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Original Article

Total intravenous anesthesia facilitates early cognitive recovery compared with inhalational anesthesia in Alzheimer's disease patients after cervical lymphatic-venous anastomosis: a randomized controlled trial

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Abstract: Background: The optimal anesthesia method for Alzheimer's disease (AD) patients undergoing cervical lymphatic-venous anastomosis remains unclear. This study compared the effects of three general anesthesia techniques on postoperative cognitive outcomes in AD patients. Methods: In this prospective randomized controlled trial, 132 AD patients were assigned (1:1:1) to receive total intravenous anesthesia (TIVA), total inhalation anesthesia (IH), or combined intravenous-inhalation anesthesia (CI). The primary outcome was cognitive function assessed by MMSE, MoCA and CDR at postoperative day 7 (P7), P90 and P180. The secondary outcome was ADL scores at P180. Results: A total of 123 patients completed the study. At P7, MMSE scores in the TIVA group significantly improved from baseline ($P < 0.05$) and were superior to the IH and CI groups, which showed no significant change. At P90, MMSE scores improved in all three groups ($P < 0.05$), but returned to baseline by P180. No significant differences were observed in MoCA, CDR, or ADL scores at any time point. Conclusion: Among the three anesthesia methods, TIVA was associated with better early cognitive performance at P7 as measured by MMSE, compared with inhalational anesthesia. However, this benefit was not sustained to P180 and no significant changes were observed in MoCA or CDR scores at any time point. These findings suggest that TIVA may reduce early postoperative psychomotor disturbance rather than confer sustained neurocognitive recovery in this population.

Keywords: General anesthesia methods, Alzheimer's disease, cognitive function, cervical lymphatic-venous anastomosis, randomized controlled trial

Introduction

Approximately 50 million people worldwide suffer from dementia due to AD and the prevalence in Europe will double by 2050, while the global prevalence is expected to triple [1]. The increasing mortality and the incidence of dementia in AD patients is becoming a critical clinical problem [2, 3]. The lymphatic system facilitates the clearance of metabolic waste and neurotoxic substances, such as amyloid and tau proteins, which are the causative factors for AD [4-6]. Therefore, cervical lymphatic drainage was considered as a potential therapy for AD [7-12]. Clinical studies indicated that cervical lymphatic-venous anastomosis is associated with short- to mid-term improvements in cognitive performance and functional outcomes in patients with AD [7, 13]. The commonly used anesthesia method for performing this kind of surgery in clinical practice is general anesthesia, which includes total intravenous anesthesia, total inhalation anesthesia and the combined intravenous - inhalation anesthesia. There are numerous factors that will affect the perioperative neurocognitive function of surgi-

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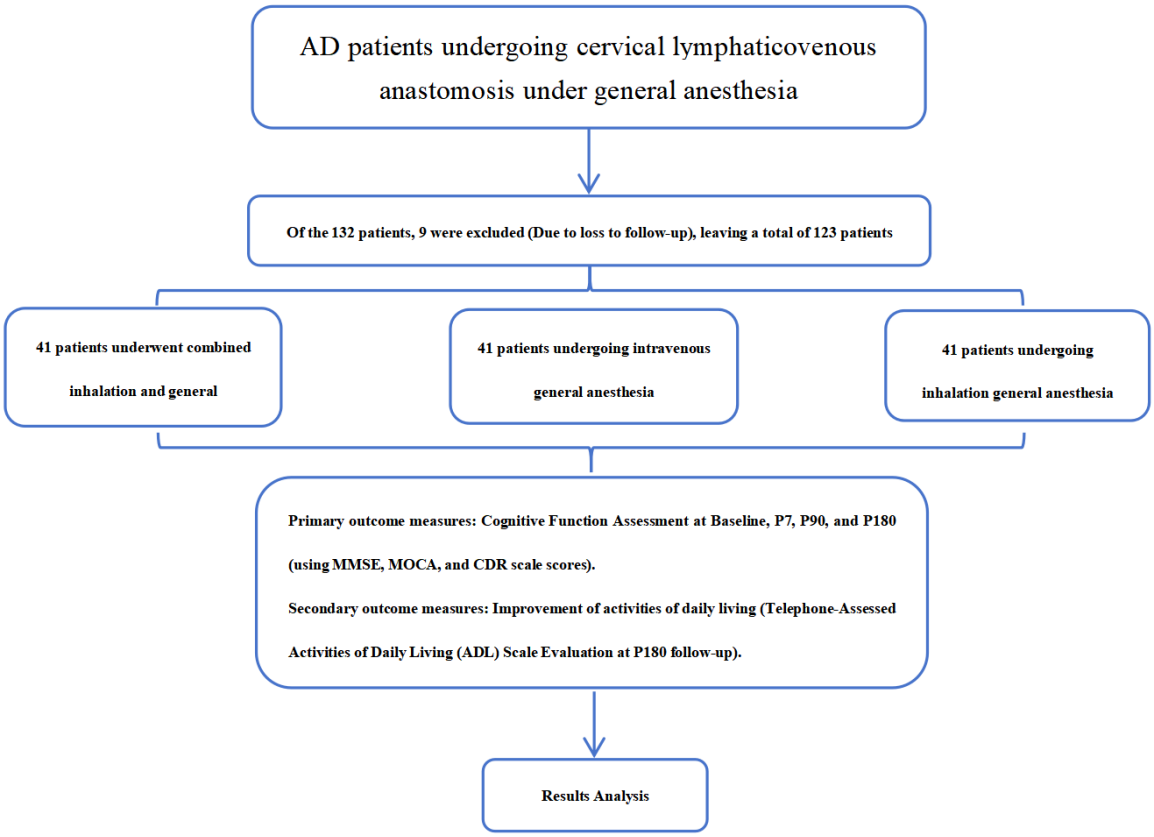

Figure 1. Flowchart of patient enrollment, grouping and outcome assessment. AD, Alzheimer's disease; LVA, lymphaticovenous anastomosis; IV, intravenous; Inh, inhalation; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CDR, Clinical Dementia Rating; ADL, activities of daily living; P7, P90 and P180, postoperative days 7, 90 and 180, respectively.

cal patients, including age, preoperative cognitive function, type of surgery, procedure duration and anesthesia methods [14-20]. However, it remains unclear which kind of general anesthesia method is most beneficial for improving postoperative cognition in AD patients undergoing cervical lymphatic-venous anastomosis. Therefore, this study was performed to compare the effects of three commonly used general anesthesia methods on the postoperative cognitive outcomes in patients with Alzheimer's disease who have undergone cervical lymphatic-venous anastomosis.

Materials and methods

This was a single-center, prospective, randomized controlled trial conducted at Zhejiang Provincial People's Hospital between October 1, 2024 and April 30, 2025. The study was approved by the Medical Ethics Committee of Zhejiang Provincial People's Hospital (KY2025-004) and was registered in the Chinese Clinical Trial Registry (ChiCTR2500099380). Written informed consent was signed by patients or their legally authorized representatives. Sample size was calculated based on the primary outcome measure (MMSE score) using data from a previous pilot study, which showed a mean difference of 3.5 points in MMSE between groups with a standard deviation of 5.2. Assuming a two-sided significance level of $\alpha = 0.05$ and a power of 80% ($\beta = 0.20$), with three groups of equal size and an anticipated dropout rate of 10%, the estimated sample size was 41 patients per group, totaling 123 patients (**Figure 1**).

Patient cohort

Study design and participants: This prospective, randomized controlled trial was conducted at Zhejiang Provincial People's Hospital. Patients with Alzheimer's disease (AD) who were scheduled to undergo cervical lymphatic-venous anastomosis during the study period were assessed for eligibility.

Inclusion criteria were: (1) diagnosis of AD with no surgical contraindications; (2) preoperative Mini-Mental State Examination (MMSE) score ≤ 20; (3) stable AD medication treatment for at least 6 months prior to admission with no symptomatic improvement; and (4) written informed consent obtained.

Exclusion criteria were: (1) concurrent neurological conditions other than neurodegenerative diseases (Parkinson's disease, or frontotemporal dementia) with potential to independently impair cognitive function; (2) documented severe stenosis (≥ 70%) of the middle cerebral artery and/or internal carotid artery; (3) prior head or neck malignancy or history of radical cervical lymph node dissection; (4) significant bleeding tendency, defined as platelet count < 100×10^9/L, heparin therapy within the preceding 48 hours with APTT ≥ 35 seconds, or current warfarin therapy with INR > 1.7; (5) active HIV infection, confirmed Treponema pallidum infection, or uncontrolled systemic infectious disease; or (6) any other condition judged by the investigator to preclude safe participation [21].

Patients who developed perioperative complications that could significantly affect cognitive outcomes, including intraoperative or postoperative hemodynamic shock or perioperative stroke, or those who withdrew consent, were excluded from the final analysis.

Randomization and blinding: Eligible patients were randomly assigned in a 1:1:1 ratio to one of three groups: total intravenous anesthesia (TIVA group), total inhalation anesthesia (I group), or combined intravenous-inhalation anesthesia (IT group). A computer-generated randomization sequence with block randomization (block size of six) was prepared by an independent statistician who was not involved in patient recruitment or data collection. The allocation sequence was implemented using sequentially numbered, opaque, sealed envelopes to ensure allocation concealment. The envelopes were opened by the attending anesthesiologist immediately before the induction of anesthesia.

Due to the nature of the interventions, anesthesiologists and patients were not blinded to group allocation. However, the outcome assessors who performed all cognitive and functional evaluations were blinded to group assignment throughout the study. To maintain blinding, assessors were not involved in patient care or the surgical procedure and had no access to intraoperative anesthesia records. Assessors were instructed to avoid discussing postoperative symptoms with patients during assessments. If patients spontaneously mentioned symptoms such as nausea or delirium, assessors were required to pause the assessment and resume after a 5-minute interval without documenting the nature of the symptom. To assess blinding success, outcome assessors were asked to guess the group assignment after the final evaluation. The correct guess rate was 14.6% (18/123), with a kappa coefficient of 0.11, indicating that blinding of assessors was largely successful.

Anesthesia methods and procedures

Anesthesia management strictly followed the allocated group assignment for each patient according to the randomization protocol.

Anesthetic induction: After arrival at the operating room, continuous monitoring was established, including electrocardiography (ECG), pulse oximetry (SpO_2), non-invasive arterial blood pressure (NIBP), end-tidal carbon dioxide ($PetCO_2$) and bispectral index (BIS) (A-2000 BIS monitoring system, Aspect Medical Systems, Norwood, MA, USA). Pre-oxygenation was performed with 100% oxygen at 8 L/min for 3 minutes prior to induction. Anesthesia was induced intravenously with propofol 1.5-2.5 mg/kg (Propofol Medium and Long Chain Fat Emulsion Injection, Fresenius Kabi, Germany), sufentanil citrate 0.4 μg/kg (Sufentanil Citrate Injection, Yichang Humanwell Pharmaceutical Co., Ltd., China) and rocuronium bromide 0.6 mg/kg (Rocuronium Bromide Injection, Zhejiang Xianju Pharmaceutical Co., Ltd., China). After tracheal intubation, mechanical ventilation was initiated using an anesthesia ventilator (Avance, GE Healthcare, Madison, WI, USA) with the following parameters: tidal volume 6 ml/kg, respiratory rate 10-16 breaths/min, positive end-expiratory pressure (PEEP) 6 cmH_2O and FiO_2 30%. Ventilation parameters were adjusted to maintain $PetCO_2$ within the range of 35-45 mmHg.

Anesthetic maintenance: The anesthesia in the TIVA group was maintained with propofol 4-12 $mg{\cdot}kg^{-1}{\cdot}h^{-1}$ (Propofol Medium and Long Chain Fat Emulsion Injection, Fresenius Kabi, Germany) to maintain BIS within the range of 45-60, remifentanil 0.1-0.3 $\mu g{\cdot}kg^{-1}{\cdot}min^{-1}$ (Remi-

fentanil Hydrochloride Injection, Yichang Humanwell Pharmaceutical Co., Ltd., China) to maintain Surgical Pleth Index (SPI) within 40-60 and rocuronium bromide 0.1 $mg \cdot kg^{-1}$ (Rocuronium Bromide Injection, Zhejiang Xianju Pharmaceutical Co., Ltd., China) given as intermittent boluses according to clinical requirement.

The anesthesia maintenance for patients in the I group was achieved using approximately 1.3 MAC sevoflurane (Sevoflurane Inhalation Anesthetic, Maruishi Pharmaceutical Co., Ltd., Japan), with remifentanil and rocuronium administered at the same dosages as those in the TIVA group.

The anesthesia maintenance for patients in the IT group was achieved using sevoflurane 1.0% [22] combined with propofol 2-6 $mg \cdot kg^{-1} \cdot h^{-1}$ (Propofol Medium and Long Chain Fat Emulsion Injection, Fresenius Kabi, Germany), with remifentanil and rocuronium administered at the same dosages as those in the TIVA group.

In all three groups, the infusion pumps used were B. Braun Perfusor® Space infusion pumps (B. Braun Melsungen AG, Germany) and the anesthesia delivery systems were Avance anesthesia workstations (GE Healthcare, Madison, WI, USA).

Anesthesia recovery: After surgery, all patients were transferred to the Post-Anesthesia Care Unit (PACU) for monitoring and standard anesthesia recovery. Patients were discharged to the ward after achieving a Modified Aldrete score ≥ 9.

Primary outcome

The primary outcome of this study was the cognitive improvement evaluated by Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA) and Clinical Dementia Rating (CDR) scores at P7, P90 and P180. The score ranges for MMSE and MoCA are from 0 to 30, with a higher score indicating better cognitive function. CDR scores of 0, 0.5, 1, 2 and 3 correspond to no dementia, questionable dementia, mild dementia, moderate dementia and severe dementia, respectively.

Secondary outcome

The secondary outcome of this study is functional independence evaluated by ADL scores at P180, which ranges from 0 to 100, with a higher score indicating better functional independence.

All of the behavioral scores were evaluated by well trained anesthesiologists who were blinded to group allocation.

Statistical methods

Statistical analysis was performed using SPSS version 27.0 (IBM Corp., Armonk, NY, USA). The normality of continuous variables was tested using the Shapiro-Wilk test. Normally distributed data are presented as mean ± standard deviation (SD), while non-normally distributed data are expressed as median (interquartile range, IQR).

For between-group comparisons of non-normally distributed behavioral scores, the Kruskal-Wallis test was used, followed by pairwise comparisons with Bonferroni correction. For within-group comparisons across multiple time points, the Friedman test was applied, with post-hoc pairwise comparisons performed using the Wilcoxon signed-rank test with Bonferroni correction. Comparisons of score changes (Δ values) between groups were also performed using the Kruskal-Wallis test.

For variables that were normally distributed, between-group comparisons were performed using one-way ANOVA, followed by post-hoc pairwise comparisons with Bonferroni correction; within-group comparisons across time points were analyzed using repeated-measures ANOVA. Effect sizes (Cohen's d) and 95% confidence intervals for mean differences were calculated only for those normally distributed variables where ANOVA was applied.

For ADL scores, between-group comparisons at baseline and P180 were performed using the Kruskal-Wallis test and within-group comparisons between baseline and P180 were performed using the Wilcoxon signed-rank test.

A two-sided p value < 0.05 was considered statistically significant for all analyses.

Results

Participant characteristics

A total of 132 patients were initially enrolled, of whom 9 were excluded due to incomplete participation in the research program. Therefore,

Table 1. Baseline characteristics

Basic Information	Grouping Details			
	IT group *(n = 41)*	TIVA group *(n = 41)*	I group *(n = 41)*	*p-value*
Sex, n (male/female)	18/23	18/23	19/22	0.968
Age (years)	70 (65, 74)	72 (63, 78)	67(61, 75)	0.309
Duration of Illness (years)	5 (3, 6.5)	5 (3, 5.5)	5 (3, 7)	0.757
Preoperative MMSE Score	3 (0, 7)	5 (2.5, 6.5)	2 (0, 9)	0.173
Preoperative MoCA Score	1 (0, 3)	1 (1, 2.5)	1 (0, 3)	0.394
Preoperative CDR Score	3 (2, 3)	3 (2, 3)	3 (2, 3)	0.752
Preoperative SBP (mm Hg)	140 (128, 150)	140 (123, 150)	131 (120, 143)	0.369
Preoperative DBP (mm Hg)	80 (70, 90)	76 (66, 80)	77 (70, 84)	0.412
Preoperative Heart Rate (beats/min)	70 (65, 77)	70 (60, 78)	73 (65, 80)	0.312
Preoperative Oxygen Saturation (%)	98 (96, 98)	98 (96, 98)	98 (96, 98)	0.208
Blood Loss (ml)	20 (20, 30)	10 (10, 20)	20 (20, 30)	0.344
Urine Output (ml)	350 (300, 700)	400 (300, 500)	400 (200, 500)	0.173
Operative Time (h)	3.8 (3.5, 4.5)	4 (3.5, 4.5)	3.8 (3.5, 4)	0.112
Anesthesia Duration (h)	3.5 (3, 4)	3.5 (3.2, 4)	3.5 (3, 3.5)	0.147
Number of Anastomoses (units)	12 (11, 14)	13 (11, 14)	12 (11, 14)	0.929

Abbreviations: IT, combined inhalation and intravenous general anesthesia; TIVA, total intravenous anesthesia; I, inhalation general anesthesia; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; CDR, Clinical Dementia Rating; SBP, systolic blood pressure; DBP, diastolic blood pressure.

123 patients were included in the final analysis, with 41 patients in each group. No statistically significant differences were observed among the three groups in baseline characteristics (all P > 0.05), indicating that the groups were well balanced (**Table 1**).

MMSE scores

There were no significant differences in preoperative MMSE scores among the three groups [median (IQR): TIVA group: 5 (2.5, 6.5); I group: 2 (0, 9); IT group: 3 (0, 7); P = 0.427]. In the TIVA group, MMSE scores showed a significant increase from baseline at P7 (mean change: 2.1 points, 95% CI: 1.4-2.8; Cohen's d = 0.52, indicating a moderate effect) and P90 (mean change: 1.8 points, 95% CI: 1.1-2.5, Cohen's d = 0.38, small effect), while at P180, the scores returned to baseline levels (mean change: 0.2 points, 95% CI: -0.5 to 0.9, P > 0.05). In both the I group and IT group, MMSE scores at P90 were significantly higher than baseline [I group: 2 (1, 9.5) vs. 2 (0, 9), P < 0.05; IT group: 3 (1, 7) vs. 3 (0, 7), P < 0.05], with small effect sizes (Cohen's d = 0.25 and 0.30, respectively), while at P7 and P180, no significant differences were observed compared to baseline in either group (all P > 0.05). At P7, the Kruskal-Wallis test showed a significant difference among the three groups (H = 6.893, P = 0.032). Post-hoc pairwise comparisons with Bonferroni correction revealed that the TIVA group showed significantly greater improvement than the I group (adjusted P = 0.038), while the difference between TIVA and IT groups was borderline (adjusted P = 0.057) and no significant difference was found between I and IT groups (adjusted P = 0.876). At P90, no significant between-group differences were observed (H = 4.234, P = 0.120). At P180, no significant between-group differences were observed (H = 2.134, P = 0.344) and the 95% confidence intervals for changes from baseline all included zero (TIVA: -0.5 to 0.9; I: -0.6 to 0.8; IT: -0.4 to 1.0), confirming the lack of sustained cognitive benefit at 6 months postoperatively (**Table 2**).

MoCA scores

No statistically significant differences were found in preoperative MoCA scores among the three groups (P > 0.05). At P7, P90 and P180, the MoCA scores in all three groups showed no significant changes compared with baseline (all P > 0.05) (**Table 3**).

Changes in CDR scores

There were no statistically significant differences in preoperative CDR scores among the three groups (P > 0.05). At P7, P90 and P180, the

Table 2. MMSE scores among the three groups

Time Point	IT Group (n = 41)	TIVA Group (n = 41)	I Group (n = 41)	*P* value*	Post-hoc pairwise comparison (adjusted P†)
Baseline	3 (0, 7)	5 (2.5, 6.5)	2 (0, 9)	0.427	-
P7	3 (0.5, 8)	6 (3, 8)‡	2 (0, 9)	0.032	TIVA vs. I: 0.038; TIVA vs. IT: 0.057; I vs. IT: 0.876
P90	3 (1, 7)	6 (2, 9)	2 (1, 9.5)	0.120	-
P180	3 (1, 6)	4 (1, 8)	1 (1, 8)	0.344	-

*Between-group comparisons: Kruskal-Wallis test; within-group comparisons across time points: Friedman test, followed by Wilcoxon signed-rank test with Bonferroni correction. †Adjusted *P* values are shown only when the overall Kruskal-Wallis test was significant ($P < 0.05$). ‡$P < 0.05$ vs. baseline within the same group (Wilcoxon signed-rank test with Bonferroni correction). MMSE, Mini-Mental State Examination; IT, combined inhalation and intravenous general anesthesia; TIVA, total intravenous anesthesia; I, inhalation general anesthesia; P7, P90 and P180, postoperative days 7, 90 and 180, respectively.

Table 3. MoCA scores among the three groups

Time Point	IT Group (n = 41)	TIVA Group (n = 41)	I Group (n = 41)	*P* value*
Baseline	1 (0, 3)	1 (1, 2.5)	1 (0, 3)	0.394
P7	1 (0, 3)	1 (1, 3)	1 (0, 3)	0.612
P90	2 (0, 3)	1 (1, 4)	1 (0, 3)	0.483
P180	1 (0, 3)	1 (1, 3)	1 (0, 3)	0.521

*Between-group comparisons: Kruskal-Wallis test; within-group comparisons across time points: Friedman test (all $P > 0.05$). Data are presented as median (IQR). MoCA, Montreal Cognitive Assessment; IT, combined inhalation and intravenous general anesthesia; TIVA, total intravenous anesthesia; I, inhalation general anesthesia; P7, P90 and P180, postoperative days 7, 90 and 180, respectively.

Table 4. CDR scores among the three groups

Time Point	IT Group (n = 41)	TIVA Group (n = 41)	I Group (n = 41)	*P* value*
Baseline	3 (2, 3)	3 (2, 3)	3 (2, 3)	0.752
P7	3 (2, 3)	3 (2, 3)	3 (2, 3)	0.812
P90	3 (2, 3)	3 (2, 3)	3 (2, 3)	0.763
P180	3 (2, 3)	3 (2, 3)	3 (2, 3)	0.788

*Between-group comparisons: Kruskal-Wallis test; within-group comparisons across time points: Friedman test (all $P > 0.05$). Data are presented as median (IQR). CDR, Clinical Dementia Rating; IT, combined inhalation and intravenous general anesthesia; TIVA, total intravenous anesthesia; I, inhalation general anesthesia; P7, P90 and P180, postoperative days 7, 90 and 180, respectively.

Table 5. Comparisons of ADL scores among the three groups

Groups	IT group *(n = 41)*	TIVA group *(n = 41)*	I group *(n = 41)*	*p-value*
Baseline	20 (20, 60)	60 (20, 90)	20 (20, 60)	0.075
P180	20 (20, 60)	60 (20, 95)	20 (20, 60)	0.086

ADL, activities of daily living; IT, combined inhalation and intravenous general anesthesia; TIVA, total intravenous anesthesia; I, inhalation general anesthesia; P180, postoperative day 180; IQR, interquartile range.

CDR scores in the three groups showed no significant changes compared with baseline (all $P > 0.05$) (**Table 4**).

ADL scores

No statistically significant differences were observed in preoperative ADL scores among the three groups ($P > 0.05$). At P180, the ADL scores in all three groups showed no significant changes compared with baseline (all $P > 0.05$) (**Table 5**).

Perioperative anesthesia-related indicators and hemodynamic stability

As shown in **Table 6**, there were no significant differences among the three groups in surgery time ($P = 0.812$), anesthesia time ($P = 0.783$), emergence time ($P = 0.724$), or extubation time ($P = 0.652$). The incidence of postoperative nausea and vomiting (PONV) was significantly lower in the TIVA group than in the I group and IT group [12.2% vs. 29.3% vs. 26.8%, respectively; $\chi^2 = 6.198$, $P = 0.046$]. None of the three groups experienced emergence agitation or severe anesthesia-related complications. Regarding hemodynamic stability, the incidence of intraoperative hypotension was significantly higher in the I group (36.6%) and IT group (34.1%) compared with the TIVA group (14.6%; $\chi^2 = 6.034$, $P = 0.049$). Similarly, the use of vasoactive agents was significantly lower in the TIVA

Table 6. Perioperative anesthesia-related indicators and hemodynamic stability among the three groups

Variable	TIVA group (n = 41)	I group (n = 41)	IT group (n = 41)	*P* value
Anesthesia-related indicators				
Surgery time (min)	120 (110, 135)	125 (115, 140)	125 (112, 138)	0.812
Anesthesia time (min)	140 (130, 158)	145 (132, 162)	145 (133, 155)	0.783
Emergence time (min)	15 (12, 18)	16 (13, 20)	15 (13, 19)	0.724
Extubation time (min)	40 (35, 50)	44 (36, 55)	42 (36, 52)	0.652
Hemodynamic stability				
Intraoperative hypotension [n (%)]	6 (14.6)	15 (36.6)	14 (34.1)	0.049†
Vasoactive agent use [n (%)]	4 (9.8)	13 (31.7)	12 (29.3)	0.038†
Postoperative complications				
PONV [n (%)]	5 (12.2)	12 (29.3)	11 (26.8)	0.046†

Continuous variables: Kruskal-Wallis test, presented as median (IQR); categorical variables: chi-square test, presented as n (%). TIVA, total intravenous anesthesia; I, inhalation general anesthesia; IT, combined inhalation and intravenous general anesthesia; PONV, postoperative nausea and vomiting; IQR, interquartile range. †P < 0.05 indicates statistically significant difference among the three groups.

Table 7. Postoperative outcomes among the three groups

Variable	TIVA group (n = 41)	I group (n = 41)	IT group (n = 41)	*P* value
Delirium within 7 days [n (%)]	3 (7.5)	9 (22.5)*	10 (25.0)*	0.037
Pulmonary infection [n (%)]	1 (2.5)	2 (5.0)	1 (2.5)	0.783
Poor wound healing [n (%)]	1 (2.5)	1 (2.5)	2 (5.0)	0.783
Postoperative hospital stay (days)	8.5 ± 2.1	11.3 ± 3.2*	10.8 ± 2.9*	0.001

Footnote: *P < 0.05 vs. TIVA group data on delirium represent the incidence based on the full intention-to-treat (ITT) analysis set (N = 123). In the subsequent sensitivity analysis that excluded all patients with postoperative delirium to assess the robustness of the primary outcome, the numbers excluded from the TIVA, I and IT groups were 3, 9 and 10, respectively. TIVA, total intravenous anesthesia; I, inhalation general anesthesia; IT, combined inhalation and intravenous general anesthesia; ANOVA, analysis of variance.

group (9.8%) than in the I group (31.7%) and IT group (29.3%; $\chi^2 = 6.567$, P = 0.038).

Comparison of postoperative complications and length of hospital stay

As shown in **Table 7**, the incidence of postoperative delirium within 7 days was significantly lower in the TIVA group than in the I group and IT group [7.5% vs. 22.5% vs. 25.0%, respectively; $\chi^2 = 6.567$, P = 0.037]. No significant differences were observed among the three groups in the incidence of pulmonary infection or poor wound healing (all P > 0.05). The postoperative length of hospital stay was significantly shorter in the TIVA group compared with the other two groups (8.5 ± 2.1 days vs. 11.3 ± 3.2 days vs. 10.8 ± 2.9 days, respectively; F = 8.234, P = 0.001).

Discussion

Our present study showed that total intravenous anesthesia (TIVA) was the most beneficial general anesthesia method for facilitating early cognitive recovery in AD patients after cervical lymphatic-venous anastomosis. Baseline characteristics of the patients were comparable among the three groups, supporting the interpretation that the observed differences in early postoperative MMSE improvement may be related to the anesthetic maintenance regimen.

The primary finding of this study was that the improvement in MMSE score at P7 was significantly greater in the TIVA group than in the inhalation anesthesia group and the combined intravenous-inhalation anesthesia group. Consistent with this finding, only the TIVA group demonstrated a significant increase in MMSE score at P7 compared with baseline [mean change: 2.1 points, 95% CI: 1.4-2.8, Cohen's d = 0.52 (moderate effect)], whereas no significant changes were observed in the other two groups [I group: 0.3 points, 95% CI: -0.4 to 1.0; IT group: 0.5 points, 95% CI: -0.2 to 1.2; both

with negligible effect sizes (Cohen's d < 0.2)]. At P90, the MMSE scores of patients in all three groups were significantly higher than their baseline, with small effect sizes (Cohen's d: 0.25-0.38), whereas at P180, all MMSE scores returned to baseline levels with no significant differences and all 95% confidence intervals for the changes crossed zero (TIVA: -0.5 to 0.9; I: -0.6 to 0.8; IT: -0.4 to 1.0). In addition, the ADL scores at P180 showed no significant differences from baseline in any group (P > 0.05). These results indicate that cervical lymphatic-venous anastomosis may have a short-term improving effect on cognitive function in AD patients and TIVA is the general anesthesia method most conducive to early cognitive recovery. Notably, this study compared the effects of different anesthesia maintenance methods on cognitive function in AD patients undergoing the same procedure, thereby minimizing the confounding influence of surgical factors on postoperative cognition. The MoCA and CDR scores did not show significant changes at any time point (P > 0.05), suggesting that MMSE may be more sensitive in detecting short-term cognitive changes in this population.

The early postoperative improvement in MMSE scores in the TIVA group warrants careful interpretation. The mean improvement of 2.1 points at P7 corresponds to a moderate effect size (Cohen's d = 0.52), suggesting a clinically meaningful, albeit modest, early cognitive benefit. However, several factors may have contributed to this short-term effect. First, the analgesic and sedative properties of propofol, as well as postoperative pain management, sleep quality and surgical stress responses, may have temporarily influenced cognitive performance at P7. The impact of residual anesthesia effects or postoperative analgesic medications on cognitive test performance cannot be excluded. Second, patients receiving inhalational anesthesia may have had a higher incidence of postoperative delirium, which could directly impair cognitive assessment at P7. Previous studies have reported that inhalational anesthetics are associated with increased delirium risk compared with propofol-based anesthesia [20]. To further clarify the specific effect of TIVA on cognitive recovery independent of delirium, we performed a sensitivity analysis excluding patients who developed postoperative delirium (TIVA: n = 3, I: n = 9, IT: n = 10). After exclusion, the MMSE score at P7 in the TIVA group remained significantly higher than baseline (P < 0.05), while the differences in the I and IT groups remained non-significant. However, the magnitude of improvement in the TIVA group was attenuated, suggesting that the beneficial effect of TIVA on early cognitive performance was partially but not entirely driven by a lower incidence of delirium. Furthermore, the present findings should be interpreted with careful attention to the distinction between true neurocognitive recovery and short-term psychomotor or delirium recovery. The improvement in MMSE scores at P7 likely reflects, at least in part, a reduction in perioperative psychomotor disturbance and delirium burden in the TIVA group, rather than sustained neurocognitive recovery. This interpretation is supported by the observation that MMSE scores in all three groups returned to baseline levels by P180 (with all 95% CIs crossing zero), indicating that the early benefit of TIVA was transient and did not translate into long-term cognitive gains.

Furthermore, the design of the anesthetic maintenance regimen in this study warrants discussion. Group I received approximately 1.3 MAC sevoflurane, while Group IT received 1.0% sevoflurane combined with low-dose propofol. BIS was maintained at 45-60 in both groups, ensuring comparable anesthesia depth; however, the total exposure to inhaled anesthetics differed between the two groups. This regimen was designed based on the clinical advantage of combined intravenous-inhalation anesthesia, which allows for the use of lower concentrations of sevoflurane while maintaining adequate anesthesia depth and potentially reducing dose-dependent adverse effects. Nevertheless, the difference in total sevoflurane exposure may be an important factor influencing neuroinflammation and postoperative delirium. Preclinical studies have demonstrated that sevoflurane exerts dose-dependent neuroinflammatory effects by activating the NF-κB pathway and promoting the release of pro-inflammatory cytokines [21, 22], while propofol has been shown to possess anti-inflammatory and antioxidant properties that may mitigate neuronal damage [23, 24]. Therefore, the lower sevoflurane exposure in Group IT, combined with the addition of propofol, may have contributed to the better early cognitive outcomes

observed in this group. Although this regimen reflects real-world clinical practice, it also represents a limitation of our study, as the varying sevoflurane exposure between Group I and Group IT precludes direct attribution of the observed differences to a single anesthetic agent. Future studies should include head-to-head comparisons of equivalent MAC sevoflurane alone versus varying doses of propofol combined with sevoflurane to further clarify the independent contributions of each anesthetic component to postoperative cognitive outcomes.

Regarding the potential mechanisms, the inhalation anesthetic sevoflurane may accelerate neurodegenerative progression and cognitive decline in AD patients by promoting β-amyloid protein deposition, inducing neuronal apoptosis and disrupting synaptic plasticity [25, 26]. In contrast, the intravenous anesthetic propofol may alleviate inflammation-mediated neuronal damage by inhibiting glial cell activation, reducing pro-inflammatory cytokine levels and alleviating oxidative stress [27, 28]. Previous studies have also shown that in elderly patients, intravenous and inhalation anesthesia have comparable incidences of short-term postoperative cognitive dysfunction (POCD), but inhalation anesthesia may cause more significant neurological damage [26]. Propofol has also been associated with a lower risk of postoperative delirium and postoperative cognitive dysfunction in patients undergoing major cancer surgery [29, 30]. Our present study further confirms that among commonly used methods of general anesthesia maintenance, propofol-based TIVA offers the best protective effect on cognition in surgical patients with AD and may be the preferred choice for such patients during surgery, though this protective effect did not persist beyond 6 months postoperatively. Our findings also suggest that propofol anesthesia may serve as a therapeutic approach to restore or preserve cognitive function in patients with AD. However, its optimal dosage and treatment duration require confirmation through well-designed prospective multicenter randomized controlled trials.

It is important to note that cervical lymphatic-venous anastomosis is still an investigational procedure for Alzheimer's disease and its therapeutic efficacy and safety profile remain to be established in larger, long-term prospective trials. Therefore, the findings of the present study regarding the optimal anesthesia strategy - specifically, the advantage of TIVA for early cognitive recovery - should be interpreted within the specific context of this procedure and patient population. Caution should be exercised when generalizing these conclusions to all AD patients undergoing other types of surgery, as the surgical procedure itself may influence the interaction between anesthesia methods and postoperative cognitive outcomes. Future studies across diverse surgical settings (e.g., orthopedic, abdominal, or other neurological procedures) are warranted to confirm whether the observed anesthetic advantages apply more broadly to the general AD surgical population.

This study has several limitations. First, this was a single-center study with a relatively limited sample size; therefore, the conclusions drawn are suggestive and require further confirmation through larger, multicenter studies. Second, cognitive function was assessed primarily using clinical scales (MMSE, MoCA, CDR and ADL), without biomarker or neuroimaging validation. Third, the postoperative follow-up period was only 6 months, which may not be sufficient to evaluate long-term cognitive outcomes. Fourth, POD was identified through clinical documentation rather than standardized screening tools, which may have led to under-identification of cases and introduced documentation bias. Finally, as noted above, the varying sevoflurane exposure between Group I and Group IT precludes direct attribution of the observed differences to a single anesthetic agent, representing an inherent limitation of the study design.

In conclusion, TIVA was associated with better early postoperative cognitive performance as measured by MMSE at P7 compared with inhalational anesthesia in AD patients undergoing cervical lymphatic-venous anastomosis. However, no significant differences were observed in MoCA or CDR scores at any time point and the early MMSE benefit was not sustained to P180, as scores in all groups returned to baseline levels. These findings suggest that TIVA may reduce early postoperative delirium burden and psychomotor disturbance rather than confer sustained neurocognitive recovery in this population. Further prospective multicenter randomized controlled trials with stan-

dardized delirium screening, broader cognitive assessments, and longer follow-up are warranted to validate these findings and determine the optimal anesthetic strategy for AD patients.

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Disclosure of conflict of interest

None.

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