Effective of general anesthesia with thoracic paravertebral block on postoperative delirium in elderly patients undergoing thoracoscopic lobectomy: RCT

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Effect of general anesthesia with thoracic paravertebral block on postoperative delirium in elderly patients undergoing thoracoscopic lobectomy: a randomized-controlled trial

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Contents

Background

- Postoperative delirium (POD) is an acute and fluctuating disorder of the mental state with reduced awareness and disturbance of attention
- POD is a relative common and serious complication
  - longer hospital stays
  - morbidity and mortality
  - long-term care
  - increased healthcare resource expenditure

Background

- Thoracic surgeries are closely related to severe pain
  - Impede recovery
  - increase the risk of postoperative delirium
  - A higher postoperative pain score : increased risk of delirium
- The precise mechanism for postoperative delirium
  - not been clarified explicitly
  - neuroinflammation remains the main research interest

Background

- Animal experiments have showed that pain could activate microglial cells and cause neuroinflammation
- Postoperative pain is an important factor in the development of delirium
- Thoracic paravertebral block (TPVB)
  - relieve postoperative pain
  - inhibit the perioperative stress and inflammatory response

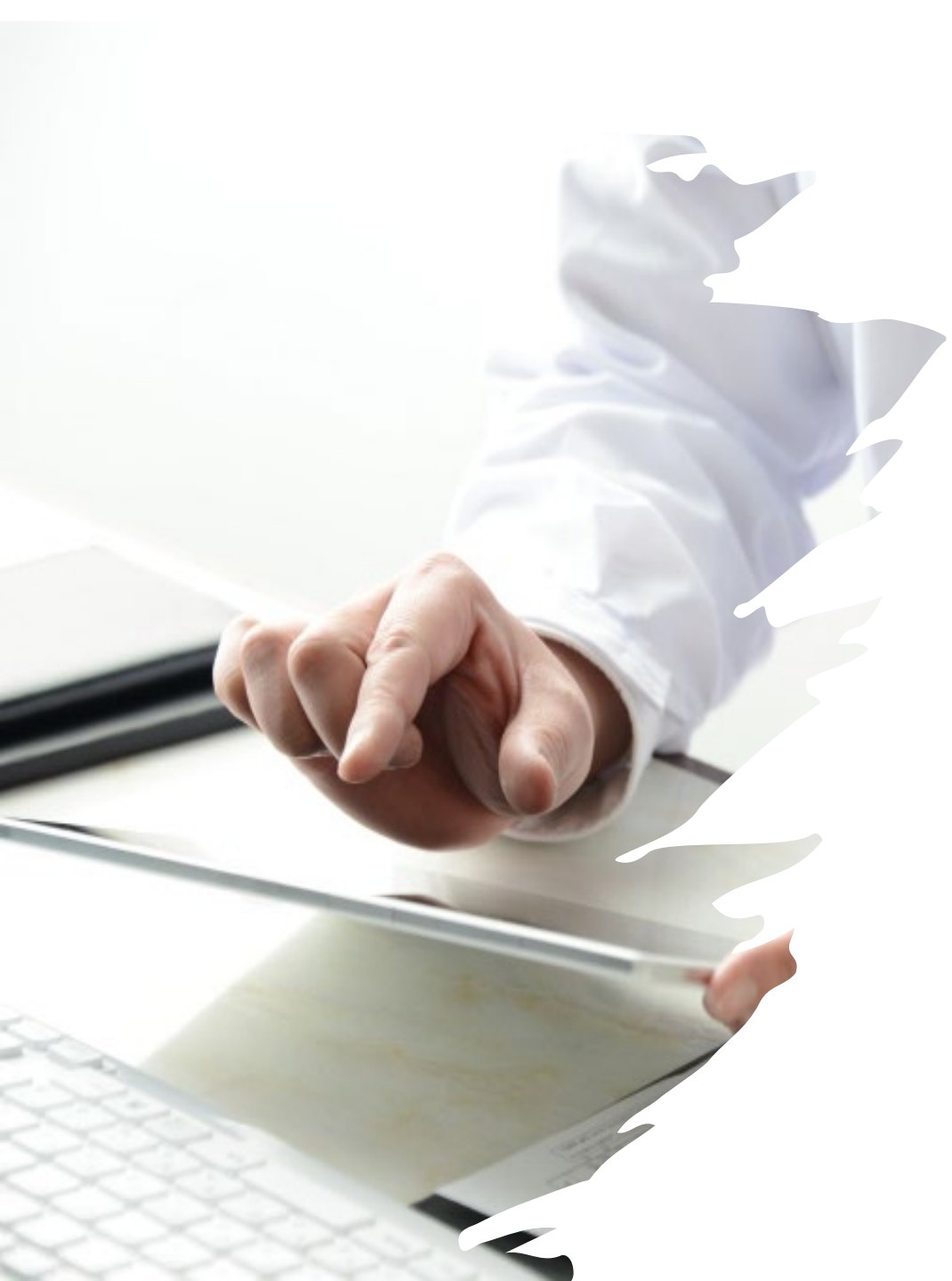
BOX 80-2 ***Predisposing and Precipitating Factors for Postoperative Delirium***

Demographic characteristics: Age older than 65 years, male
Cognitive impairment or depression
Functional impairment
Sensory impairment, especially visual and hearing
Decreased oral intake
Drugs: Polypharmacy, alcoholism, psychoactive, sedatives, opioids, anticholinergic
Comorbidity: Severe illness and neurologic disease
Some types of surgery: High-risk surgery (American Heart Association guidelines) and orthopedic surgery
Intensive care unit admission
Pain
Sleep deprivation
Immobility or poor physical condition

Background

- Aimed to compare the effects of two postoperative analgesic regimes on POD
- Assumed that postoperative paravertebral analgesia
  - provide preferable analgesia
  - reduce opioid consumption postoperatively
  - decrease the incidence of POD

Methods



Study Design

- Single-center RCT with 2 parallel arms
- Conducted at Chinese Clinical Trial Center
- Study from From April 2018 to December 2020
- Was approved by the ethical committee of Cancer hospital and institute of Guangzhou Medical University (ZN201857)

Inclusion Criteria

- ❑ Elderly patients aged 65–80 years undergoing video-assisted thoracic surgery (VATS) lobectomy
- ❑ ASA status classification I-III

Exclusion Criteria

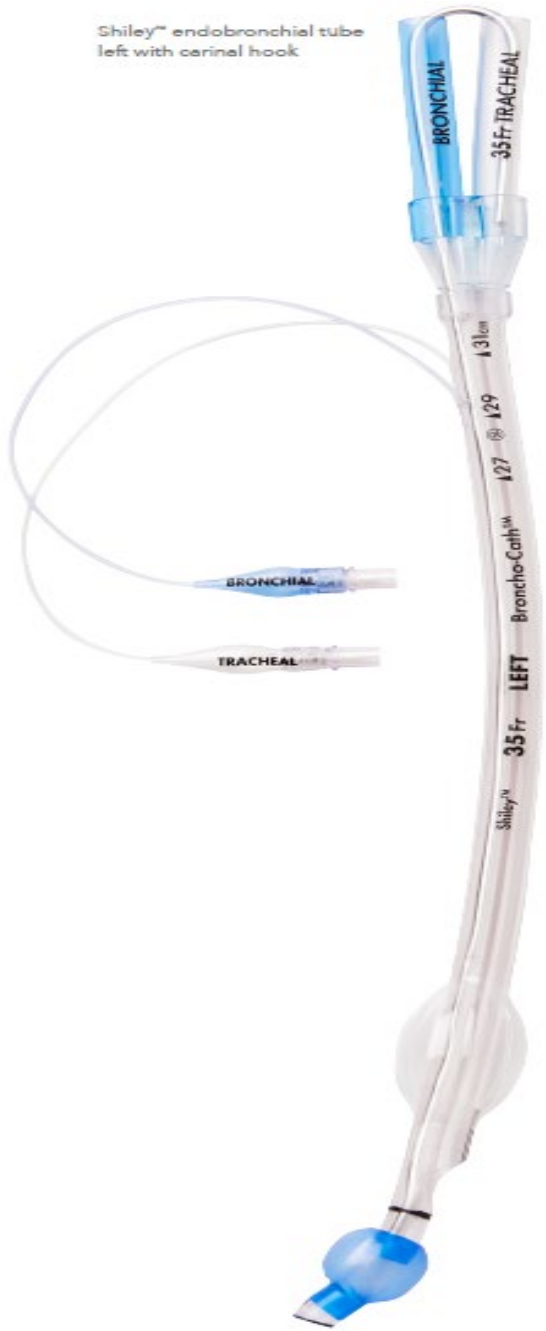
- ❑ History of psychiatric disease
- ❑ A baseline dementia
- ❑ Mini-Mental State Examination (MMSE) score < 23
- ❑ BMI > 35 kg/m^2
- ❑ Severe audio-visual impairments
- ❑ Inability to speak Mandarin or Cantonese precluding communication
- ❑ Surgery duration > 4 h
- ❑ If they were alcohol or drug abuse
- ❑ Contraindications to regional anesthesia

Randomization

- Computer generated random numbers table in a 1:1 ratio
- Divided the patients into
  - patient-controlled intravenous analgesia group (PIA)
  - Patient-controlled paravertebral-block analgesia group (PBA)
- Sealed in sequentially numbered envelopes
- Patients, the investigators responsible for postoperative follow up
- The statisticians were all blinded to the randomization until the final statistical analyses were completed

Anesthesia Management

- General anesthesia with endobronchial intubation
  - A left- or right-sided double lumen endobronchial tube tube (Shiley™ endobronchial tube accessories; Covidien, Mansfield, US)
  - Confirmed using a flexible fiberoptic bronchoscope
- Induced using
  - Sufentanil 0.2 to 0.4 mcg/kg
  - Propofol 1–2 mg/kg
  - Cisatracurium 0.2 mg/kg

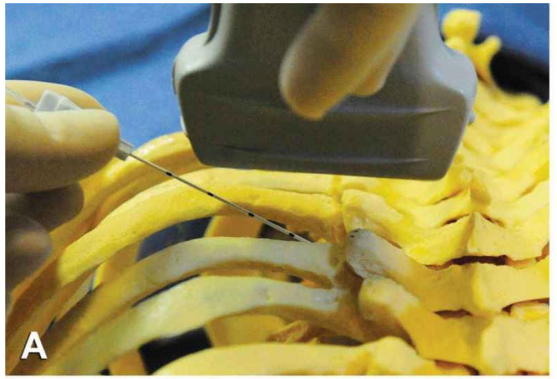


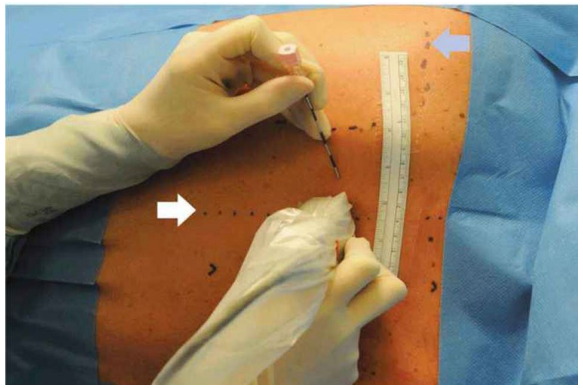
Anesthesia Management

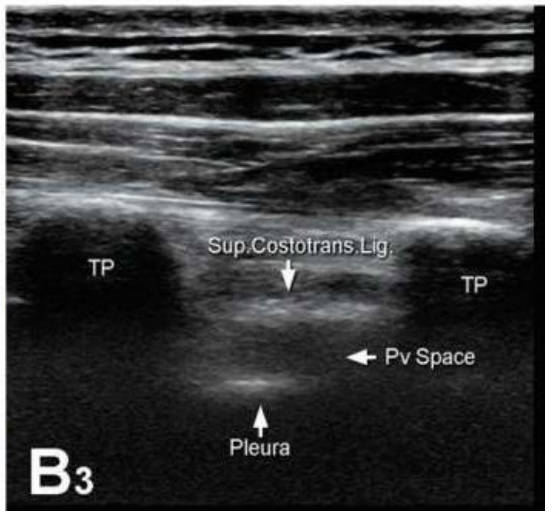
- Maintained with
  - Sevoflurane
  - Remifentanil (0.1–0.3 mcg/kg/min) by intravenous infusion
  - 0.05 mg/kg cisatracurium as intermittent IV bolus
- Bispectral index (BIS) monitor
- sevoflurane concentration was adjusted
  - Maintain a BIS value of 50 ± 10
  - 20% of the baseline values were controlled for HR and BP
- Forced air warm blanket : intraoperative body temperature of 36–37 °C

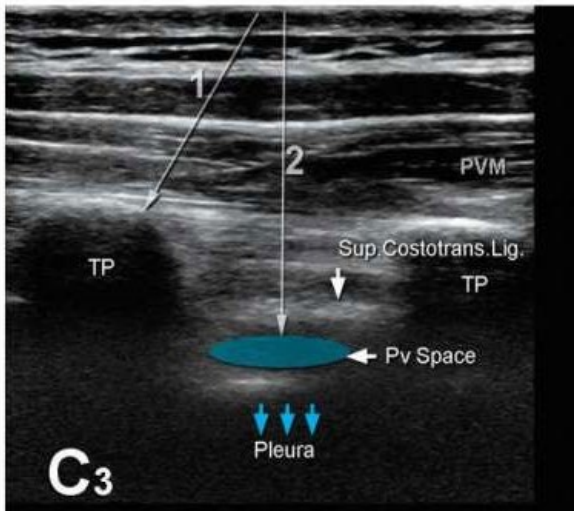
PBA Group

- ❑ Thoracic paravertebral block (TPVB) guided by an ultrasound prior to induction
- ❑ 1 mg midazolam and 5 mcg sufentanil before the TPVB procedure
- ❑ Lateral decubitus position
- ❑ Skin entry points : 2.5–3 cm from the spinal processes at T4 level
- ❑ Confirmed between superior costotransverse ligament and pleura under U/S guidance
- ❑ Epidural catheter was placed into the thoracic paravertebral space



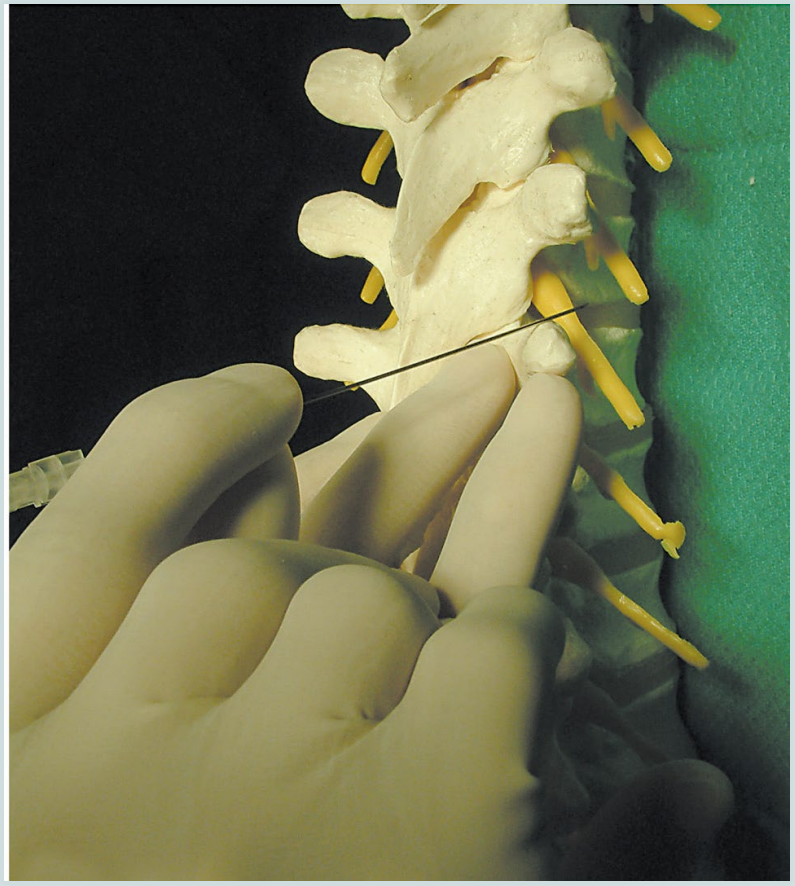






PBA Group

- Bolus of 5 ml of 1% lidocaine
- PCA device was connected to the patients at the end of surgery, with 0.2% ropivacaine
- Background dose of 2 ml/h
- a bolus dose of 0.5 ml with a lockout interval of 15 min for 48 h



PIA Group

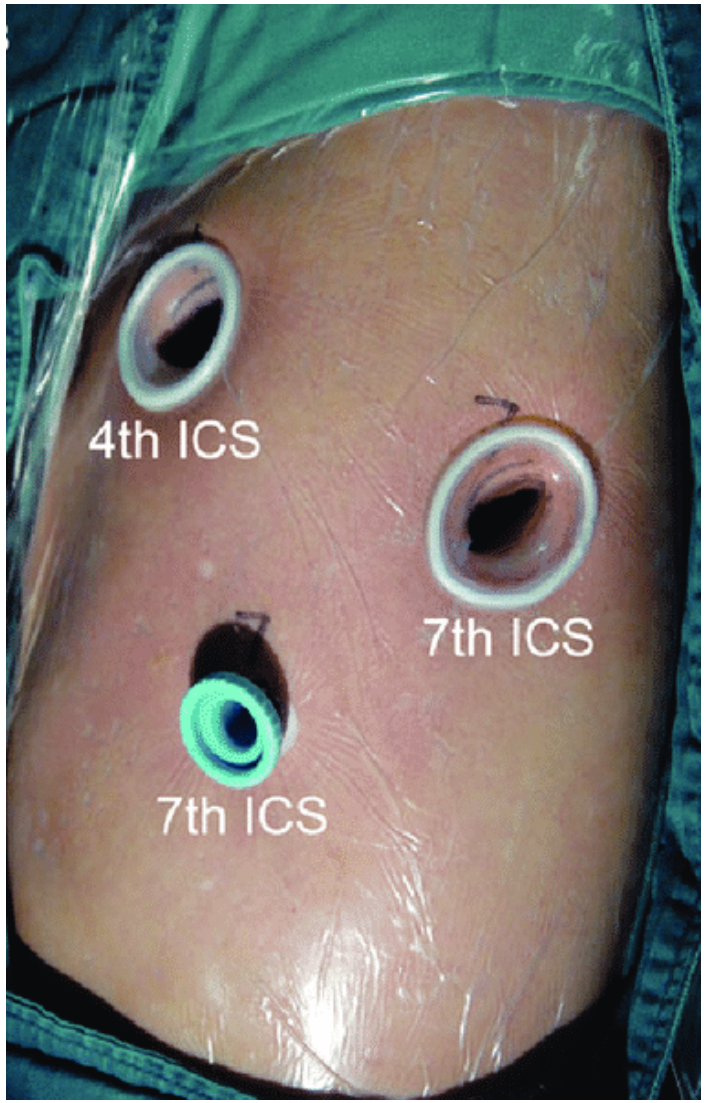
- ❑ 2 mcg/kg sufentanil in a total volume of 100 ml
- ❑ Background dose of 2 ml/h
- ❑ a bolus dose of 0.5 ml with a lockout interval of 15 min for 48 h

Methods

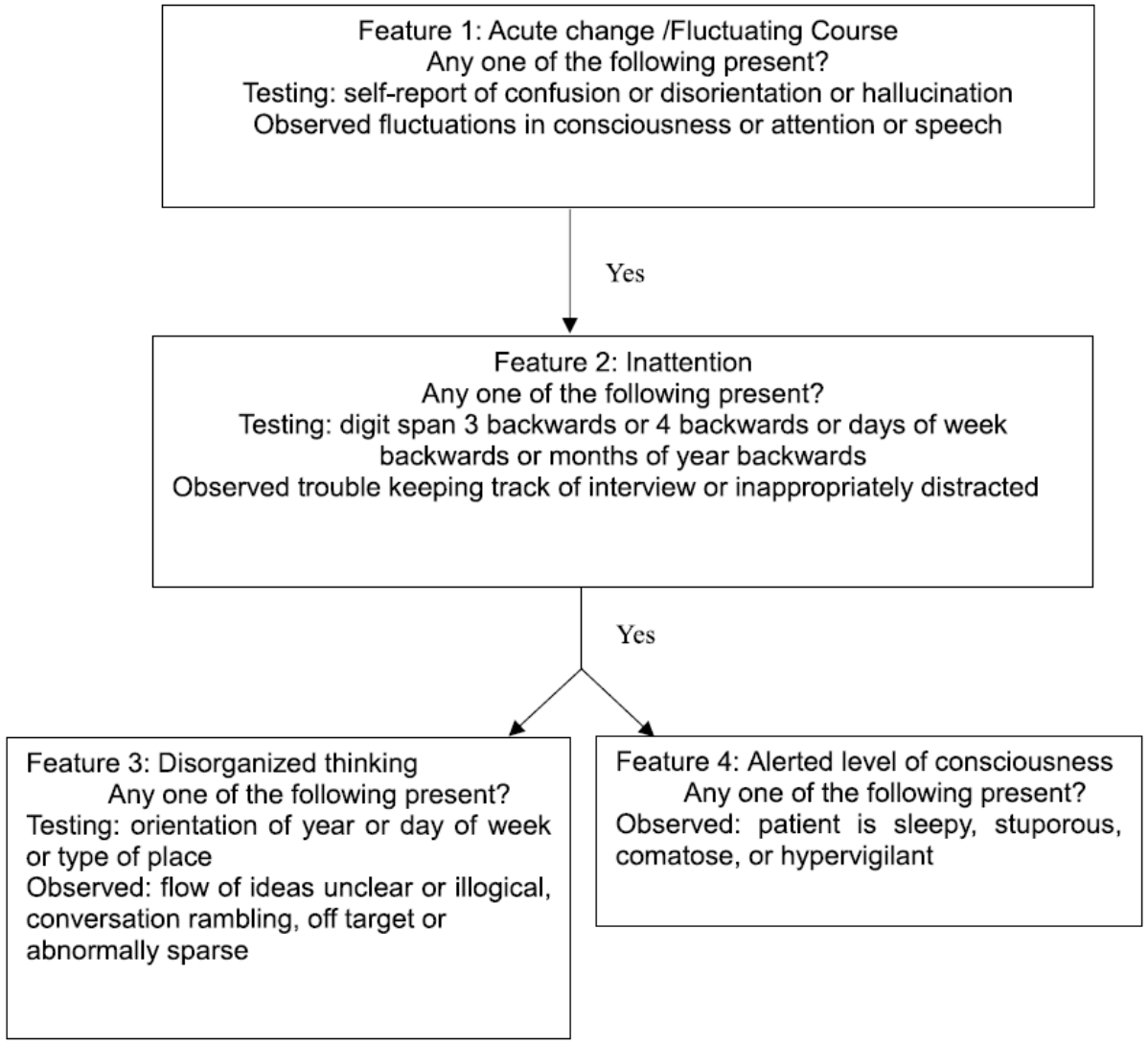
- ❑ All patients will be given sufentanil 0.15 mcg/kg when a chest tube was inserted
- ❑ Parecoxib 40 mg : if VAS 3-5
- ❑ Hydromorphone 0.008 mg/kg : if the VAS score > 5

Surgical Procedure

- Incision of 5 cm length at the 4th intercostal space
- Two additional incisions of 1–2 cm length entering the 7th intercostal space in the posterior and anterior axillary lines at the diaphragm level were located
- A 24-Fr chest tube was placed where exiting the anterior lower incision at the level of 7th intercostal space at the end of surgery
- Chest tube was removed when
  - No air leakage was observed for 6 h
  - Drainage volume for 24 h did not exceed 200 mL



Delirium Assessment



- ❑ 3-min Diagnostic Confusion Assessment Method (3D-CAM)
- ❑ At 3 and 7 days after surgery twice daily (8:00–10:00 am) with an interval of at least 6 h
- ❑ CAM positive for features 1 and 2, in addition to either feature 3 or 4

Pain Evaluation

- Visual analog scale (VAS) score from 0 to 10 by the trained clinical staff
- VAS score and relevant rescue analgesics were documented at 24 and 48 h postoperatively

TNF-α and Neurofilament light(NFL) Levels measurement

- Stored at − 80 °C at the following time points: pre-operation (T1), postoperative day 3 (T2), and day 7 (T3) in the morning (06:00–10:00)
- Enzyme-linked immunosorbent assay (ELISA)
- Single-molecule array method

Statistical Analysis

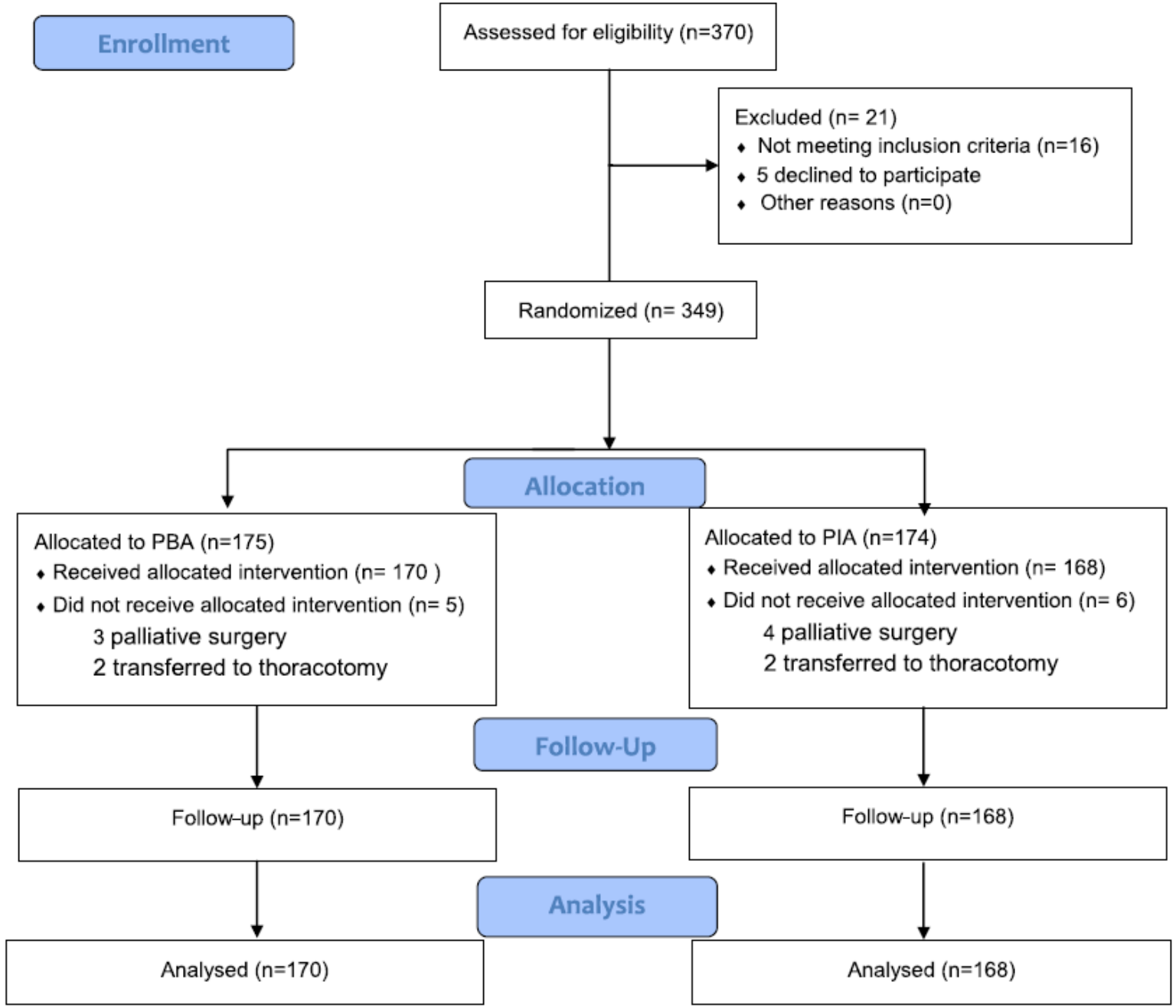
- SPSS (version 22.0 for Windows; IBM Corporation, Armonk, NY, USA)
- Graph-Pad Prism (version 5.03, GraphPad Prism Software, California, USA)
- Quantitative data are expressed as
  - the mean ± standard deviation (SD), compared with the Student t-test (normal distribution), or
  - median with interquartile range (IQR) compared with the Mann–Whitney U test (non-normal distribution)
- Differences and 95% confidence intervals (CI)
- Categorical data are expressed as
  - Chi-square test
  - the Fisher's exact test
  - Kruskal-Wallis test

Statistical Analysis

- Relative risk (RR) and 95% CI
- Repeated analysis of variance test
  - Bonferroni correction
  - comparisons among the concentrations of TNF% and NFL at different time points
  - statistical significance was set at $p < 0.05$

Sample Size

- Assuming a delirium incidence of 23% in PIA group and a 10% reduction in PBA group
- 167 patients were required for each group (total of 334 patients)
- Difference in the incidence of delirium at a 0.05 significance level with a power of 0.8
- Estimated 10% attrition rate, a final sample size : 368 patients


Enrollment
Assessed for eligibility (n=370)
Excluded (n= 21)
Not meeting inclusion criteria (n=16)
5 declined to participate
Other reasons (n=0)
Randomized (n= 349)
Allocation
Allocated to PBA (n=175)
Received allocated intervention (n= 170)
Did not receive allocated intervention (n= 5)
3 palliative surgery
2 transferred to thoracotomy
Allocated to PIA (n=174)
Received allocated intervention (n= 168)
Did not receive allocated intervention (n= 6)
4 palliative surgery
2 transferred to thoracotomy
Follow-Up
Follow-up (n=170)
Follow-up (n=168)
Analysis
Analysed (n=170)
Analysed (n=168)

Results

Table 1 Demographic Characteristics of the Participating Patients

Variables	PIA ($n=168$)	PBA ($n=170$)	*P*-value
Age (year)	73.5 ± 7.1	76.2 ± 6.3	0.471
Sex (M/F)	80/88	83/87	0.229
BMI (kg/m^2)	24.4 ± 3.6	24.9 ± 4.0	0.337
ASA classification			0.227
II	137	146	
III	31	34	
Hypertension	77 (45.8%)	81 (47.6%)	0.802
Diabetes mellitus	39 (23.2)	36 (21.2)	0.830
COPD	17 (10.1%)	20 (11.8%)	0.567
Smoking	82 (48.8%)	96 (56.4%)	0.397
MMSE	26 [24–28]	26 [24–28]	0.920
TNM classification			0.619
I	72	76	
II	62	57	
III	34	37	

Table 2 Intraoperative and postoperative profiles

Variables	PIA ($n = 168$)	PBA ($n = 170$)	MD	95% CI	*P*-Value
Surgery time (min)	113 ± 17.1	116 ± 18.8	−2.01	− 22.13 to 20.42	0.410
Anesthesia time (min)	133 ± 19.8	141 ± 20.6	−7.94	−17.36 to 11.51	0.384
OLV time (min)	96.5 ± 14.6	98.6 ± 12.8	−2.12	−11.43 to 18.46	0.259
Blood loss (ml)	44.6 ± 5.2	43.8 ± 3.0	0.82	0.44 to1.32	0.183
Fluid balance (ml)	1670 ± 412	1741 ± 427	−71.09	− 189.3 to 57.5	0.655
Remifentanil (mg)	2.3 ± 0.6	2.2 ± 0.5	0.102	−0.17 to 0.31	0.495
Sufentanil (μg)					
Intro-operative (μg)	44 ± 3	42 ± 2	1.710	−0.75 to 2.27	0.403
Post-operative (μg)	128.8 ± 21.6	0	128.6	128.6 to 139.7	< 0.001
Parecoxib (mg)	80 [40,120]	40 [40,80]	40	20 to 80	< 0.001
Hydromorphone (mg)	0.456 [0.416–0.648]	0.184 [0.08–0.336]	0.275	0.230 to 0.315	< 0.001

postoperative requirement for rescue analgesics in PBA group was significantly lower than in PIA group

Table 3 Comparison of complications between the two study groups

	PIA ($n=168$)	PBA ($n=170$)	RR	95% CI	*P*-value
Delirium	47 (28%)	28 (16.5%)	1.70	1.29 to 1.93	0.030
3rd day incidence	21 (12.5%)	15 (8.8%)	1.42	1.22 to 1.71	0.034
7th day incidence	26 (15.5%)	13 (7.7%)	2.01	1.48 to 2.46	0.012
PVS	5 (3%)	4 (2.4%)	1.25	0.94 to 1.27	0.730
Atelectasis	6 (3.6%)	6 (3.5%)	1.02	0.76 to 1.19	0.065
Hemorrhage	1 (0.6%)	1 (0.6%)	1.00	0.42 to 1.12	0.865
Pneumonia	3 (1.8%)	2 (1.2%)	1.5	0.51 to 1.98	0.520
Incision infection	2 (1.2%)	2 (1.2%)	1.00	0.56 to 1.14	0.225
DVT	5 (3%)	3 (1.8%)	1.67	0.89 to 2.13	0.445
Ileus	11 (6.5%)	7 (4.1%)	1.59	0.94 to 2.18	0.976
AF	10 (6%)	8 (4.7%)	1.28	0.75 to 1.81	0.617

Table 4 Visual analogue scale pain scores at 24 and 48 h after surgery in each group

	PIA ($n = 168$)	PBA ($n = 170$)	*P*-value
VAS pain score at 24th hour after surgery	4.13 ± 0.65	1.51 ± 0.40	< 0.001
VAS pain score at 48th hour after surgery	3.58 ± 0.49	1.70 ± 0.62	0.033

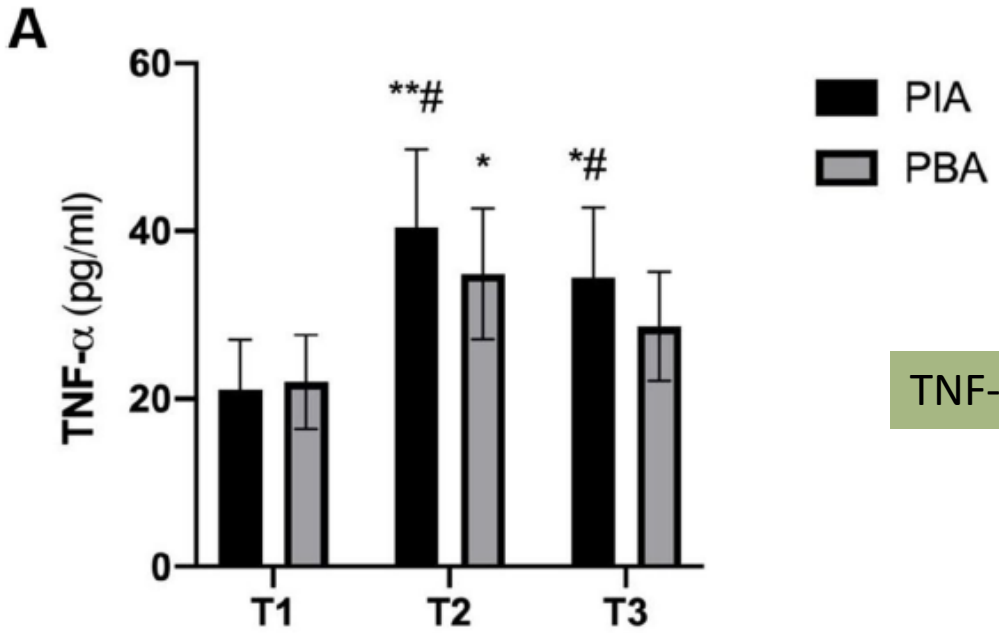
VAS scores in the PBA group were significantly lower at 24 and 48 h postoperatively compared to those in the PIA group

Table 5 Overall recovery rates and recovery rates by different dimensions of QoR-40 scale at day 3 and 7 postoperatively

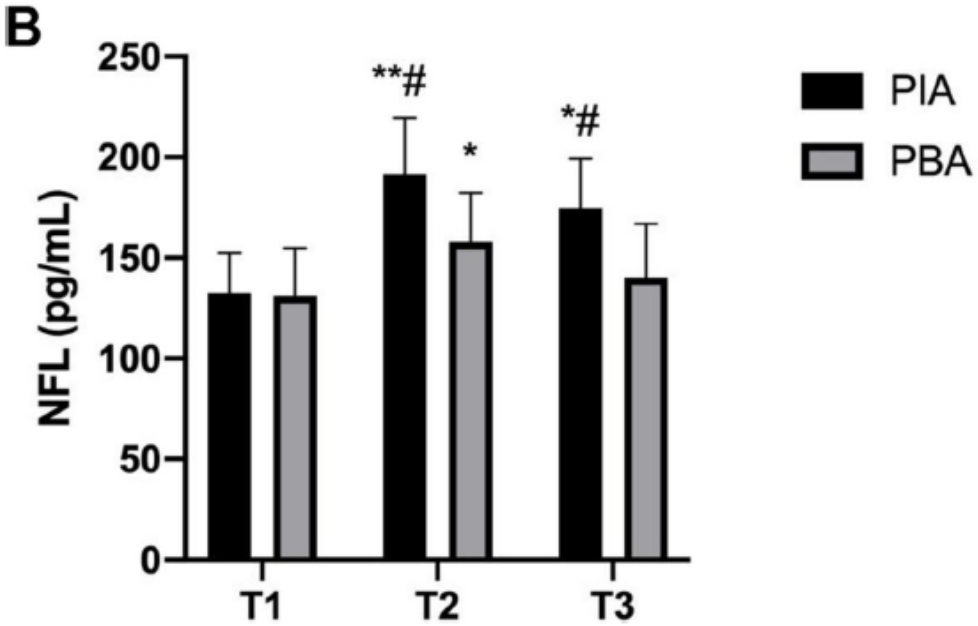
	PIA ($n=168$)	PBA ($n=170$)	*P*-value
Postoperative day 3			
Overall recovery	3 (1.8%)	4 (2.4%)	0.751
Physiology	44 (27.9%)	52 (30.6%)	0.260
Nociception	42 (25%)	65 (38.2%)	0.013
Emotion	56 (33.3%)	78 (45.9%)	0.027
Cognition	117 (69.6%)	139 (81.8%)	0.011
Activities of day living	39 (23.2%)	67 (39.4%)	0.026
Postoperative day 7			
Overall recovery	29 (17.3%)	46 (27.1%)	0.038
Physiology	89 (52.9%)	104 (61.2%)	0.021
Nociception	134 (79.8%)	151 (88.8%)	0.454
Emotion	144 (85.7%)	152 (89.4%)	0.172
Cognition	140 (83.3%)	156 (91.8%)	0.019
Activities of day living	122 (72.6%)	135 (79.4%)	0.043
DCTP (day)	4.53 ± 1.71	3.72 ± 1.44	0.042
LOS (day)	6.57 ± 2.21	5.92 ± 2.03	0.054

PBA group had a higher overall recovery rate at day 7 after surgery

PBA group : early chest tube withdrawn



TNF-α% and NFL, both were lower in the PBA group



Discussion

Discussion

- Incidence of POD : decreased with PBA compared to PIA postoperatively
- Paravertebral block not only preferable analgesic but also opioid-sparing effects
- Minimize the opioid consumption for curtailing POD
- Non-opioid analgesic dramatically reduced POD compared with opioid-only
- Thoracic paravertebral block (TPVB) blocked the neural afferents
  - Reducing postoperative acute pain
  - Opioid consumption
  - Neurocognitive dysfunction

Discussion

- Current study also confirmed that paravertebral block analgesia was superior to intravenous analgesia in reducing the incidence of POD
- One-Lung Ventilation(OLV) initiates pathophysiological changes
  - Hypoxic pulmonary vasoconstriction
  - Severe oxidative stress and free radicals
  - Promotes the neuroinflammatory responses
  - Development of POD in elderly patients
- The complicated interaction of pain, OLV, stress and inflammatory response
  - Promote neuroinflammation
  - Exacerbate postoperative delirium

Discussion

- Thoracic paravertebral block (TPVB)
  - Intercept the sympathetic nerve conduction
  - Suppress the nociceptive stress
  - Suppress Inflammatory response, especially neuroinflammation
- Correlation between neuroinflammation and postoperative delirium
  - TNF- α as an inflammatory marker to elucidate the plausible mechanism
- PBA group exhibited lower incidence of delirium and level of TNF-α and NFL

Limitations

Limitations

- Delirium rating scale (DRS) may be more objective when delirium severity is Considered
- Postoperative delirium and postoperative neurocognitive dysfunction may co-occur in the elderly, relationship between them is not clearly elucidated
- Thoracic epidural block (TEB) and paravertebral block (PVB)
  - Equally effective in controlling acute pain
  - PVB is superior in reducing postoperative delirium
- Combination of sufentanil with hydromorphone in the PIA group
  - It would been better to use the same opioid after surgery between two groups

Conclusion

- TPVB analgesia : lower incidence of postoperative delirium
  - Its anti-neuroinflammatory effects
- TPVB provides not only superior analgesic but also opioid-sparing effects

Clinical Appraisal :RCT

Journal Appraisal

1. Were the following clearly stated:	Yes	Can't tell	No
• Patients	✓		
• Intervention	✓		
• Comparison Intervention	✓		
• Outcome(s)	✓		

Journal Appraisal

2. Was the assignment of patients to treatments randomised?	Yes ✓	Can't tell	No
3. Was the randomisation list concealed? Can you tell?	✓		
4. Were all subjects who entered the trial accounted for at it's conclusion?	✓		
5. Were they analysed in the groups to which they were randomised, i.e. intention-to-treat analysis	✓		

Journal Appraisal

6. Were subjects and clinicians 'blind' to which treatment was being received, i.e. could they tell?	Yes	Can't tell	No ✓
7. Aside from the experimental treatment, were the groups treated equally?	✓		
8. Were the groups similar at the start of the trial?	✓		

Journal Appraisal

9. How large was the treatment effect? Consider • How were the results expressed (RRR, NNT, etc).	X
10. How precise were the results? Were the results presented with confidence intervals?	✓

Journal Appraisal

	Yes	Can't tell	No
11. Do these results apply to my patient? • Is my patient so different from those in the trial that the results don't apply? • How great would the benefit of therapy be for my particular patient?	✓ ✓		
12. Are my patient's values and preferences satisfied by the intervention offered? • Do I have a clear assessment of my patient's values and preferences? • Are they met by this regimen and its potential consequences?	✓ ✓		

Thank you