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ORIGINAL STUDY

Chronotropic Response to Intratracheal versus Intravenous Atropine in Anesthetized Adult Patients: A Randomized Controlled Trial

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ABSTRACT

Atropine is a commonly used anticholinergic agent in anesthetic practice, administered primarily to counteract bradycardia. Rapid treatment of intraoperative bradycardia is clinically critical, as delays may lead to hemodynamic compromise. This study aimed to compare the onset, magnitude, and duration of the chronotropic response to atropine administered via the intravenous (IV) versus intratracheal (IT) route in anesthetized adult patients. A prospective, single-blind, randomized controlled study was conducted on 60 adult patients classified as American Society of Anesthesiologists (ASA) physical status I-II, scheduled for elective peripheral surgery under general anesthesia. Patients were randomly allocated into three equal groups (n = 20 each). Group A received 0.6 mg atropine intratracheally; Group B received 0.6 mg atropine intravenously with 1 mL saline instilled intratracheally; Group C (control) received 1 mL of 0.9% saline intratracheally. The primary outcome was onset of chronotropic effect (time to 10% increase in heart rate from baseline). Heart rate (HR) was recorded at 15-second intervals for the first minute, then every minute for 15 minutes. Both Groups A and B showed a statistically significant increase in heart rate ($p < 0.01$). The maximum HR increase was comparable between groups (Group A: +28.15 bpm; Group B: +29.15 bpm; $p > 0.05$), confirming equivalent efficacy. Onset of action was significantly faster in Group A (21 sec vs. 46.5 sec; $p < 0.01$), as was time to peak effect (49.5 sec vs. 267 sec; $p < 0.01$). Group C showed no significant chronotropic change. Intratracheal atropine produces a chronotropic response equivalent in magnitude but significantly faster in onset than the intravenous route, and may be considered as an effective alternative route, particularly when intravenous access is unavailable or delayed.

Keywords: Atropine, General anesthesia, Intratracheal, Heart rate, Chronotropic, Bradycardia

1. Introduction

Intraoperative bradycardia is a clinically significant event, occurring in approximately 11% of perioperative arrhythmias, and may result in hemodynamic compromise if not promptly treated [1, 2]. Atropine, a competitive antagonist at muscarinic acetylcholine receptors, remains the first-line pharmacological agent for the management of symptomatic bradycardia in anesthetic practice [3].

While intravenous (IV) administration is the standard route, situations arise in which IV access is unavailable or delayed, particularly in emergency or resource-limited settings. The intratracheal (IT) route has been proposed as an alternative, based on evidence from cardiopulmonary resuscitation (CPR) protocols [4]. However, data specifically comparing the two routes in anesthetized patients with a secured airway and intact hemodynamics remain scarce. Existing literature has largely focused on the cardiac

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arrest setting, where severely reduced pulmonary perfusion may impair drug absorption [5], making results difficult to extrapolate to the anesthetic context. This gap justifies the present investigation.

The primary outcome of this study was the onset of chronotropic effect, defined as time to a 10% increase in heart rate from baseline, a validated surrogate marker for systemic drug absorption [1, 3]. Secondary outcomes included time to peak heart rate, maximum heart rate increase, and duration of chronotropic effect.

1.1. Pharmacology of atropine

Atropine is a tertiary amine derived from Atropa belladonna, producing reversible, non-selective blockade of muscarinic receptor subtypes (M1, M2, M3). Its principal cardiovascular effect is vagolysis, leading to increased heart rate, enhanced atrioventricular conduction, and facilitated His-Purkinje conduction [6, 7].

1.2. Rationale for the intratracheal route

Pulmonary drug absorption is governed by lipid solubility, tidal volume, and integrity of the alveolocapillary membrane [8, 9]. The pulmonary circulation offers a large absorptive surface and bypasses delays inherent in peripheral venous delivery, which requires transit through the right heart before reaching the systemic circulation [10, 11]. In the present study, the same dose (0.6 mg) was used for both routes to allow direct pharmacodynamic comparison, rather than the guideline-recommended 2-3x IT dose used in CPR settings [4, 12].

2. Patients and methods

2.1. Study design and ethical considerations

This prospective, single-blind, randomized controlled trial was conducted from January 7 to February 28, 2026, in the Department of Anesthesia at Al-Nasiriya Teaching Hospital, Thi Qar Governorate, Iraq. Ethical approval was granted by the Institutional Ethics Committee (Approval No. 447/1/2026). The study was conducted in accordance with the Declaration of Helsinki, following the research standards previously applied in randomized anesthesia trials conducted by our group at the same institution [13, 14]. All patients provided written informed consent. Participants were blinded to group assignment; outcomes were assessed by a blinded observer separate from the drug preparation team, minimizing observer bias.

2.2. Sample size calculation

Sample size was calculated based on an expected difference of 10 beats per minute (bpm) in onset heart rate change (SD = 8 bpm; power = 80%; alpha = 0.05), estimated from pilot data and prior literature [15]. This yielded a minimum of 11 patients per group. To allow for a 40% safety margin, 20 patients per group were enrolled (total n = 60).

2.3. Patient selection

Sixty adult patients undergoing elective peripheral surgery under general anesthesia were enrolled irrespective of sex.

Inclusion criteria: age 18–45 years; ASA physical status Class I or II; BMI less than 30 kg/m2; stable baseline heart rate 60–90 bpm.

Exclusion criteria: current smokers or history of pulmonary disease (which may impair pulmonary drug absorption); baseline HR > 90 bpm; intraabdominal or intrathoracic surgery; estimated intraoperative blood loss > 10% of calculated blood volume; requirement for isoflurane > 1.2% to maintain adequate anesthetic depth; known allergy to atropine.

2.4. Randomization and allocation concealment

Patients were randomly allocated to three equal groups (n = 20 each) using a computer-generated random number table. Allocation was concealed using sequentially numbered, sealed opaque envelopes opened by an independent research assistant immediately before drug preparation. The outcome assessor was blinded to group allocation throughout.

2.5. Group allocation

Group A: Atropine 0.6 mg administered intratracheally (IT) + 1 mL 0.9% saline IV flush.

Group B: Atropine 0.6 mg administered intravenously (IV) + 1 mL 0.9% NaCl instilled intratracheally (to ensure equivalent tracheal stimulation across all groups).

Group C (Control): 1 mL of 0.9% sodium chloride (NaCl) administered intratracheally.

2.6. Anesthetic protocol

No premedication was administered. Standard monitoring was applied (continuous ECG, SpO2, noninvasive blood pressure). Anesthesia was induced with propofol 1.5–2.5 mg/kg IV and rocuronium 0.6 mg/kg IV. Endotracheal intubation was performed following complete muscular relaxation; no lidocaine

laryngeal spray was applied. Maintenance was achieved with isoflurane 1.2% in 100% oxygen. The study drug was administered once HR had been stable for a minimum of three consecutive minutes and during a period of minimal surgical stimulation. Intratracheal instillation was performed via a fine-bore suction catheter advanced as distally as possible into the trachea, followed by five manual lung hyperinflations to promote distal drug distribution and enhance alveolar drug contact [10, 16].

2.7. Outcome measures and adverse effect monitoring

Heart rate was recorded continuously at 15-second intervals for the first minute following drug administration, then every minute for 15 minutes. The primary outcome was onset of action, defined as time to a 10% increase in HR from stable baseline. Secondary outcomes were: time to peak heart rate, maximum HR increase from baseline, and duration of chronotropic effect (time from onset to return of HR to within 10% of baseline). Adverse effects, including excessive tachycardia (HR $>$ 120 bpm), arrhythmias, and hemodynamic instability, were monitored and recorded throughout.

2.8. Statistical analysis

Data were tested for normality using the Shapiro-Wilk test. Within-group changes in heart rate over time were analyzed using repeated-measures analysis of variance (ANOVA) with post-hoc Bonferroni correction. Between-group comparisons of primary outcome parameters were performed using the independent-sample Student's t-test. A p-value $<$ 0.05 was considered statistically significant. Results are expressed as mean $\pm$ standard deviation (SD). No data were missing; all 60 enrolled patients completed the study.

3. Results

All 60 patients completed the study without dropout or missing data. Baseline characteristics were comparable across groups. No adverse effects including excessive tachycardia, arrhythmias, or hemodynamic instability were observed in any patient throughout the observation period.

3.1. Within-Group heart rate analysis

Group A (IT Atropine): Mean baseline HR 80.25 $\pm$ 7.36 bpm. Mean peak HR 107.70 $\pm$ 9.38 bpm; mean increase 28.15 $\pm$ 8.74 bpm ($t = 14.43$, $df = 19$, $p <$ 0.01).

Group B (IV Atropine): Mean baseline HR 81.20 $\pm$ 6.98 bpm. Mean peak HR 110.40 $\pm$ 11.85 bpm; mean increase 29.15 $\pm$ 7.92 bpm ($t = 16.48$, $df = 19$, $p <$ 0.01).

Group C (Control): No patient demonstrated a heart rate increase exceeding 5% of baseline over 15 minutes. (Fig. 1)

3.2. Primary outcome: Onset of chronotropic effect

Group A showed significantly faster onset of action (IT atropine: 21.0 $\pm$ 7.54 sec) compared to Group B (IV atropine: 46.5 $\pm$ 12.78 sec; $p <$ 0.01). Time to peak heart rate was also markedly shorter in Group A (49.5 $\pm$ 8.57 sec) than Group B (267.0 $\pm$ 68.75 sec; $p <$ 0.01) (Fig. 2). Statistically significant differences do not automatically imply clinical superiority; however, in a patient experiencing acute symptomatic bradycardia with hemodynamic compromise, an onset advantage of approximately 25 seconds and a peak-effect advantage of more than 3.5 minutes may substantially reduce the window of hemodynamic risk.

3.3. Secondary outcomes: Magnitude and duration

The maximum HR increase was comparable between Group A (28.15 $\pm$ 8.74 bpm) and Group B (29.15 $\pm$ 7.91 bpm; $p >$ 0.05), confirming equivalent peak chronotropic efficacy. The duration of effect was significantly shorter in Group A ($p <$ 0.01). Group C showed no clinically significant HR change (maximum increase $<$ 4 bpm in all patients) (Fig. 3).

4. Discussion

This randomized controlled trial demonstrates that intratracheal administration of atropine 0.6 mg produces a significantly faster onset of chronotropic action than the intravenous route, while achieving an equivalent peak effect. These findings are consistent with the pharmacokinetic basis for pulmonary drug absorption: the alveolar-capillary membrane provides rapid drug transit directly to the left-sided circulation, bypassing the delay inherent in peripheral venous delivery [1, 17]. This distinction is also supported by comparative vascular access data demonstrating that the route and speed of drug delivery significantly influence systemic onset time [18].

An important distinction must be made between statistical significance and clinical superiority. In elective, hemodynamically stable patients, the

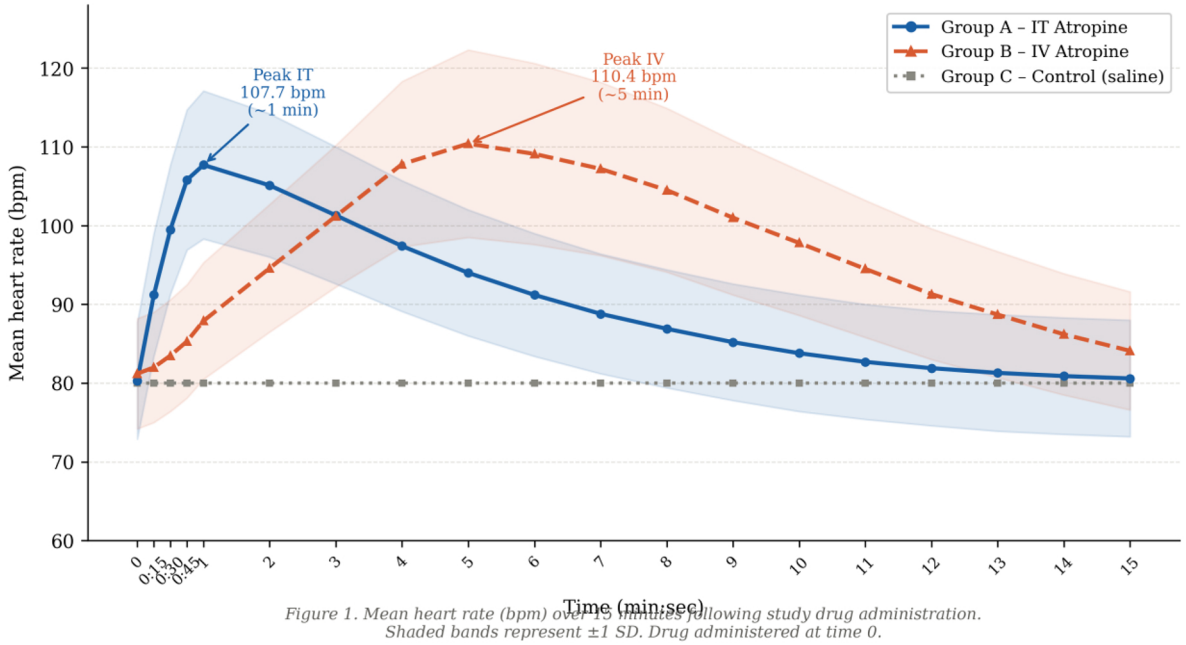

Fig. 1. Mean heart rate (bpm) over 15 minutes following study drug administration. Group A (IT atropine, blue) rises steeply and rapidly; Group B (IV atropine, orange dashed) rises more slowly; Group C (control, gray dotted) remains flat. Shaded bands = ±1 SD.

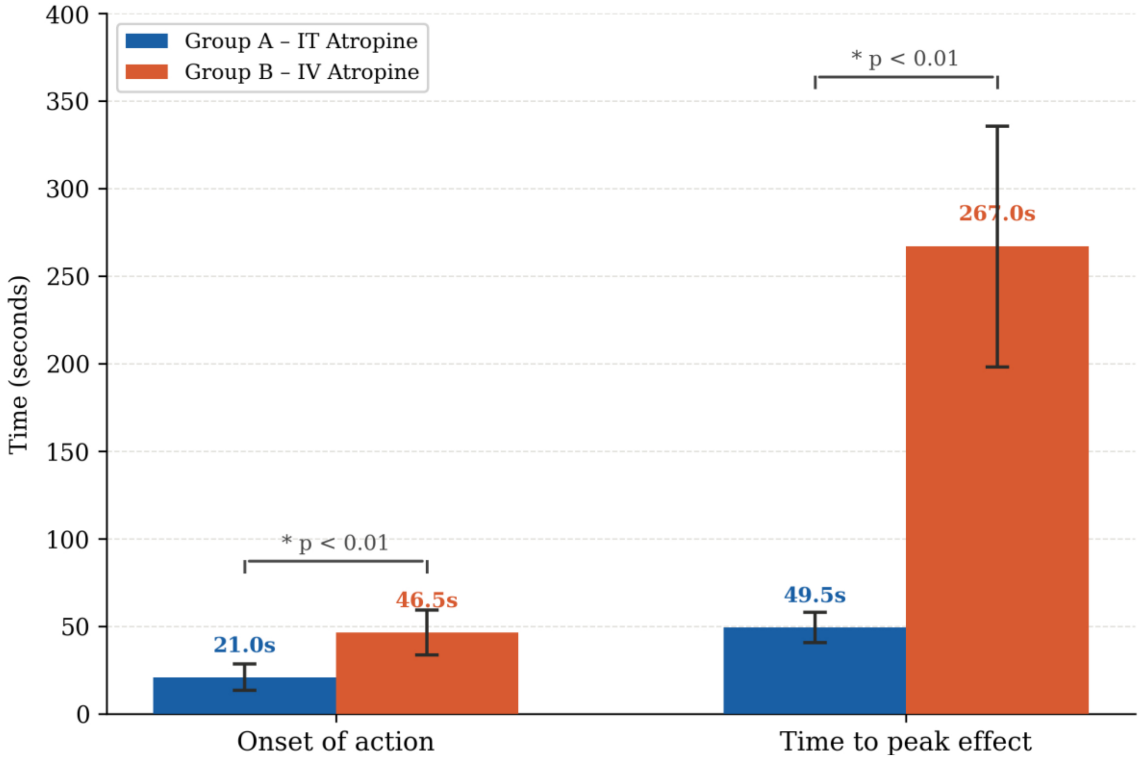

Fig. 2. Onset of action and time to peak heart rate elevation comparing intratracheal (Group A, blue) vs. intravenous (Group B, orange) atropine. Both parameters were significantly faster in Group A ($p < 0.01$). Error bars = ±1 SD.

difference in onset between 21 and 46.5 seconds may have limited practical impact. However, in the context of acute symptomatic bradycardia associated with hypotension, the approximately 25-second onset advantage and the more than 3.5-minute peak-effect advantage of the IT route may substantially reduce the window of hemodynamic risk. We therefore caution against interpreting 'faster = superior' in all

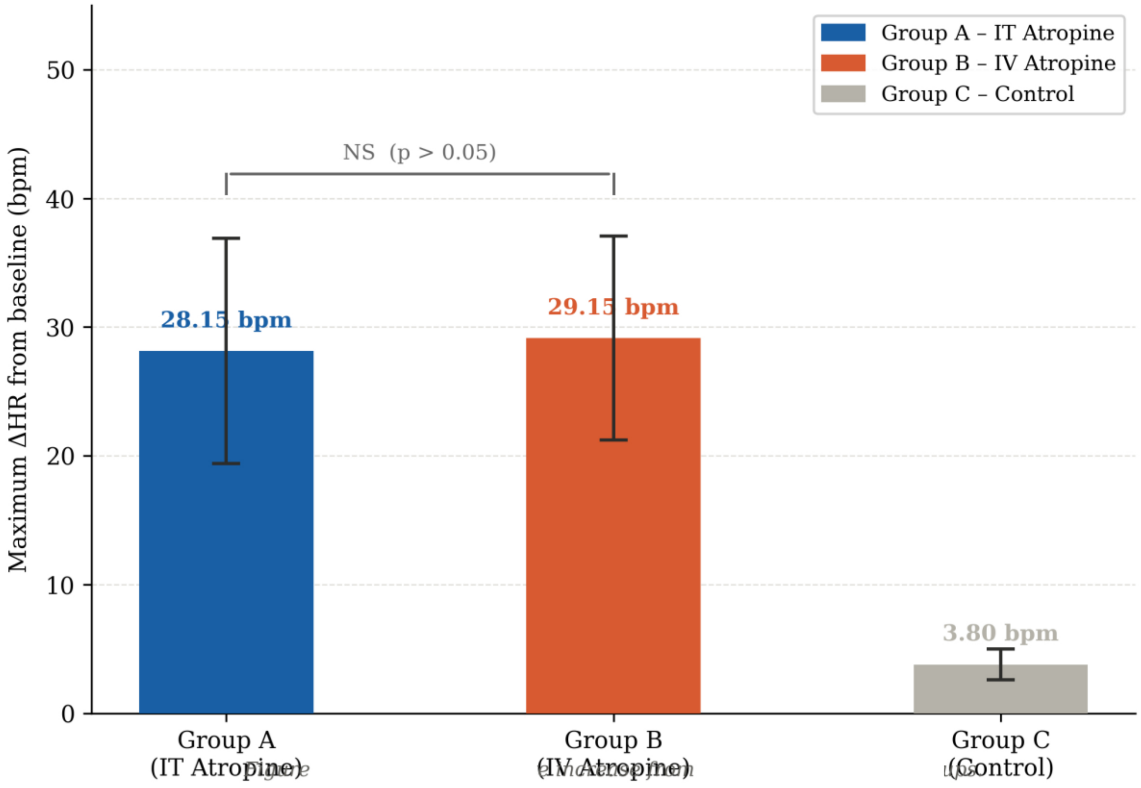

Fig. 3. Maximum heart rate increase from baseline across all groups. No significant difference between Groups A and B ($p > 0.05$, NS). Both atropine groups significantly exceeded control ($p < 0.01$). Error bars = ±1 SD.

circumstances: the clinical relevance of the IT route's speed advantage is context-dependent.

The control of potential bias was a key methodological consideration. Observer bias was minimized by blinding the outcome assessor to group allocation. Tracheal stimulation as a confounding variable was controlled by administering 1 mL of saline intratracheally in all three groups, ensuring equivalent mechanical stimulation. The exclusion of smokers and patients with pulmonary disease eliminates conditions known to impair alveolar drug absorption [8, 9]. Five manual lung hyperinflations were performed following intratracheal instillation to optimize distal drug distribution and alveolar contact [16, 19].

The shorter duration of IT effect, despite equivalent peak magnitude, likely reflects more rapid redistribution from the pulmonary vasculature compared to sustained systemic release following IV bolus — a pharmacokinetic difference observed with other intratracheally administered drugs, including aminoglycosides and resuscitation agents [19, 20]. Our group has previously demonstrated reliable pharmacodynamic outcomes in randomized anesthesia trials conducted in the same institutional setting, supporting the methodological consistency of the present study [21, 22].

This study has several limitations that must be acknowledged. First, its single-center design limits its generalizability. Second, the sample size, while adequately powered, is relatively small; larger multicenter trials are needed [13, 14]. Third, monitoring was limited to 15 minutes. Fourth, the absence of plasma atropine concentration measurements prevents full pharmacokinetic characterization. Fifth, only ASA I-II patients with normal pulmonary function were studied; results may not apply to patients with COPD, pulmonary edema, or inhalational injury [5, 8]. Sixth, results should not be directly extrapolated to cardiac arrest, where severely reduced pulmonary perfusion fundamentally alters intratracheal drug kinetics [12, 23].

Recent registry data confirm variability of the intratracheal route under reduced perfusion states [5]. By contrast, our anesthetized patients had intact cardiac output and normal pulmonary circulation, producing reliable rapid pulmonary absorption. This distinction underscores the importance of patient context when interpreting intratracheal drug data [3, 18].

5. Conclusion

This study demonstrates that intratracheal administration of atropine 0.6 mg in anesthetized adult patients produces a chronotropic response equivalent in magnitude but significantly faster in onset than intravenous administration, with a shorter duration of effect. The intratracheal route may be considered as a viable alternative to intravenous atropine, particularly when IV access is unavailable or delayed and a rapid vagolytic response is urgently required. When a sustained chronotropic effect is needed, the intravenous route remains preferred. Future multicenter trials incorporating pharmacokinetic measurements are warranted.

6. Recommendations

Future studies should investigate the optimal intratracheal dose relative to the IV dose, ideal dilution volumes, and the impact of pulmonary pathology on intratracheal drug absorption. Multicenter trials with larger sample sizes and plasma drug concentration measurements would substantially strengthen the evidence base for this route of administration.

Conflicts of interest

None declared.

Ethical approval

This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was granted by the Institutional Ethics Committee of Al-Nasiriya Teaching Hospital, Thi Qar Governorate, Iraq (Approval No. 447/1/2026). All patients provided written informed consent prior to participation.

Data availability

Data are available from the corresponding author upon reasonable request.

Funding

None.

Author contributions

Ammar H. Mahdi: Conceptualization, study design, data collection, manuscript drafting. Majid Alhamaidah: Conceptualization, study design, supervision, manuscript writing and revision. Myasar J. Mohammed: Clinical support, patient management, data interpretation. Hussein Ali Hussein: Data collection, statistical analysis, manuscript revision. Hussein Alkhfaji: Literature review, data collection, manuscript revision.

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