

Supplement 2

For: Ting Yan, Xin-Quan Liang, Guo-Jun Wang, et al. Prophylactic penehyclidine inhalation for prevention of postoperative pulmonary complications in high-risk patients: A double-blind randomized trial

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Table S1. Definition of postoperative pulmonary complications.

Complication	Definition
Respiratory infection	Receiving antibiotics for a suspected respiratory infection and meet at least one of the following criteria: new or changed sputum, new or changed lung opacities, fever, leukocyte count $>12 \times 10^9/L$
Respiratory failure	$PaO_2 < 60$ mmHg on room air, a ratio of PaO_2 to inspired oxygen fraction < 300 , or arterial oxyhemoglobin saturation measured with pulse oximetry $< 90\%$ and requiring oxygen therapy
Pleural effusion	Chest X-ray demonstrating blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures, or (in supine position) a hazy opacity in one hemithorax with preserved vascular shadows
Atelectasis	Lung opacification with a shift of the mediastinum, hilum, or hemidiaphragm toward the affected area, and compensatory overinflation in the adjacent nonatelectatic lung
Pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura
Bronchospasm	Newly detected expiratory wheezing treated with bronchodilators
Aspiration pneumonitis	Acute lung injury after inhalation of regurgitated intragastric contents

Table S2. Criteria of Clavien-Dindo classification of postoperative pulmonary complications.

Complications	I	II	IIIa	IIIb	IVa	IVb	V
Respiratory infections	Clinical observation or diagnostic evaluation only; intervention not indicated except for nebulizers, expectorants, or lung physiotherapy (e.g., postural drainage)	Medical management indicated (e.g., antibiotics)	Intervention not under general anesthesia (e.g., bronchoscopic aspiration, tracheal puncture)	Intervention under general anesthesia (e.g., tracheostomy under general anesthesia or sedation)	Mechanical ventilation indicated	Sepsis or multiple organ failure	Death
Respiratory failure	–	–	–	–	Mechanical ventilation indicated	Sepsis or multiple organ failure	Death
Pleural effusion	Clinical observation or diagnostic evaluation only; intervention not indicated (drainage only through existing drainage tube)	Medical management indicated (e.g., diuretics)	Intervention not under general anesthesia (e.g., image-guided drain placement or thoracentesis including drain replacement indicated)	Intervention under general anesthesia indicated	Mechanical ventilation indicated	Multiple organ failure	Death
Atelectasis	Clinical observation or diagnostic evaluation only; intervention not indicated, except for nebulizers, expectorants, or lung physiotherapy (e.g., postural drainage)	Medical management indicated (e.g., antibiotics)	Intervention not under general anesthesia (e.g., bronchoscopic aspiration, tracheal puncture)	Intervention under general anesthesia (e.g., tracheostomy under general anesthesia or sedation)	Mechanical ventilation indicated	Sepsis or multiple organ failure	Death
Pneumothorax	Clinical observation or diagnostic evaluation only;	–	Intervention not under general anesthesia (e.g.,	Intervention under general anesthesia	Mechanical ventilation	Multiple organ	Death

	intervention not indicated (drainage only through existing drainage tube)		closed drainage of thoracic cavity or thoracentesis including drain replacement indicated)	indicated	indicated	failure	
Bronchospasm	Clinical observation or diagnostic evaluation only; intervention not indicated except for nebulizers (bronchodilators not included), expectorants, or lung physiotherapy (e.g., postural drainage)	Medical management indicated (e.g., bronchodilators)	–	–	Mechanical ventilation indicated	Multiple organ failure	Death
Aspiration pneumonitis	Clinical observation or diagnostic evaluation only; intervention not indicated except for nebulizers, expectorants, or lung physiotherapy (e.g., postural drainage)	Medical management indicated (e.g., antibiotics, or bronchodilators, or glucocorticoids)	Intervention not under general anesthesia (e.g., bronchoscopic aspiration)	Intervention under general anesthesia (e.g., tracheostomy under general anesthesia or sedation)	Mechanical ventilation indicated	Sepsis or multiple organ failure	Death

Table S3. Withdraw consents, dropouts, and protocol deviations during the study period

	Penehyclidine group (n = 417)	Placebo group (n = 409)	P value
Withdrew consents	5 (1.2%)	2 (0.5%)	0.451
Dropouts due to adverse events	5 (1.2%) ^a	7 (1.7%) ^b	0.538
Protocol deviations	29 (7.0%)	20 (4.9%)	0.209
Changed surgical procedures	1 (0.2%) ^c	1 (0.2%) ^d	>0.999
Prophylactic aerosol inhalations ^e	28 (6.7%)	19 (4.6%)	0.199
Ipratropium	21 (5.0%)	16 (3.9%)	0.435
Budesonide	15 (3.6%)	8 (2.0%)	0.152
Ambroxol	8 (1.9%)	5 (1.2%)	0.422

Data are n (%).

^a Includes cardiac arrest (n=1), nausea (n=1), hand numbness (n=1), tachycardia (n=1), and supraventricular tachycardia (n=1).

^b Includes cardiac arrest (n=1), sneeze (n=1), feel suffocated (n=1), acute myocardial infarction (n=1), hypotension (n=1), delirium (n=1), and mouth numbness (n=1).

^c Changed to lower abdominal surgery.

^d Changed to thyroid surgery.

^e Administered during the first 2 postoperative days.

Table S4. Supplemental baseline data

	Penehyclidine group (n = 417)	Placebo group (n = 409)	Absolute standardized difference
NYHA classification			0.060
Class I	308 (73.9%)	300 (73.3%)	
Class II	106 (25.4%)	104 (25.4%)	
Class III	3 (0.7%)	5 (1.2%)	
Glomerular filtration rate classification			0.116
G3a (45-59 ml/min/1.73m ²)	32 (7.7%)	39 (9.5%)	
G3b (30-44 ml/min/1.73m ²)	20 (4.8%)	11 (2.7%)	
G4 (15-29 ml/min/1.73m ²)	4 (1.0%)	4 (1.0%)	
Arterial blood gas (breathing air) ^a	(n=289)	(n=292)	
pH	7.416 (7.397, 7.432)	7.413 (7.397, 7.427)	0.015
PaO ₂ , mmHg	83 (77, 93)	84 (77, 91)	0.058
PaCO ₂ , mmHg	39 (37, 42)	39 (37, 41)	0.058
PaO ₂ /FIO ₂ , mmHg	393 (364, 439)	401 (365, 435)	0.020
SaO ₂ , %	96 (95, 97)	96 (95, 97)	0.047
Preoperative SpO ₂ , %	95 (95, 97)	96 (95, 97)	0.105
Abnormal chest computed tomography ^a	222 (97.8%) (n=227)	228 (99.6%) (n=229)	0.120
Lung tumor	133 (58.6%)	107 (46.7%)	0.240
Esophageal/mediastinal tumor	37 (16.3%)	52 (22.7%)	0.173
Pulmonary infection	34 (15.0%)	34 (14.8%)	0.004
Diffusive lung lesions	43 (18.9%)	50 (21.8%)	0.074
Abnormal pulmonary function ^a	136 (57.4%) (n=237)	150 (61.0%) (n=246)	0.072
Ventilatory impairment	102 (43.0%)	107 (43.5%)	0.009
Diffusion impairment	50 (21.1%)	56 (22.8%)	0.041
Positive bronchodilator test	0 (0.0%)	5 (2.0%)	-
Non-respiratory medication			
ACEI/ ARB	50 (12.0%)	61 (14.9%)	0.090
α -adrenoreceptor blocker	1 (0.2%)	2 (0.5%)	0.051
β -adrenoreceptor blocker	26 (6.2%)	38 (9.3%)	0.126
Calcium channel blockers	89 (21.3%)	98 (24.0%)	0.064
Nitrates	13 (3.1%)	9 (2.2%)	0.053
Statins	23 (5.5%)	19 (4.6%)	0.038
Anticoagulants	15 (3.6%)	22 (5.4%)	0.096
Oral diabetic drugs	51 (12.2%)	54 (13.2%)	0.030
Diuretics	14 (3.4%)	10 (2.4%)	0.051

Data are n (%) or median (interquartile range). An absolute standardized difference of ≥ 0.147 (marked in bold) is considered imbalanced between the two groups.

NYHA, New York Heart Association; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

^a Results of patients who received the examination.

Table S5. Study drug inhalation

	Penhexylidine group (n = 417)	Placebo group (n = 409)	<i>P</i> value
Number of study drug inhalations			0.960
0	0 (0.0%)	0 (0.0%)	
1	2 (0.5%)	2 (0.5%)	
2	3 (0.7%)	2 (0.5%)	
3	3 (0.7%)	5 (1.2%)	
4	1 (0.2%)	1 (0.2%)	
5	2 (0.5%)	1 (0.2%)	
6	0 (0.0%)	0 (0.0%)	
7	406 (97.4%)	398 (97.3%)	

Data are n (%).

Table S6. Individual extrapulmonary complications after surgery

	Penethylidine group (n = 417)	Placebo group (n = 409)	P value
Neurovascular complications	59 (14.1%)	53 (13.0%)	0.617
Stroke ^a	2 (0.5%)	1 (0.2%)	>0.999
Transient ischemic accident ^b	0 (0.0%)	2 (0.5%)	0.245
Delirium ^c	58 (13.9%)	50 (12.2%)	0.473
Cardiovascular complications	27 (6.5%)	18 (4.4%)	0.189
Acute coronary syndrome ^d	3 (0.7%)	4 (1.0%)	0.723
Circulatory insufficiency ^e	5 (1.2%)	3 (0.7%)	0.725
Congestive heart failure ^f	8 (1.9%)	4 (1.0%)	0.259
New onset arrhythmia ^g	16 (3.8%)	9 (2.2%)	0.170
Thromboembolic complications	4 (1.0%)	1 (0.2%)	0.374
Pulmonary embolism ^h	3 (0.7%)	1 (0.2%)	0.624
Deep venous thrombosis ⁱ	1 (0.2%)	0 (0.0%)	>0.999
Gastrointestinal complications	9 (2.2%)	5 (1.2%)	0.298
Gastrointestinal hemorrhage ^j	3 (0.7%)	3 (0.7%)	>0.999
Acute pancreatitis ^k	1 (0.2%)	0 (0.0%)	>0.999
Ileus ^l	5 (1.2%)	2 (0.5%)	0.451
Surgical complications	13 (3.1%)	20 (4.9%)	0.193
Anastomotic leakage ^m	10 (2.4%)	14 (3.4%)	0.381
Surgical site infection ⁿ	2 (0.5%)	4 (1.0%)	0.447
Surgical bleeding ^o	2 (0.5%)	2 (0.5%)	>0.999
Infectious complications	7 (1.7%)	6 (1.5%)	0.807
Sepsis ^p	5 (1.2%)	6 (1.5%)	0.737
Septic shock ^q	2 (0.2%)	0 (0.0%)	0.499
Liver and kidney complications	29 (7.0%)	22 (5.4%)	0.347
Acute hepatic injury ^r	4 (1.0%)	6 (1.5%)	0.543
Acute kidney injury ^s	25 (6.0%)	17 (4.2%)	0.229

Data are presented as n (%).

^a Persisted new focal neurologic deficit thought to be vascular in origin with signs or symptoms lasted for more than 24 hours. The diagnoses were confirmed by neurologists.

^b A sudden onset of focal neurologic signs and/or symptoms that lasted for less than 24 hours. The diagnoses were confirmed by neurologists.

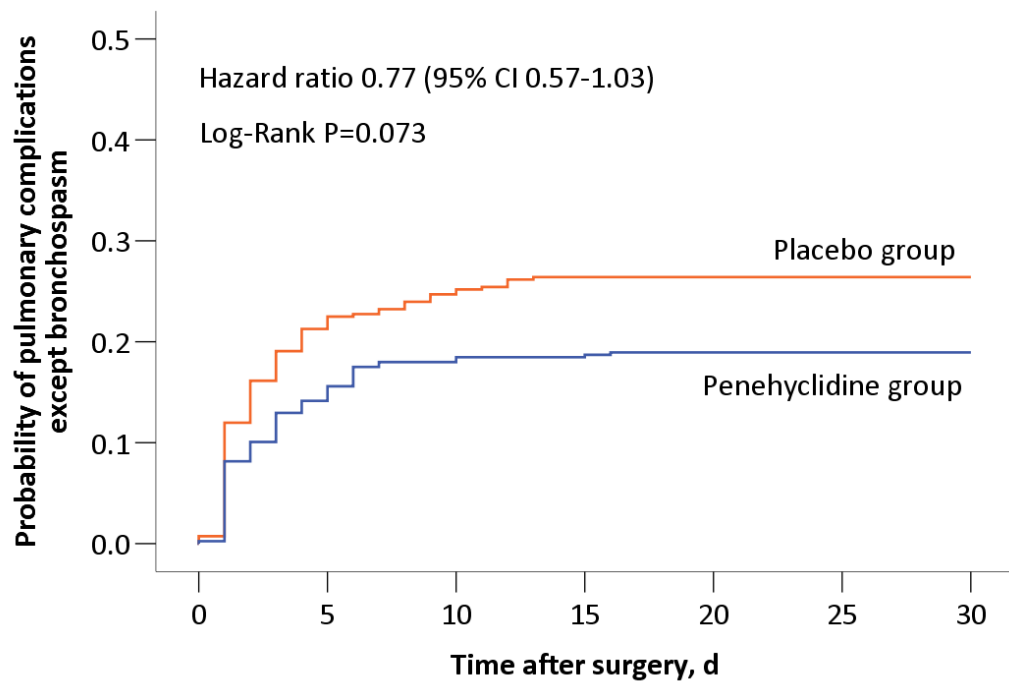
^c Diagnosed according to the Confusion Assessment Method for the Intensive Care Unit within 6 days after surgery, including those that occurred during study drug administration.

^d Included acute myocardial infarction and unstable angina, which were confirmed by clinical symptoms, electrocardiographic changes, and serum cardiac troponin I concentration.

^e Requirement of vasopressors and/or inotropics for more than 24 hours after surgery.

^f New onset orthopnea with evidence of fluid retention (i.e., elevated jugular venous pressure, evidence of pulmonary oedema, and/or peripheral oedema) and an elevated plasma brain natriuretic peptide of above 400 pg/mL.

- ^g Included atrial fibrillation, atrial flutter, supraventricular tachycardia, ventricular premature beats, and cardiac arrest that required medical treatment.
- ^h Diagnosed by a filling defect in any branch of the pulmonary artery in computed tomographic pulmonary angiography.
- ⁱ Non-compressibility of one or more venous segments on B-mode ultrasonography.
- ^j Decrease of hemoglobin level combined with positive gastrointestinal occult blood test results that required treatment, excluding bleeding at surgical site.
- ^k Diagnosed by the presence of persistent and severe epigastric pain radiating to the back, combined with the elevation in serum amylase to greater than three times the upper limit of normal.
- ^l Lack of bowel movement, flatulence, and requirement of parenteral nutrition for more than 1 week after surgery.
- ^m Appearance of gut luminal contents in the abdominal drainage tube, or confirmed by imaging examination or surgical findings.
- ⁿ Infection related to an operative procedure, occurred at or near the surgical incision within 30 days of the procedure, and required surgical intervention.
- ^o Bleeding after surgery that required secondary surgical hemostasis.
- ^p Presence of both infection and a systemic inflammatory response syndrome, and required upgrade of the antibiotic therapy.
- ^q Requirement of vasopressors to maintain a mean arterial pressure of ≥ 65 mmHg despite adequate fluid resuscitation in patients with sepsis and a serum lactate of >2 mmol/L.
- ^r Increase in serum aminotransferase of higher than normal, combined with hyperbilirubinemia.
- ^s Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 $\mu\text{mol/L}$) within 48 hours or to ≥ 1.5 times baseline within seven days, or urine volume <0.5 mL/kg/hour for six hours.



Number at risk							
Placebo Group	409	327	317	312	312	312	312
Penehyclidine Group	417	353	341	340	339	339	339

Figure S1. Probability of postoperative pulmonary complications except bronchospasm by day 30 after surgery.