mg, repeat once if required.

Postoperative sedation was assessed 15 minutes after PACU arrival using Ramsay Sedation Score (1–6). Patients were followed for 72 hours for post-dural puncture headache (PDPH).

Statistical analysis

Data were summarized as mean±SD for continuous variables and n (%) for categorical variables. Between-group comparisons used independent-samples t tests for continuous measures and chi-square–based association tests for categorical outcomes. Repeated-measures ANOVA assessed changes over time. A two-sided p value <0.05 was considered statistically significant. Analyses were performed using SPSS v20.0.

RESULTS

Narrative summary

Sixty participants completed the study (30 per group). The age distribution, anthropometrics (weight, height, BMI), and ASA grades were comparable between groups, demonstrating successful randomization and a balanced baseline risk profile. The duration of surgery was comparable (IT 78.63 vs IV 80.56 minutes; p=0.275), limiting procedural time as a confounder.

Hemodynamic patterns diverged most clearly during the pneumoperitoneum window. Before insufflation, both groups showed modest reductions from baseline after induction and stabilization (T1–T2), with no clinically meaningful separation except for slightly lower pre-pneumoperitoneum SBP/DBP/MAP in the intrathecal group (T2 p≤0.008). Once pneumoperitoneum was created, Group IV tended to return toward baseline HR and exhibited higher arterial pressures (SBP/DBP/MAP), whereas Group IT maintained values below baseline across T3–T5, reflecting stronger attenuation of insufflation-associated sympathetic activation.

Particularly (for T3–T5) during pneumoperitoneum, HR was significantly lower in Group IT compared to Group IV (p=0.013, 0.004, 0.001) and this was true despite CO_2 release at T6 (p=0.015). The force attenuation was more acute: SBP, DBP and MAP were notably decreased in Group IT compared to Group IV at T3–T6 (all p≤0.011 at important points), indicating the combination of chronotropic and vasomotor dampening effects with intrathecal clonidine.

Early postoperative sedation (Ramsay score at 15 minutes in PACU) did not differ between groups (p=0.590). Adverse event patterns suggested a trade-off: hypertension episodes were more frequent with intravenous clonidine (6 vs 1), while hypotension was more frequent with intrathecal clonidine (4 vs 1). No bradycardia occurred in either group, and no PDPH was observed in Group IT over 72 hours.

Table 1. Baseline and perioperative characteristics

Variable	Group IT (n=30)	Group IV (n=30)	p value
Age distribution (39–55 years)	Comparable	Comparable	0.655
Weight (kg), mean±SD	52.23±3.54	53.29±3.92	0.278
Height (cm), mean±SD	153.38±6.43	154.26±5.80	0.578
BMI (kg/m²), mean±SD	22.26±2.42	22.40±1.38	0.779
ASA I / ASA II, n (%)	14 (46.7) / 16 (53.3)	17 (56.7) / 13 (43.3)	0.633
Duration of surgery (min), mean	78.63	80.56	0.275

Comparability with baseline for demographic and perioperative variables was high. Both groups had comparable anthropometrics and ASA grades, suggesting that differences in hemodynamic trajectories were unlikely to reflect unequal baseline cardiovascular risk and/or body habitus. A similar procedure duration also decreased confounding of exposure time to pneumoperitoneum and anesthetic depth. This balanced profile lends credence to the attribution of intraoperative differences largely to the clonidine route rather than to patient- or surgery-associated heterogeneity.

Table 2. Hemodynamic variables across timepoints (mean±SD)

Variable	Time	Group IT	Group IV	p value
HR (bpm)	T0	89.43±13.30	87.03±11.77	0.462
	T3	80.16±11.75	87.46±10.30	0.013
	T4	79.20±10.23	87.50±10.95	0.004
	T5	78.00±10.40	86.83±9.60	0.001
	T6	74.20±10.08	80.00±7.70	0.015
SBP (mmHg)	T0	133.13±14.38	134.73±11.16	0.632
	T3	125.36±13.99	140.96±13.01	<0.001
	T4	123.23±13.42	140.56±14.06	<0.001
	T5	123.00±13.78	140.86±13.35	<0.001
	T6	112.16±13.75	123.63±12.40	0.001
MAP (mmHg)	T0	98.15±9.51	100.29±7.29	0.331
	T3	91.00±9.08	104.80±7.90	<0.001
	T4	89.65±10.16	103.96±9.95	<0.001
	T5	89.35±9.07	104.50±9.38	<0.001
	T6	85.34±11.77	93.71±9.04	0.003

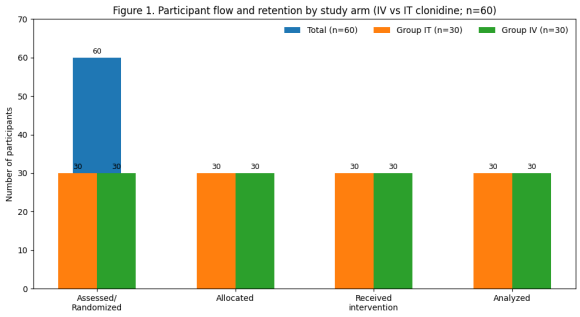
In the intrathecal group, the chronotropic and pressor profiles were consistently lower during pneumoperitoneum. When compared to the intravenous group (where baseline HR and pressures were similar), insufflation drove a relative return to baseline, whilst intrathecal clonidine sustained HR and MAP values below baseline during 30 min of pneumoperitoneum and following CO_2 release. The extent and duration of separation—MAP more especially—indicate route-dependent sympathetic modulation and, in particular, greater attenuation with intrathecal clonidine.

Table 3. Sedation and adverse events

Outcome	Group IT (n=30)	Group IV (n=30)	p value
Ramsay Sedation Score (PACU 15 min)	Comparable distribution	Comparable distribution	0.590
Hypertension episodes	1	6	—
Hypotension episodes	4	1	—
Tachycardia episodes	0	2	—
Bradycardia episodes	0	0	—
PDPH within 72 hours	0	Not applicable	—

Early PACU sedation did not differ despite different clonidine routes, implying that the intrathecal 50 µg dose did not translate into clinically meaningful early oversedation when used with general anesthesia. The safety signal was instead hemodynamic: intravenous clonidine was associated with more hypertension/tachycardia episodes, aligning with less effective pressor attenuation, whereas intrathecal clonidine shifted the profile toward hypotension. Absence of PDPH supports technical safety in this cohort, though larger samples would be needed for rare-event certainty.

FIGURE 1. PARTICIPANT FLOW AND RETENTION BY STUDY ARM (IV VS IT CLONIDINE; N=60)



The following bar chart represents the flow and retention of participants in the randomized comparative trial. All 60 eligible patients were randomized, with equal allocation to intrathecal clonidine (Group IT, n=30) and intravenous clonidine (Group IV, n=30). Each allocated participant received the designated intervention and was included in analyses, reflecting 100% adherence and no attrition from either arm. This thorough follow-through minimizes attrition bias while increasing internal validity within hemodynamic comparisons.

FIGURE 2. TREND DEPICTION OF HR AND MAP OVER TIME

Figure 2A. Heart Rate Trend Across Study Timepoints

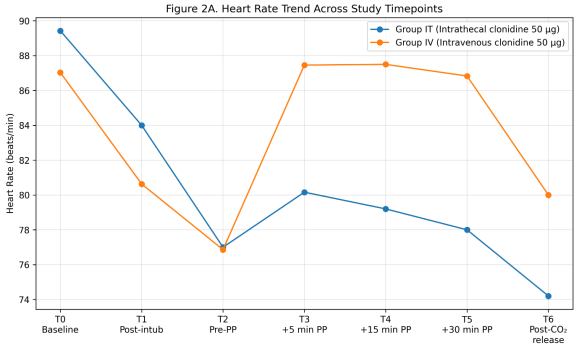
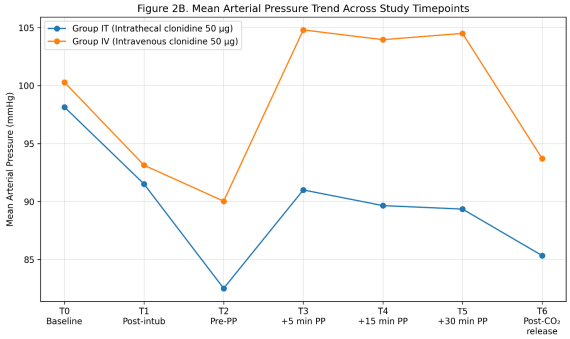


Figure 2B. Mean Arterial Pressure Trend Across Study Timepoints



The pattern is clinically intuitive: sympathetic stimulation during pneumoperitoneum is reflected as a relative rise (or return toward baseline) in HR/MAP, most visible in the intravenous group. Intrathecal clonidine appears to flatten this trajectory, maintaining lower HR and MAP despite the same insufflation pressures and anesthetic regimen. Persistence after CO_2 release suggests not only reduced peak response but also faster recovery toward a lower steady-state, consistent with spinal sympatholysis.

DISCUSSION

We showed that intrathecal clonidine 50 µg attenuated the rates of pneumoperitoneum-related tachycardia and pressor responses more strongly than intravenous clonidine 50 µg in adults undergoing LAVH under general anesthesia. The hemodynamic differential is consistent with classic physiology: pneumoperitoneum raises arterial pressure and systemic vascular resistance through mechanical action and neurohumoral activation, such as the release of catecholamines and vasopressin. Controlled physiological studies have documented remarkable hemodynamic perturbations during pneumoperitoneum and have demonstrated that higher intra-abdominal pressures augment catecholamine elevations. [2],[3] In parallel, laparoscopy—despite reduced overall surgical stress compared with open procedures—still triggers measurable endocrine and metabolic stress responses during key intraoperative periods. [4],[9],[10]

Clonidine's pharmacologic rationale is strong: as an α2-agonist, it reduces central sympathetic outflow and blunts circulating catecholamines. Prior work has shown that clonidine can modulate the endocrine correlates of laparoscopy-associated hemodynamic changes, supporting its mechanistic fit for this problem. [11] Clinically, oral clonidine premedication has been associated with greater perioperative hemodynamic stability and reduced anesthetic requirements in laparoscopic cholecystectomy, consistent with a sympathetic-dampening effect. [5] Intravenous clonidine dosing studies have further suggested that clonidine attenuates the hemodynamic stress response to pneumoperitoneum, with higher doses offering stronger effects but at the cost of more hypotension. [6]

The current comparison is remarkable because the two arms both utilized a small absolute dose (50 µg) but the intrathecal pathway produced a greater suppression during pneumoperitoneum. A more plausible rationale is that intrathecal clonidine presents a direct spinal sympatholytic effect by lowering sympathetic efferent tone, and by modifying baroreflex responsiveness at a segmental level. There is a body of data from systematic trials showing that neuraxial clonidine has a relevant impact on perioperative physiology, whilst the side effects of dose-induced hypotension and sedation are already to be anticipated. [7] Here the pattern of hypotension (4 vs 1 episodes) agrees with that profile and sedation also did not differ; presumably due to low doses and assessed early (15 minutes in the PACU), when the consciousness of the patient is also affected by residual anesthetic effects.

The broader take is reinforced by comparative literature concerning other sympatholytic strategies. Furthermore, in laparoscopic surgery, both esmolol and dexmedetomidine (another α2-agonist) are reported to suppress hemodynamic responses related to pneumoperitoneum, illustrating a mechanism in which blockade of sympathetic pathways is effective regardless of drug class or the mode of administration. In a similar vein, esmolol and calcium-channel blockade regimens also have been shown to reduce hemodynamic variability during pneumoperitoneum in randomized trials but in different surgical populations. [13] Other adjuncts, including magnesium sulfate, may also attenuate pneumoperitoneum-related hemodynamic instability and neurohumoral activation that were found in controlled trials, indicating that several mechanisms of action (sympatholysis, vasopressin suppression, and SVR modulation) can reach the same clinical endpoint.

The implication is that intrathecal clonidine—used immediately before general anesthesia—can flatten the peaks of HR and arterial pressure associated with

pneumoperitoneum in a meaningful way, which may be beneficial for patients in whom tachycardia or hypertension are not desirable (e.g., coronary disease, uncontrolled hypertension—though such patients were excluded here). Nevertheless, this raised frequency of hypotension reinforces the importance of a personalized fluid regimen, careful titration of anesthetic, and preparation with vasopressors. Because intraoperative management protocols (isoflurane increments, fentanyl boluses, fluids/ephedrine) may drive hemodynamic trajectories, while the protocolized approach used here facilitated comparability, it may restrict the degree of generalization to other anesthetic techniques.

Limitations and research implications

This was a single-center study with a modest sample size and inclusion restricted to ASA I–II, limiting extrapolation to higher-risk populations. Hemodynamic measures were non-invasive and endocrine markers (catecholamines/vasopressin) were not measured, limiting mechanistic confirmation. Sedation was assessed at a single early PACU timepoint, which may miss later sedative differences. Future multicenter trials should evaluate dose-response by route, incorporate invasive hemodynamic indices and neurohumoral biomarkers, and study clinically meaningful outcomes such as myocardial ischemia surrogates, recovery quality, and analgesic consumption.

CONCLUSION

In the adults with laparoscopic assisted vaginal hysterectomy, immediate intrathecal clonidine 50 µg pre-induction was associated with more consistent attenuation of pneumoperitoneum-associated tachycardia and pressor responses than intravenous clonidine 50 µg given pre-induction. Improved HR and arterial pressure control was observed at all time points during pneumoperitoneum and continued for a short period after CO_2 release. Early postoperative sedation was similar, suggesting that improved intraoperative stability did not come at the cost of early PACU oversedation. The main trade-off was the increased incidence of hypotension with intrathecal clonidine, which justified ongoing hemodynamic monitoring and selective fluid/vasopressor treatment.

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