Drug Design, Development and Therapy

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CLINICAL TRIAL REPORT

Comparison of the Effects of Glycopyrrolate and Atropine on Postoperative Delirium in Older Adult Patients Undergoing Laparoscopic Colorectal Surgery: A Randomized Controlled Trial

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Background: Postoperative delirium (POD) is a common complication that hinders recovery in older patients. This study aimed to compare the effects of glycopyrrolate and atropine, used to counteract the peripheral effects of neostigmine, on POD incidence in older patients undergoing laparoscopic colorectal surgery.

Methods: This single-centre, double-blind, randomized controlled trial recruited patients (aged 65–80 years) undergoing laparoscopic colorectal surgery. Patients were randomized to receive either glycopyrrolate (0.04 mg kg^{-1} neostigmine and 0.008 mg kg^{-1}glycopyrrolate) or atropine (0.04 mg kg^{-1} neostigmine and 0.016 mg kg^{-1} atropine) during emergence from anaesthesia. The primary outcome was the incidence of POD within the first 3 postoperative days, assessed using the 3-minute Diagnostic Interview for Confusion Assessment Method. Secondary outcomes included comparing the hemodynamic effects of glycopyrrolate and atropine and examining POD biomarkers.

Results: Among 121 patients, the glycopyrrolate group had a significantly lower incidence of POD compared with the atropine group (11.7% vs 27.9%; relative risk, 0.42; 95% confidence interval, 0.19–0.94; p = 0.045). Glycopyrrolate better maintained baseline heart rate and mean arterial pressure. No significant differences were observed in plasma levels of neurofilament light chain, neuron-specific enolase, and Tau protein between groups at different time points.

Conclusion: The combination of glycopyrrolate and neostigmine was associated with a lower incidence of POD than atropine in older adults undergoing laparoscopic colorectal surgery.

Registration: Chinese Clinical Trial Registry, ChiCTR2300072798.

Keywords: postoperative delirium, glycopyrrolate, atropine, older adult patients, colorectal surgery

Introduction

Postoperative delirium (POD) is a serious neuropsychiatric complication following and surgery, characterized by inattention, altered consciousness, and cognitive impairment, and it primarily affects adults aged 65 years and older.[1] Its incidence varies by surgical procedure, reaching up to 53.3% in high-risk surgeries such as cardiac operations.[2] In noncardiac surgery cohorts, POD occurs in 13–50% of older adults, with specific rates of 22.1% after hip fracture repair and 10.0–43.8% following abdominal surgery.[3–5] Elective colorectal surgery has been reported to have a POD prevalence of 14.1%.[6] This condition is associated with prolonged hospital stays (2–3 days), increased mortality (5.8%), reduced quality of life, greater dependency, higher healthcare costs, and long-term cognitive decline.[7–9] These outcomes underscore the need for effective prevention and management in older surgical patients.[10]

https://doi.org/10.2147/DDDT.S580157
Received: 9 November 2025
Accepted: 23 January 2026
Published: 5 February 2026

The exact mechanism of POD remains unclear, but cholinergic deficiency is thought to play a central role.[11] The cholinergic system is one of the brain's most critical neurotransmitter systems. Acetylcholine acts on muscarinic and nicotinic receptors in both the central and peripheral nervous systems and is involved in cognitive functions such as attention and memory.[12] Anticholinergic drugs impede cholinergic transmission, and their effects on central cholinergic activity may contribute to cognitive impairment and an increased risk of delirium.[13] The 2023 guidelines from the European Society of Anaesthesiology and Intensive Care highlight the importance of preventing POD and screening high-risk patients.[14] A key preventive strategy is preserving cholinergic function while minimizing perioperative anticholinergic exposure.[15] Therefore, the use of drugs with low anticholinergic activity or drugs that do not cross the blood brain barrier is recommended.[16]

Current clinical practice for reversing residual neuromuscular blockade in laparoscopic surgery recommends the use of either neostigmine with anticholinergic agents or sugammadex.[17] The primary purpose of administering anticholinergic agents (eg, atropine or glycopyrrolate) is to counteract the peripheral muscarinic effects induced by neostigmine. Recently, owing to persistent shortages in the supply of glycopyrrolate, there has been a relative scarcity of updated research in this area.[18] In contrast, atropine, with its long history of clinical application, remains a widely used anticholinergic agent. Previous studies have shown that neostigmine has no significant effect on POD.[19] However, high-quality comparative evidence regarding the neurocognitive safety of atropine relative to glycopyrrolate in the older surgical population is still lacking. Therefore, the main objective of this study was to evaluate the effects of glycopyrrolate and atropine on POD in older patients undergoing laparoscopic colorectal surgery within 3 days after surgery. We hypothesized that the combination of neostigmine and glycopyrrolate would result in a lower incidence of early delirium compared with the combination of neostigmine and atropine. As secondary outcomes, we compared the hemodynamic changes induced by glycopyrrolate and atropine and investigated POD-related biomarkers. We selected NfL, NSE, and Tau to capture neuroaxonal injury, neuronal injury, and microtubule/BBB-related processes that may accompany perioperative delirium.

Materials and Methods

Study Design and Ethics

Ethical approval for this study (Approval No.: B2023-028) was obtained from the Ethics Committee of Zhongshan Hospital (Xiamen Branch), Fudan University, on 23 May 2023. The study was conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent was obtained from all patients or their legal surrogates before enrollment. The trial was registered prior to patient enrollment at the Chinese Clinical Trial Registry (https://www.chictr.org.cn) (ChiCTR2300072798) on June 26, 2023. This study was conducted at Xiamen Branch of Zhongshan Hospital, affiliated with Fudan University from June 27 to September 22, 2023, and followed the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Participants

Inclusion criteria: Eligible patients were aged 65–80 years, scheduled for elective laparoscopic colorectal surgery under general anesthesia, classified as American Society of Anesthesiologists (ASA) physical status I or II, with a body mass index (BMI) of 18–32 kg/m^2, and without severe preoperative sensory or motor impairments or major organ dysfunction.

Exclusion criteria: Patients were excluded if they had known allergies to glycopyrrolate or atropine; were participating in other trials; had a history of psychological trauma, dementia, or psychiatric disorders; had severe cardiovascular, respiratory, hepatic, or renal disease; had a history of alcohol, drug, or narcotic abuse; had preoperative exposure to anticholinergics, sedatives, or corticosteroids; had communication barriers or were uncooperative; or required reoperation.

Randomization and Blinding

This block-randomized, parallel-group experiment study comprised two groups of equal size. A randomization chart was created using an online randomization technique with a block size of four. The allocation ratio was established as a 1:1 ratio. No stratification was used, and randomization was implemented locally.

An independent investigator, not otherwise involved in the trial, performed the randomization and prepared sequentially numbered, sealed, opaque envelopes for each participant. A nurse anesthetist, uninvolved in patient care or outcome assessment, opened an envelope preoperatively to disclose the allocation, thereby maintaining allocation concealment until the time of reversal. In accordance with a standardized protocol, either glycopyrrolate or atropine, each combined with neostigmine, was diluted with sterile normal saline to 15 mL in an opaque, labeled syringe by the nurse, who subsequently handed it to the attending anesthesiologist. Owing to the potential side effects of the drugs, the attending anesthesiologist was unblinded. The allocation sequence remained concealed from the rest of the research team until the conclusion of the trial. Participants, surgeons, POD assessors, and data analysts were all blinded, and perioperative management followed a prespecified protocol to minimise performance bias.

Study Procedures and Interventions

Preoperative Assessment

One day before surgery, a trained independent researcher conducted a baseline Mini-Mental State Examination (MMSE) under the supervision of a neuropsychologist. Patients with an MMSE score greater than 20 were considered eligible for the study.[20] Baseline data were collected, and informed consent was obtained. No patients received anticholinergic drugs, sedatives, or analgesics before surgery, and all followed ASA guidelines for preoperative fasting and abstinence. After entry into the operating room, standard monitoring was performed, including electrocardiography, invasive arterial blood pressure monitoring, and peripheral pulse oximetry. Internal jugular and radial artery catheterizations were performed under local anesthesia.

Anesthesia Induction

General anesthesia was induced with propofol using a target-controlled infusion (TCI) device (Perfusor Space, B. Braun Melsungen AG, Germany, Marsh model), targeting an initial plasma concentration of 3–4 μg mL^{-1}. Remifentanil was simultaneously administered via TCI, with a initial plasma concentration of 3–4 ng mL^{-1}. Rocuronium (0.6 mg kg^{-1}) was administered after loss of consciousness. Following tracheal intubation, patients were mechanically ventilated with a tidal volume of 6–8 mL kg^{-1}, a respiratory rate of 10–12 breaths per minute, an inspiratory-to-expiratory ratio of 1:2, and an inspired oxygen fraction (FiO_2) of 50%. The $PETCO_2$ was monitored and maintained within 35–45 mmHg.

Anesthesia Maintenance

Anesthesia was maintained with desflurane at 0.8–1.0 minimum alveolar concentration, with a bispectral index (BIS) target of 40–60. Sufentanil was administered as needed. Heart rate (HR) and mean arterial pressure (MAP) were maintained within 20% of baseline using vasoactive drugs when required. If MAP decreased by more than 20% from baseline, 6 mg of ephedrine was administered; if MAP increased by more than 20%, 5–10 mg of urapidil was given.[19] For HR >90 bpm, esmolol (1 mg kg^{-1}) was administered; for HR <45 bpm, atropine 0.5 mg was given in atropine group, and glycopyrrolate 0.2 mg in glycopyrrolate group. Hypoxia was defined as oxygen saturation <90%.[21] In such cases, FiO_2 was adjusted. Blood pressure and heart rate were closely monitored after treatment, with further interventions provided as necessary. Intraoperative train-of-four (TOF) count remained at 0, while the post-tetanic count ranged from 1 to 2.[22,23] Additional rocuronium was administered based on neuromuscular monitoring results.

Interventions During Anesthetic Emergence

In this study, patients received standard muscle relaxant antagonists when their TOF ratio reached 0.4.[24] The glycopyrrolate group received neostigmine (0.04 mg kg-1) with glycopyrrolate (0.008 mg kg^{-1}), whereas the atropine group received neostigmine (0.04 mg kg^{-1}) with atropine (0.016 mg kg^{-1}). The prepared study drug was administered as a slow intravenous push over 2 min. TOF was continuously monitored, and MAP and HR were measured every minute for 5 minutes. Patients were extubated when their TOF ratio exceeded 0.9 and were then transferred to the post anaesthesia care unit (PACU) for further observation. They were moved to the ward once their Aldrete score was ≥9.[25]

Postoperative Care

After surgery, patients received hydromorphone (0.04 mg mL^{-1}) and tropisetron (10 mg) via patient-controlled intravenous analgesia, with a continuous infusion of 1 mL h^{-1} and a 3 mL bolus, followed by a 10-minute lockout. This regimen was maintained for 48 hours. Pain was assessed by a blinded nurse using the Numeric Rating Scale (NRS), ranging from 0 (no pain) to 10 (worst possible pain). If a patient's NRS score at rest was ≥4, they were administered intravenous tramadol (0.5 mg kg^{-1}).

Primary Outcome

The primary outcome was the incidence of delirium within the first three postoperative days.[26] Delirium assessment was conducted by trained researchers under the supervision of our hospital's neuropsychologists. To ensure consistency, all assessors underwent internal reliability testing. Delirium was assessed twice daily using the 3-minute Diagnostic Interview for Confusion Assessment Method (3D-CAM) in combination with the Richmond Agitation–Sedation Scale (RASS).[27] Only patients with RASS scores above –4 were assessed.[28] Any positive assessment was classified as POD.

Secondary Outcomes

Hemodynamic Changes

Hemodynamic measurements were recorded at baseline, after induction, after establishment of pneumoperitoneum, at the end of the operation, and within five minutes after intravenous injection of the antagonistic drug during anaesthetic emergence. Additional measurements were obtained at extubation and before leaving the PACU.

Measurement of NfL, NSE, and Tau

Plasma levels of Tau protein, neuron-specific enolase (NSE), and neurofilament light chain (NfL) were measured preoperatively, before leaving the PACU, and on postoperative days 1 and 3. Blood samples (3 mL) were collected from the internal jugular vein into EDTA tubes, centrifuged at 3000 g for 10 minutes, and the plasma was stored in 1.5 mL cryogenic tubes at –80 °C. Plasma levels of NfL, NSE, and Tau were quantified using enzyme-linked immunosorbent assay following the manufacturer's instructions. Analytical sensitivity (lower limit of detection, LOD), dynamic range, and manufacturer-reported intra- and inter-assay coefficients of variation (CV) for each biomarker are summarized in Supplementary Table S1. All samples were assayed in duplicate and the mean value was used for analysis. Each plate included a full set of calibrators/standards and internal quality-control samples; samples were re-assayed if the duplicate CV exceeded a prespecified threshold (eg, 15%). Laboratory personnel performing the assays were blinded to treatment allocation and sampling time point. Samples were stored at −80°C and were thawed on ice; repeated freeze–thaw cycles were avoided.

Sample Size Calculation

Based on published data, we estimated a POD incidence of 29.2% in the control group receiving atropine among older adults undergoing elective colorectal cancer surgery.[29] In our single-center pilot study, POD was observed in 30% of patients administered atropine compared to 10% of those receiving glycopyrrolate. Although this pilot estimate is imprecise owing to the limited sample size, it informed the anticipated effect size for further planning, corresponding to an absolute risk reduction (ARR) of 20%, with an expected POD incidence of approximately 10% in the glycopyrrolate group, and an estimated relative risk (RR) of 0.33. Using a two-sided α of 0.05 and power of 80%, the PASS software (version 15.0) indicated that each group requires 59 participants. To account for a potential 10% attrition rate, we planned to recruit 65 participants per group.

Statistical Analysis

The Kolmogorov–Smirnov test was used to assess the normality of continuous data. Normally distributed quantitative variables were presented as mean (standard division) and compared using an unpaired two-tailed *t*-test, whereas non-normally distributed data were presented as median (interquartile range) and analysed using the Mann–Whitney *U*-test.

Categorical variables were reported as numbers (%) and compared using Fisher's exact test or the χ^2 test. Data analyses were performed with R version 3.6. For delirium outcomes, Fisher's exact test was used to compare groups, and relative risk (RR) with 95% confidence intervals (CIs) was calculated. Changes in HR and MAP following the injection of atropine or glycopyrrolate were analysed with repeated-measures analysis of variance, as were plasma concentrations of POD biomarkers (Tau protein, NSE, NfL). All tests were two-sided, and statistical significance was set at $p < 0.05$.

Results

Participants

Figure 1 presents the CONSORT flow diagram. Between June 27 and September 22, 2023, 136 older adults scheduled for laparoscopic colorectal surgery were assessed for eligibility. Of these, 130 were randomized: 65 to the glycopyrrolate group and 65 to the atropine group. After randomization, nine participants were excluded due to severe arrhythmia (n = 2), conversion to open surgery (n = 4), and fistula surgery (n = 3). The final analysis therefore included 60 participants in the glycopyrrolate group and 61 participants in the atropine group.

Baseline Characteristics

Table 1 presents the baseline demographic characteristics. No statistically significant differences were observed between the two groups in terms of age, sex, BMI, ASA physical status classification, underlying diseases, or education history. Baseline MMSE scores were also comparable. Table 2 shows that perioperative variables for surgery and anesthesia were well matched. No patient had an NRS >4 during postoperative assessments.

Primary Outcome

Between postoperative days 1 and 3, the overall incidence of POD was 19.8%. A significantly lower incidence was observed in the glycopyrrolate group (11.7%, 7/60) relative to the atropine group (27.9%, 17/61) ($p = 0.045$). The association was quantified as a relative risk of 0.42 (95% CI, 0.19–0.94) and an absolute risk reduction (ARR) of 16.2%. The number needed to treat (NNT) was 6, which can be interpreted as six patients needing to receive glycopyrrolate instead of atropine to prevent one instance of POD.

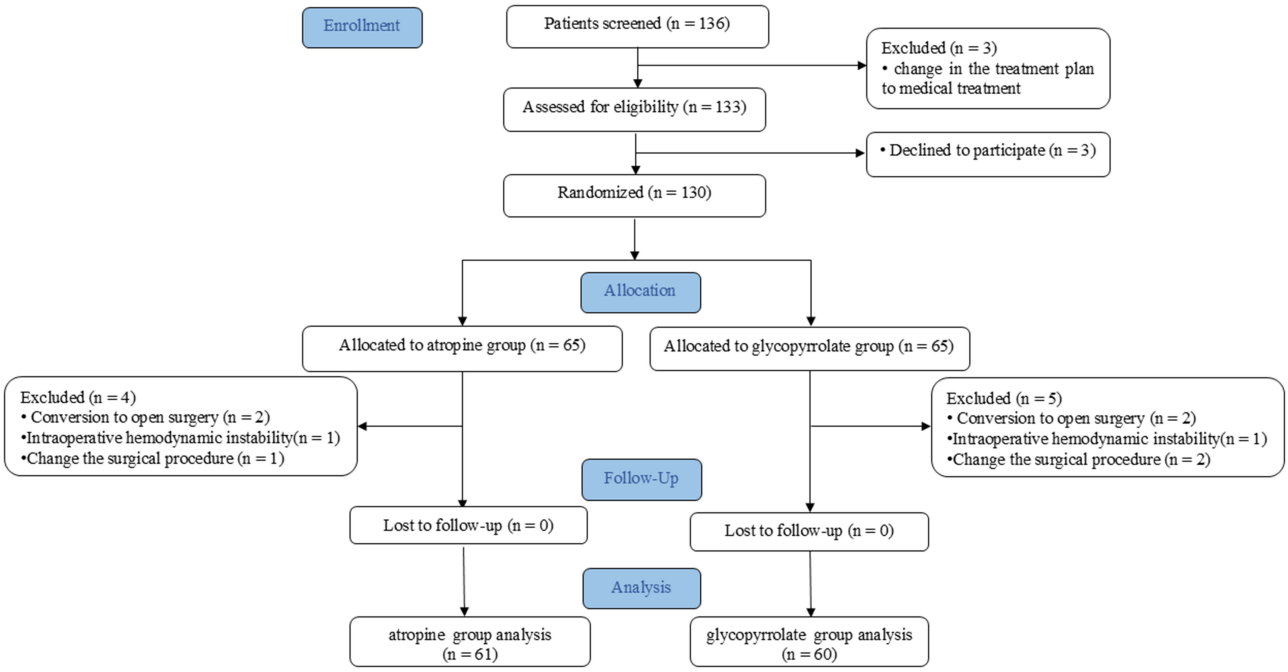

Figure 1 Subject recruitment, randomization, and analysis. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

https://doi.org/10.2147/DDDT.S580157

Table 1 Baseline Characteristics of Participants Receiving Atropine or Glycopyrrolate

	Atropine Group (n=61)	Glycopyrrolate Group (n=60)
Age, y	69.0 (67.0, 74.0)	69.0 (67.0, 72.0)
Sex, n (%)		
Male	31 (50.8)	36 (60.0)
BMI; kg m^{-2}	22.9 ± 3.1	23.5 ± 2.9
ASA Physical Status, n (%)		
1	22 (36.1)	26 (43.3)
2	39 (63.9)	34 (56.7)
Educational history, y	11.2 (9.1, 12.3)	12.2 (9.3, 12.7)
Underlying disease, n (%)		
Hypertension	35 (57.4)	28 (46.7)
Diabetes mellitus	11 (18.0)	9 (15.0)
Cardiovascular	6 (9.8)	8 (13.3)
Respiratory	2 (3.3)	1 (1.7)
Pre MMSE	27.0 (26.0, 29.0)	27.0 (26.0, 28.0)

Notes: Values are presented as mean ± SD, Median (IQR), or n (%).
Abbreviations: BMI, body mass index; ASA, American Society of Anaesthesiologists; MMSE, Mini-mental State Examination.

Table 2 Perioperative Surgical and Anaesthetic Variables of Participants Receiving Atropine or Glycopyrrolate

	Atropine Group (n=61)	Glycopyrrolate Group (n=60)	P-value
Surgery time, min	131 (108, 160)	152 (115, 178)	0.114
Anaesthesia time, min	150 (122, 175)	172 (130, 200)	0.072
Extubation time, min	11 (7, 19)	13 (5, 20)	0.944
Estimated blood loss, mL	50 (40, 50)	50 (25, 50)	0.966
Crystalloid, mL	1,000 (1,000, 1,500)	1,000 (1,000, 1,500)	0.079
Colloid, mL	327 (137.0, 520.2)	350 (230, 537.0)	0.554
Urine, mL	300 (200, 500)	300 (200, 550)	0.797
Modified observer's assessment of alertness/sedation score at PACU	5(5, 5)	5(5, 5)	0.993
Propofol, mg	107.1±20.5	113.3±16.5	0.068
*Morphine equivalent	16.7 (15.0, 19.6)	18.3 (14.5, 20.8)	0.513
Rocuronium, mg	73 (62, 79)	83 (73, 91)	0.072
Total dose of desflurane, mL	52.8±17.5	48.7±13.2	0.089
Atropine, mg	1.00 (1.00, 1.00)	0.00 (0.00, 0.00)	<0.001
Glycopyrrolate, mg	0.00 (0.00, 0.00)	0.45 (0.40, 0.50)	<0.001
Neostigmine, mg	2.50 (2.30, 2.80)	2.42 (2.00, 2.70)	0.063
Ephedrine, mg	6.0 (3.0, 6.0)	6.0 (6.0, 6.0)	0.798
Phenylephrine, mg	0.1±0.11	0.0±0.08	0.182
Norepinephrine, μg	0(0, 47.6)	0(0, 53.8)	0.987
Urapidil, mg	2.7 (0,2.5)	1.4 (0,0)	0.084
Esmolol, mg	0(0,0)	0(0,0)	0.981
Labetalol, mg	0(0,0)	0(0,0)	1.000
Nicardipine, mg	0(0,0)	0(0,0)	0.718
BIS value	48±4	47±3	0.972
MAP, mmHg			
Before drugs	77.5±10.53	75.0±6.05	0.579
After drugs	84.5±9.15	81.0±7.66	0.431
At PACU	79.7±8.81	82.5±8.85	0.552

(*Continued*)

Table 2 (Continued).

	Atropine Group (n=61)	Glycopyrrolate Group (n=60)	P-value
HR, beats min^{-1}			
Before drugs	61.4±4.08	61.2±6.17	0.949
After drugs	69.7±5.74	72.2±9.41	0.547
At PACU	62.7±8.42	57.8±7.76	0.256
HR < 45bpm, n (%)	11 (18)	8 (13)	0.618
PACU stay, min	34 (33.25–36.56)	35 (34.37–37.15)	0.583
Length of stay, d	5.3 (4.2, 6.4)	5.2 (4.1, 6.7)	0.753
Pain			
D 1	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)	0.526
D 3	2.00 (1.00, 2.00)	1.50 (1.00, 2.00)	0.825

Notes: Values are presented as mean ± SD, Median (IQR), or n (%). MAP = 1/3 systolic blood pressure + 2/3 diastolic blood pressure. *Calculated as intravenous morphine equivalent. Included intraoperative and postoperative opioids: 30mg of morphine (per os) = 10mg morphine (intravenously [IV]) = 10 μg sufentanil (IV) = 100 μg remifentanil (IV) = 100mg tramadol (IV) = 200mg tramadol (per os) = 20mg oxycodone (per os).
Abbreviations: PACU, Postanaesthesia care unit; BIS, bispectral index; MAP, mean arterial pressure; HR, heart rate; D1, postoperative day 1; D3, postoperative day 3.

On postoperative day 1, POD occurred in 10% (6/60) of patients in the glycopyrrolate group compared with 27.9% (17/61) in the atropine group (p = 0.023), yielding an RR of 0.36 (95% CI, 0.15–0.85) and an ARR of 17.9% (NNT = 5). However, no statistically significant differences were found on postoperative day 2 (the atropine group: 4.92% [3/61] vs the glycopyrrolate group: 3.33% [2/60]; RR, 0.68; ARR, 1.6%; p > 0.99; NNT = 63) or day 3 (4.92% [3/61] vs 5.0% [3/60]; RR, 1.02; ARR, –0.1%; p > 0.99). Similarly, no significant difference was observed for continuous delirium across days 1–3 (4.92% [3/61] vs 3.33% [2/60]; RR, 0.68; ARR, 1.6%; p > 0.99; NNT = 63). Both groups exhibited the highest POD incidence on postoperative day 1. (Table 3).

Secondary Outcome

Hemodynamic Outcomes

Figure 2 Hemodynamic changes in heart rate (HR) and mean arterial pressure (MAP) over key perioperative time points. Time points include baseline, post-intubation, pneumoperitoneum, end of operation, immediately before administration of the reversal drugs (neostigmine plus atropine or glycopyrrolate), 1–5 min after drug administration, extubation, and leaving PACU. Data are presented as mean ± SD. Asterisks indicate significant between-group differences at the corresponding time points (*p < 0.05; observed at 2–4 min after drug administration).

Table 3 Comparison of POD Incidence Between Atropine and Glycopyrrolate

Outcome Time Point	Atropine (n = 61)	Glycopyrrolate (n = 60)	Relative Risk (95% CI)	Absolute Risk Reduction (%)	P value	NNT
Delirium (Any, Day 1–3)	17 (27.9%)	7 (11.7%)	0.42 (0.19–0.94)	16.2	0.045	6
POD1 (Postoperative Day 1)	17 (27.9%)	6 (10.0%)	0.36 (0.15–0.85)	17.9	0.023	5
POD2 (Postoperative Day 2)	3 (4.92%)	2 (3.33%)	0.68 (0.12–3.91)	1.6	>0.990	63
POD3 (Postoperative Day 3)	3 (4.92%)	3 (5.0%)	1.02 (0.21–4.84)	−0.1	>0.990	–
Continuous POD (Day 1–3)	3 (4.92%)	2 (3.33%)	0.68 (0.12–3.91)	1.6	>0.990	63

Notes: Values are Number (Proportion). RR and 95% CI were calculated using Fisher's exact test. NNT was calculated as the reciprocal of ARR. NNT not shown for negative or negligible ARR.
Abbreviations: POD, Postoperative Delirium; RR, Relative Risk; CI, Confidence Interval; ARR, Absolute Risk Reduction; NNT, Number Needed to Treat.

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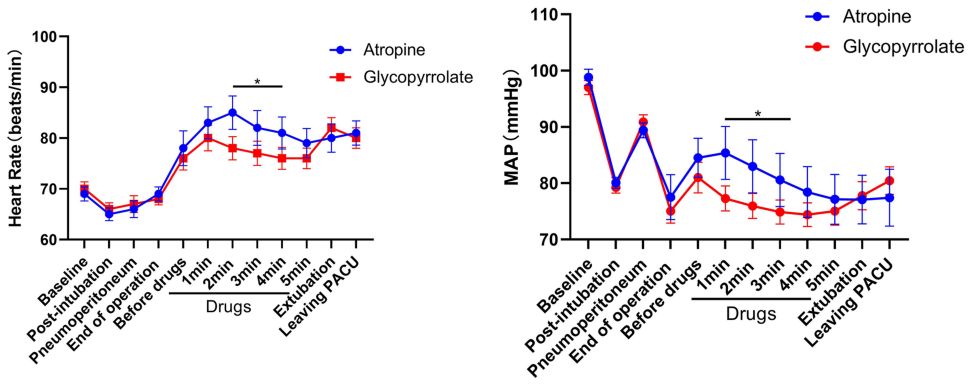

Figure 2 Perioperative heart rate and mean arterial pressure curve between Groups. Time points include baseline, post-intubation, pneumoperitoneum, end of operation, immediately before administration of the reversal drugs (neostigmine plus atropine or glycopyrrolate), 1–5 min after drug administration, extubation, and leaving PACU. Data are presented as mean ± SD. The P values were obtained by repeated measures analysis of variance. Asterisks indicate significant between-group differences at the corresponding time points (*p < 0.05; observed at 2–4 min after drug administration).

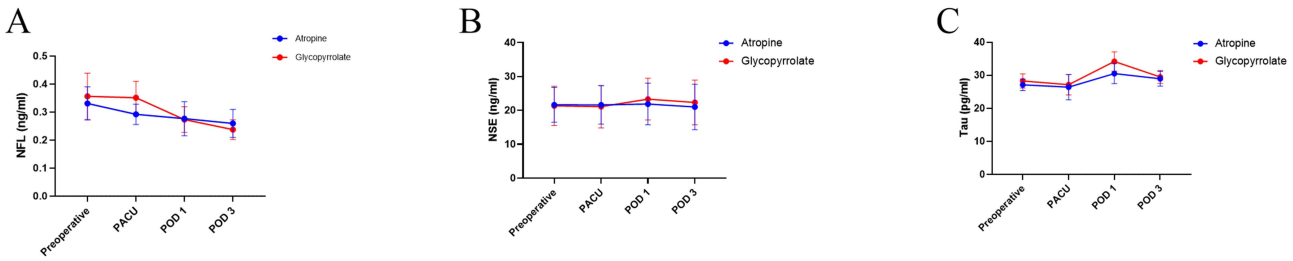

Figure 3 Perioperative trajectories of plasma biomarkers associated with postoperative delirium (POD). Panels show (**A**) neurofilament light chain (NfL), (**B**) neuron-specific enolase (NSE), and (**C**) Tau measured at preoperative baseline (before surgery), in the post-anaesthesia care unit (PACU), postoperative day 1 (POD1), and postoperative day 3 (POD3) in the neostigmine–atropine and neostigmine–glycopyrrolate groups. Data are presented as mean ± SD (or median [IQR] if non-normally distributed; specify as appropriate). No significant between-group differences were observed across time points for any biomarker (all p>0.05).

Biomarker of POD

Plasma concentrations of Nfl, NSE, and Tau were measured preoperatively, before leaving the PACU, and on postoperative days 1 and 3. No significant differences were observed in the plasma levels of NfL, NSE, and Tau between the two groups (Figure 3 and Table 4).

Table 4 Changes in Perioperative Biomarkers of Participants Receiving Atropine or Glycopyrrolate

	Atropine Group (n=61)	**Glycopyrrolate Group (n=60)**	**P-value**
Nfl, Mean±SD, ng mL^{-1}			
Preoperative	0.33 ± 0.43	0.36 ± 0.58	>0.999
PACU	0.29 ± 0.26	0.35 ± 0.41	>0.999
D1	0.27 ± 0.44	0.27 ± 0.32	>0.999
D3	0.26 ± 0.36	0.24 ± 0.24	>0.999
NSE, Mean±SD, ng mL^{-1}			
Preoperative	21.64 ± 5.12	21.33 ± 5.78	0.997
PACU	21.62 ± 5.66	21.10 ± 6.28	0.987
D1	21.89 ± 6.15	23.31 ± 6.16	0.682
D3	21.02 ± 6.71	22.33 ± 6.61	0.788

(*Continued*)

Table 4 (Continued).

	Atropine Group (n=61)	Glycopyrrolate Group (n=60)	P-value
Tau, Mean±SD, pg mL^{-1}			
Preoperative	27.11 ± 12.49	8.28 ± 14.75	>0.999
PACU	26.40 ± 27.55	27.16 ± 21.41	>0.999
D1	30.52 ± 21.91	34.17 ± 20.12	>0.999
D3	28.95 ± 16.03	29.47 ± 13.59	>0.999

Notes: The data are given as mean ± SD. The P values were obtained by repeated measures analysis of variance.

Abbreviations: Nfl, neurofilament light; NSE, neuron-specific enolase; PACU, Post-anesthesia care unit; D1, on postoperative days 1; D3, on postoperative day 3.

Discussion

In this randomized controlled trial, we used the 3D-CAM to evaluate the effects of glycopyrrolate and atropine on POD in older patients undergoing laparoscopic colorectal surgery. Glycopyrrolate was associated with a lower incidence of POD compared with atropine. We also compared haemodynamic changes between groups and explored associations between biomarkers (NfL, NSE, Tau) and POD.

Neuromuscular blockers are routinely used in laparoscopic surgery to improve conditions but increase the risk of residual blockade and postoperative pulmonary complications.[30] Full reversal during recovery is essential. Sugammadex, a modified γ-cyclodextrin, effectively reverses aminosteroid relaxants such as rocuronium and vecuronium but not benzylisoquinoline or depolarizing agents.[17] It is unsuitable in patients with creatinine clearance <30 mL/min,[31] more costly than neostigmine ($500,000–$1 million annually for a medium-sized health system), and has a 0.02% allergy risk.[32,33] These limitations have restricted its widespread use, making neostigmine with anticholinergics a common alternative.[18,19]

Though previous studies on the relationship between glycopyrrolate and POD are limited, our overall incidence of POD is consistent with Fanghao et al,[19] who found that 0.04 mg kg^{-1} neostigmine and 0.02 mg kg^{-1} atropine has no significant effect on POD. Similarly, a retrospective study also revealed that selection of neuromuscular block reversal agents was not associated with an increased risk of POD.[34] These findings further support the potential role of anticholinergic drugs in POD. By inhibiting central and peripheral cholinergic transmission, anticholinergic drugs reduce central cholinergic activity, leading to cognitive impairment and increased risk of delirium.[35] This is relevant in older adults, since they are more sensitive to the adverse effects of anticholinergic actions, predisposing them to drug-induced cognitive impairment.[36] The systematic review and meta-analysis by Leong et al, which included nine prospective cohort studies with 3,791 patients, found that the effect of anticholinergic drug burden on delirium may strengthen with aging.[13] Exposure to anticholinergic drugs is as an independent risk factor for POD in older adults undergoing elective surgery.[37] Different anticholinergic drugs vary in their selectivity for muscarinic receptors.Glycopyrrolate, is a typical muscarinic anticholinergic drug and belongs to the quaternary ammonium base compounds. Theoretically, its chemical structure restricts it from crossing the blood–brain barrier (BBB), resulting in minimal effects on the central nervous system.[38,39] Contrastingly, atropine, with its tertiary amine structure, readily crosses the BBB and competitively antagonizes central M cholinergic receptors, resulting in decreased cholinergic neurotransmission, thereby causing adverse reactions related to the central nervous system. Studies have shown a significant correlation between the postoperative atropinic burden of antimuscarinic drugs and occurrence of delirium following hip fracture surgery.[12] These factors provide a reasonable explanation for the relatively high incidence of POD in the atropine group.

During emergence from anesthesia after intravenous neostigmine with either atropine or glycopyrrolate, the glycopyrrolate group experienced significantly fewer changes in HR and MAP at 2–4 min compared to the atropine group. This finding supports previous research showing that both agents counteract neostigmine-induced bradycardia, with glycopyrrolate providing better hemodynamic stability.[40] This is likely attributed to differences in chemical structure and pharmacokinetics. Glycopyrrolate, a selective M-receptor antagonist, is 3–5 times more selective for M3 and M1 receptors than for M2.[41] The M2 receptors are involved in the regulation of heart rate at the presynaptic terminal.

Moreover, the time onset (1–2 min) and duration of action (2–4 h) of glycopyrrolate are synchronized with those of neostigmine, which is more conducive to maintain a stable HR.[42] Contrastingly, atropine is a non-selective M receptor antagonist with a rapid onset (30–60 s) and short duration (15–30 min) and asynchronous with neostigmine. If used to reverse muscle relaxation, atropine can significantly increase the HR, leading to tachyarrhythmia. Subsequently, as the effect of atropine weakens, the HR may decrease, resulting in fluctuations and disrupting the hemodynamic stability.[43] An unstable hemodynamic state can significantly increase the risk of myocardial ischemia in older patients, which is unfavorable for this group.[44] Therefore, our study results verified that glycopyrrolate is suitable to be an adjunct for reversing nondepolarizing neuromuscular blockers in older adults owing to its advantages in chemical structure and pharmacokinetics.

This study further explored the biomarkers associated with POD. However, our findings revealed no statistically significant differences in the plasma levels of NfL, NSE, and Tau protein between the two patient groups across all time points. From a biological perspective, these markers were selected to reflect complementary pathways that have been implicated in perioperative neurocognitive disorders.[45] NfL is released with axonal injury and is considered a sensitive indicator of diffuse neuroaxonal damage; NSE reflects neuronal injury and metabolic stress; and Tau is involved in microtubule stability and may increase with acute neuronal injury or BBB disruption.[46–48] Delirium is thought to arise from a convergence of predisposing vulnerability (age-related neurodegeneration and reduced cognitive reserve) and perioperative insults (surgical stress, inflammation, hypoxia, and BBB dysfunction), ultimately manifesting as impaired network connectivity and cholinergic dysregulation. In this framework, atropine could plausibly increase POD risk predominantly through central antimuscarinic effects (crossing the BBB) without necessarily producing measurable neuroaxonal injury; therefore, between-group differences in NfL/NSE/Tau may be small even when a clinical delirium signal is present. Conversely, if delirium is accompanied by acute neuronal injury in susceptible patients, these biomarkers may be more informative when analysed in relation to POD status (POD vs no POD) rather than treatment group alone. Future studies could prespecify biomarker hypotheses, incorporate additional inflammatory/BBB markers (eg, IL-6, CRP, S100β), and use longitudinal mixed-effects models to better capture trajectories and their relationship to delirium onset and duration.

Several factors may explain the absence of between-group biomarker differences despite the hypothesized relationship. First, the intervention can modify delirium risk primarily via central cholinergic modulation (atropine crossing the BBB); thus, a clinical delirium signal may occur without measurable changes in injury-related biomarkers. Second, NfL, NSE, and Tau exhibit heterogeneous postoperative kinetics, and the selected sampling time points (preoperative, PACU, POD 1, and POD 3) may not coincide with peak concentrations for all analyses. Third, plasma levels may be relatively insensitive to subtle CNS changes if BBB permeability is not markedly disrupted; CSF or neuroimaging biomarkers could be more sensitive. Fourth, most POD cases were mild and clustered on POD 1, and the number of delirium events was limited, reducing the ability to detect small biomarker shifts. Fifth, perioperative stress responses may elevate biomarkers in both groups, and inter-individual and batch/assay variability may further attenuate detectable between-group differences. Finally, the trial was powered for the clinical endpoint rather than biomarker differences; with approximately 60 participants per group, there is approximately 80% power to detect only moderate between-group biomarker effects (standardized mean difference = 0.52), and smaller differences may have been missed (type II error). These considerations support interpreting the negative biomarker findings as exploratory and not necessarily inconsistent with the observed clinical outcome.

There are several limitations to our trial. First, as a single-center study with a focus on patients undergoing colorectal cancer surgery, the generalizability of our findings was limited. Second, all observed POD cases were mild, and severity stratification was excluded, which may limit interpretability but did not affect incidence estimates. Third, POD occurred mainly on the first postoperative day, consistent with Shin et al.[26] However, a three-day follow-up period may not capture all cases of delayed delirium and may affect the inference of long-term cognitive prognosis. Future studies should include longer-term follow-up to comprehensively evaluate the long-term effects of interventions on postoperative neurocognitive recovery. Fourth, the administering anaesthesiologists were unavoidably unblinded for safety, which could introduce performance bias. This risk was mitigated by using a standardized anaesthesia protocol and by blinding outcome assessors, data analysts, and patients. Fifth, biomarker analyses were exploratory and not specifically powered; therefore, the negative biomarker findings should be interpreted cautiously as they may reflect limited statistical power to detect small between-group differences.

Sixth, the trial was powered using an effect size informed by a small single-centre pilot (n=20 per group); therefore, the RR/ARR was uncertain, and the study may be underpowered to detect smaller but clinically meaningful differences.

However, this study strongly supports using anticholinergic drugs as adjuncts to reverse non-depolarizing neuromuscular blockers in older patients. Nevertheless, the precise mechanisms linking anticholinergic drug use to POD warrant further investigation to clarify the causal relationship and optimize clinical decision-making.

Conclusions

In older adults undergoing laparoscopic colorectal surgery, neostigmine–glycopyrrolate was associated with a lower incidence of POD within the first three postoperative days than neostigmine–atropine. Clinically, if an anticholinergic adjunct is required for neostigmine reversal in older patients, glycopyrrolate may be preferred considering its limited BBB penetration (lower central anticholinergic burden) and a pharmacodynamic profile that is more closely aligned with neostigmine, likely contributing to the more stable short-term hemodynamics observed during emergence. Biomarker differences were not detected, and larger multicentre trials with prespecified biomarker endpoints are warranted.

Data Sharing Statement

For reasonable data requests, please contact the corresponding author (Chao Liang) by email.

Acknowledgment

An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com).

Funding

This study was supported by the Xiamen Medical and Health Guidance Project (No. 3502Z20214ZD1063; Jun-Mei Wu).

Disclosure

The authors disclose no conflicts of interest with respect to this work.

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