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Penehyclidine hydrochloride on postoperatively cognitive function

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ABSTRACT

There are many drugs that affect postoperative cognitive function in patients under general anesthesia. Pentanethaquine hydrochloride (PHC), as a new type of anti-cholinergic drug, has been widely used. In clinical practice, many patients, especially elderly patients, have suffered from obvious postoperative cognitive dysfunction, but the incidence of pulmonary infection, reduced probably due to the decease of secretion production. Therefore, the effect of PHC on postoperative cognitive functions and inflammatory factors in elderly lung cancer patients under general anesthesia were mainly discussed to determine the clinical advantages and disadvantages. Ninety elderly patients undergoing thoracoscopic surgery for lung cancer under general anesthesia were selected and divided into PHC group (group A, n = 30), atropine group (group B, n = 30) and normal saline control group (group C, n = 30). The incidence of postoperative blurred vision was higher in group A compared to group B and C (both $p < 0.05$). The incidence of other adverse reactions was higher in group A compared to group C (all $p < 0.05$), but there was no difference between group A and group B (all $p > 0.05$). There was no significant difference in preoperative and day 1 post-surgery mini-mental state examination (MMSE) scores among the three groups (both $p > 0.05$), but the day 1 post-surgery MMSE scores of three groups were lower (all $p < 0.05$). PHC increased the incidence of postoperative cognitive impairment and postoperative delirium in elderly lung cancer patients undergoing thoracoscopic surgery under general anesthesia, but reduced the incidence of postoperative pulmonary complications possibly by reducing the expression of pro-inflammatory cytokines.

Introduction

Postoperative cognitive dysfunction (POCD) is a kind of cognitive function after surgery, which is characterized by a decrease in attention, logical thinking, memory, comprehension and learning abilities, including changes in personality and behavior following a surgical procedure [1]. Although the exact pathogenesis of POCD is not clear, it may be related to various factors like depth of anesthesia, time of anesthesia, education level, secondary operation, postoperative infection, hypotension, etc [2,3]. Advanced age is the only confirmed risk factor for POCD [4,5]. A study has confirmed that the probability of POCD significantly increases in elderly patients over 70 years old compared to those under the age of 70. Shallow sulcus and gyrus, brain atrophy, progressive decline of central nervous system and the decline of nerve reserve function in elderly patients are the possible reasons [6]. Some study has also shown that increased stress-related cortisol secretion may increase the incidence of POCD [7].

Postoperative delirium (PD) is an acute encephalopathy syndrome, which involves changes in consciousness level, changes in responsiveness, sleep disorders, etc [8,9]. The pathogenesis of PD represents unclear, but some studies have reported that preoperative malnutrition, alcoholism, electrolyte disturbance, hypoproteinemia, hypotension, hypoxemia, may increase the incidence of PD, and advanced age has been confirmed an independent risk factor [10–12]. PD is a reversible change that can be restored within a short duration, but may last for months or even years, and progress to POCD or senile dementia [13].

Postoperative pulmonary complications (PPCs) include pulmonary inflammation, atelectasis, respiratory failure, etc [14]. PPC increases mortality risk and length of hospital stay. Some studies have confirmed advanced age as an independent risk factor for the development of PPC, and the levels of the inflammatory cytokines interleukin-6 (IL-6), interleukin-8 (IL-8), and tumor necrosis factor-alpha (TNF-α) are significantly increased in patients with PPC [15,16].

Lung cancer is a common malignancy, especially in elderly people,

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and has a high mortality and morbidity in China. At present, the treatment of lung cancer is mainly surgical resection. However, open thoracic surgery is highly invasive and causes significant tissue damage and severe pain. The elderly patients are usually in a terrible condition, and have difficulty tolerating the surgery. In addition, the post-operative pain affects postoperative drainage capacity and increases lung infection, which is not conducive to recovery. In recent years, with the development of endoscopy techniques, many complicated surgeries have been performed under the endoscope. The use of thoracoscopes to perform lung cancer surgery has greatly reduced the damage and pain caused by surgery, and is therefore a feasible and effective surgical method.

Pentanethaquine hydrochloride (PHC) is a novel, selective anti-cholinergic drug. Due to its strong anti-cholinergic effect on the central and peripheral nerves and no side effect of accelerated heart rate, it has been increasingly used in general anesthesia recently [17]. However, studies have shown that PHC may increase the incidence of POCD and PD and may decrease the concentration of inflammatory cytokines, but there is no clear evidence to confirm either the pros and cons of this drug [18,19].

Therefore, the elderly patients with lung cancer undergoing thoracoscopic surgery under general anesthesia were selected to determine whether PHC is suitable for use in elderly patients.

Hypothesis. *There are many drugs that affect postoperative cognitive function in patients under general anesthesia. Pentanethaquine hydrochloride (PHC), as a new type of anti-cholinergic drugs, has been widely used. In clinical practice, many patients, especially elderly patients, have obvious postoperative cognitive dysfunction, but the incidence of pulmonary infection may be reduced due to the reduction of secretion production. Therefore, the effect of PHC on postoperative cognitive functions and inflammatory factors in elderly lung cancer patients under general anesthesia were mainly discussed to determine the clinical advantages and disadvantages.*

Materials and methods

General data

This study was approved by the Ethic Committee of Central Hospital of Zibo City and patients were informed of possible treatment risks and other treatment options in case of sub-optimal efficacy. All patients provided a signed informed consent. A total of 90 elderly patients with lung cancer undergoing thoracoscopic surgery under general anesthesia admitted in Central Hospital of Zibo City from January 2017 to January 2018 were selected in this study.

Inclusion criteria: Patients aged 65–80 years; tumor grade I-III according to the American Society of Anesthesiologists (ASA) grading [20]; patients with body mass index (BMI) of 18.5–23.9; lung cancer patients undergoing elective lobectomy with expected operation time ≤ 3 h; and no previous history of PD or POCD.

Exclusion criteria: Patients with glaucoma, cataract and other eye diseases; patients with central nervous system and psychiatric disorders, linguistically ineffective communication with psychologists; mini-mental state examination (MMSE) scores ≤ 23 points [21]; patients with severe disorders of the heart, lung, brain, liver, kidney and other major organs; patients with poor preoperative pulmonary oxygenation, finger pulse oxygen $< 90\%$ and inhalation of pure oxygen $< 95\%$; patients with severe vision or hearing impairment with inability to perform postoperative assessment; patients were allergic to the drugs used.

Research objects

The patients were randomized into three groups (n = 30 each) on the basis of pre-anesthetic medication: group A (PHC), group B (atropine), and group C (normal saline control) according to numerical random method.

Anesthetization

All patients were instructed to fast and not drink any liquids for 8 h before operation. Prior to the operation, the uninjured side radial artery was punctured under local anesthesia to monitor blood pressure, mean arterial pressure; in addition, heart rate respiratory rate and oxygen saturation were also monitored. The bispectral index was used to monitor the depth of anesthesia, and 5 l/min oxygen was given under a full mask. Five minutes before anesthetization, the group A, B and C patients were given intramuscular injections of PHC (Chengdu List Pharmaceutical Co., Ltd, Chengdu, China), atropine (Huazhong Pharmaceutical Co., Ltd, Xiangyang, China) and saline (Jiangsu Hengrui Medicine Co., Ltd, Lianyungang, China) respectively, each at 0.01 mg/kg. All patients were anesthetized intravenously with midazolam (Jiangsu Nhwa Pharmaceutical Co., Ltd, Xuzhou, China) at 0.03 mg/kg, propofol (Xi'an Libang Pharmaceutical Co., Ltd, Xi'an, China) at 1–1.5 mg/kg, fentanyl (Jiangsu Nhwa Pharmaceutical Co., Ltd, Xuzhou, China) at 2–3 μg/kg, and rocuronium (Jiangsu Nhwa Pharmaceutical Co., Ltd, Xuzhou, China) at 0.8 mg/kg. Three minutes later, the endotracheal tube was inserted and the bronchial occluder was placed, and after confirming that the latter was positioned correctly, mechanical ventilation was started. The tidal volume was maintained at 8 ml/kg during double lung ventilation and the respiratory rate was 12 breath/minute. After the thoracoscope was prepared, the ventilation was switched to one-lung, and the tidal volume and the respiratory rate were 6 ml/kg and 14 breath/min, respectively. The specific tidal volume and respiratory rate were adjusted according to the CO_2 partial pressure at the end of the breath, so that the latter was maintained at 35–45 mmHg, the inspiratory and expiratory ratio was 1:2, the oxygen flow rate was 1.5 l/min, and the positive end expiratory pressure was 3 mmHg. In one-lung ventilation, oxygen saturation can be maintained over 90% by adjusting the above ventilation parameters. Sevoflurane (Jiangsu Hengrui Medicine Co., Ltd, Lianyungang, China) and remifentanil (Jiangsu Nhwa Pharmaceutical Co., Ltd, Xuzhou, China) were injected at 0.1 μg/kg/min, and the inhalation concentration of sevoflurane was adjusted to maintain the bispectral index value in the range of 50 to 60. Muscle relaxation was maintained by intermittent injection of rocuronium bromide, and intraoperative hemodynamic fluctuations were restricted to no $> 20\%$ of the baseline value. All anesthetic drugs were stopped 5 min before the end of surgery. During the recovery period, no antagonistic drugs were used. When the vital signs were stable and the extubation indication was clear, the endotracheal tube was removed [22].

Surgical approach

In this research, lung cancer patients with single lung resection were selected. Each patient was placed in a 90 degrees lateral position using a 3-hole procedure at the 7th or 8th intercostal space in the midaxillary line, the 5th or 6th intercostal space in the auscultation triangle, and the 4th or 5th intercostal space in the anterior axillary line. Lymph nodes were dissected systematically or selectively, and the chest drainage tubes were removed after chest drainage was $<$ 150–200 ml [23,24].

Observation indicators

Primary observation indicators

MMSE and the incidence of POCD were recorded 1 day before surgery and at the 1st, 4th, and 7th day after surgery and compared among the three groups [25]. The MMSE score includes 7 aspects: time orientation, site orientation, instant memory, attention and calculation,

delayed memory, language and visual space. The total score is 30 points, and the criteria for determining postoperative cognitive impairment: illiterate (uneducated), < 17 points; primary education (≤6 years of education), < 20 points; middle school education and above (education ≥6 years), < 24 points. The incidence rate of POCD = number of patients with POCDs/total number of patients * 100% [26].

The rate of delirium at the 1st day before surgery and at the 1st, 4th and 7th day after surgery were recorded and compared. Confusion assessment method was used to grade the level of delirium as A: acute onset with fluctuating condition; B: lack of concentration or attention; C: thinking disorder; D: altered consciousness [27]. If the patient has A and B, plus either C or D, then delirium can be diagnosed. The delirium rate = number of delirious patients/total number of patients * 100%.

Venous blood was drawn from the fasting patients 1 day before surgery and at the 1st, 4th and 7th day after surgery. The serum concentrations of IL-6, IL-8, and TNF-α were measured by ELISA (Abcam Company, USA). Briefly, the serum samples were pipetted into antibody coated ELISA plates, mixed gently, and sealed for 60 min; after incubation, the plate was washed 5 times, and the HRP-labeled antibody, color developer and reaction terminator were successively added. A new reagent was added each time, the plate was incubated for 30 min, and then washed 5 times. The optical density values of each sample well were normalized to that of the blank controls and the concentration of the respective proteins were calculated [28].

Secondary observation indicators

The time of one-lung ventilation, operation time, intraoperative blood loss, extubation time, postoperative adverse reactions, PPCs and length of hospital stay were recorded and compared in the three groups. Incidence of PPC = number of patients with PPC/total number of patients * 100%.

Safety evaluation

A case was counted as invalid if the operation failed due to uncontrollable factors and open-thorax surgery was performed, or if a patient failed to complete the index collection for various reasons. Mild reactions were not treated till observation, and severe cases were treated with symptomatic drugs.

Statistical methods

Experimental data was analyzed by SPSS19.0 and GraphPad Prism 5 software. Measurement data are expressed as mean ± standard deviation ($\bar{x} \pm SD$). Independent sample *t*-test or repeated measurement analysis of variance was used to compare two groups. Bonferroni post hoc test was used to compare differences in measurement data at each time point between two groups. Analysis of variance test was used to compare three groups. The count data are expressed as ratios, and the χ^2 test was used to compare groups. The rank sum test was used for the ranking variables. $p < 0.05$ is considered statistically significant.

Results

General characteristics

There were no significant differences in age, gender, ASA grade, surgical site, operation time, single lung ventilation time, intraoperative blood loss and extubation time among the three groups (all $p > 0.05$). See Tables 1 and 2.

Comparison of the MMSE scores and the incidence of POCD one day before surgery and the 1st, 4th and 7th day after surgery

There was no significant difference in the degree of education ($p > 0.05$) or MMSE scores on day 1 before surgery across the three groups ($p = 0.854$, $F = 4.326$). See Table 3. The MMSE scores of all three groups decreased post-surgery compared to pre-surgery scores ($p = 0.045$, $F = 15.321$; $p = 0.038$, $F = 16.532$; $p = 0.041$, $F = 16.318$ in groups A, B and C respectively), but there was no significant difference among the three groups ($p = 0.573$, $F = 5.218$). Similarly, there was no significant difference among the three groups in the pre-operative incidence of POCD ($p = 0.835$, $\chi^2 = 4.285$). On the 4th day after operation, the MMSE scores in group A were significantly decreased ($p = 0.042$, $F = 16.427$; $p = 0.007$, $t = 23.536$), and the incidence of POCD was significantly increased ($p = 0.016$, $\chi^2 = 18.926$; $p = 0.008$, $\chi^2 = 25.838$) compared to groups B and C. The incidence of POCD was higher in group B compared to group C ($p = 0.027$, $\chi^2 = 17.647$). At the 7th day after operation, the MMSE scores in group A were significantly decreased ($p = 0.004$, $F = 25.575$; $p < 0.001$, $F = 28.538$), and the POCD incidence was significantly increased ($p = 0.003$, $\chi^2 = 25.258$; $p < 0.001$, $\chi^2 = 29.957$) compared to groups B and C. Furthermore, the incidence of POCD was higher in group B than in group C ($p = 0.006$, $\chi^2 = 22.744$). The POCD incidences in group A at postoperative day 1 and 4 were significantly higher than the pre-operative POCD incidence ($p = 0.006$, $\chi^2 = 24.783$; $p < 0.001$, $\chi^2 = 31.637$). See Tables 4 and 5.

Comparison of the rates of postoperative delirium

There was no significant difference among the three groups ($p = 0.846$, $\chi^2 = 3.689$) on the 1st day after surgery. At the 4th day after surgery, the deliriumrate of group A increased significantly compared to groups B and C, ($p = 0.005$, $\chi^2 = 24.685$; $p = 0.002$, $\chi^2 = 26.567$), and was maintained at the 7th day ($p < 0.001$, $\chi^2 = 31.458$; $p < 0.001$, $\chi^2 = 30.478$). The delirium rate was significantly higher at the 4th and 7th day in group A compared to day 1 post-surgery ($p = 0.017$, $\chi^2 = 17.678$; $p = 0.003$, $\chi^2 = 21.583$). Furthermore, the delirium rates in group B were higher than that in group C at the 4th and 7th days after operation ($p = 0.045$, $\chi^2 = 15.799$; $p = 0.016$, $\chi^2 = 19.567$). See Table 6.

Comparison of the adverse reactions, postoperative PPC incidence, and the duration of hospital stay among the three groups

Group A had a higher incidence of postoperative blurred vision compared to groups B and C ($p = 0.020$, $\chi^2 = 16.467$; $p < 0.001$, $\chi^2 = 27.357$). The incidence of adverse reactions such as dry mouth, skin flushing, and dizziness were not significantly different between groups A and B ($p = 0.647$, $\chi^2 = 4.578$; $p = 0.689$, $\chi^2 = 3.699$; $p = 0.854$, $\chi^2 = 2.848$). The incidence of postoperative PPC was significantly lower in group A compared to groups B and C ($p = 0.003$, $\chi^2 = 14.368$; $p = 0.001$, $\chi^2 = 16.864$). The length of hospital stay was significantly shorter in group A compared to groups B and C ($p = 0.006$, $t = 16.579$; $p = 0.002$, $t = 17.747$), while no significant difference was present between groups B and C ($p = 0.589$, $t = 5.790$). See Table 7.

Comparison of pre-operative levels of inflammatory factors IL-6, IL-8 and TNF-α

IL-6, IL-8 and TNF- α were similar across the three groups on the day before surgery ($p = 0.574$, $F = 6.689$; $p = 0.785$, $F = 5.458$; $p = 0.357$, $F = 7.568$). The expression of all these factors increased in the three groups on day 1 post-surgery ($p = 0.032$, $F = 18.654$; $p = 0.014$, $F = 22.467$; $p = 0.028$, $p = 20.638$), and were not significantly different among the three groups ($p = 0.756$, $F = 4.578$;

Table 1
Comparison of age, gender, ASA grade, surgical site among the groups.

Group	Age (years old)	BMI	Gender (case)		ASA grade (case)			Surgical site (case)	
			Male	Female	I	II	III	Left lung	Right lung
Group A	72.43 ± 5.75	20.65 ± 1.92	16	14	8	16	6	16	14
Group B	71.82 ± 6.53	21.05 ± 1.57	14	16	9	13	8	17	13
Group C	69.10 ± 8.29	19.88 ± 2.16	17	13	7	15	8	15	15
p	0.638	0.594	0.721	0.492	0.821	0.574	0.559	0.825	0.667
F/H	5.273	6.447	4.872	7.912	4.251	6.196	6.018	3.952	5.172

Note: ASA – American Society of Anesthesiologists; BMI – body mass inde; Group A – penehyclidine hydrochloride group; Group B – atropine group; Group C – normal saline control group.

p = 0.268, F = 7.896; p = 0.579, F = 4.736). At the 4th day after operation, the expression levels of IL-6, IL-8 and TNF-α decreased significantly in group A compared to group B (p = 0.024, F = 20.536; p = 0.015, F = 22.356; p = 0.003, F = 27.578) and group C (p = 0.005, F = 25.684; p = 0.036, F = 19.784; p = 0.046, F = 17.468). There were no significant differences between groups B and C (p = 0.466, F = 5.577; p = 0.743, F = 3.786; p = 0.834, F = 3.468). At the 7th day after operation, the expression levels of IL-6, IL-8 and TNF-α were significantly lower in group A compared to group B (p = 0.466, F = 5.577; p = 0.743, F = 3.786; p = 0.834, F = 3.468) and group C (p = 0.466, F = 5.577; p = 0.743, F = 3.786; p = 0.834, F = 3.468), and there were no significant differences between groups B and C (p > 0.05). Compared to postoperative day 1, the expression of the three inflammatory cytokines decreased at the 4th and 7th day after surgery in group A (Fig. 1).

Discussion

PHC is an anticholinergic drug developed in China. It selectively antagonizes M1, M3, and N receptors on both the central and peripheral nerves, and has little effect on M2 receptors [29]. Due to the failure to selectively antagonize the M receptor, PHC does not have side effects like tachycardia and increased intraocular pressure caused by atropine and other hyoscyamine drugs. M1 receptors are mainly distributed in the alveolar walls, glands, and parasympathetic nerves in the lungs, while M3 receptors are mainly distributed in the smooth muscles of the trachea and bronchi and can mediate bronchial contraction and glandular secretion [30]. PHC blocks the parasympathetic excitation caused by the release of acetylcholine, which relaxes the bronchial smooth muscles, relieves the contraction of the pulmonary blood vessels, improves pulmonary microcirculatory dysfunction, improves pulmonary hypoxia, and also regulates autonomic nervous function. Effective inhibition of the vagus nerve reflex improves the effective circulating blood volume, and increases tolerance to ischemia and hypoxia [29]. A study has confirmed that the levels of inflammatory cytokines such as IL-6, IL-8, and TNF-α are significantly increased in patients with PPC [31]. Since buttercup choline can inhibit the production of inflammatory factors, we hypothesized that its analogue PHC could also inhibit the production of inflammatory cytokines, and therefore had a protective effect on the lungs. We demonstrated that PHC could reduce the incidence of PPCs and reduce IL6, IL-8 and TNF-α expression.

Table 3
Comparison of education degree among three groups (n).

Group	Illiterate	Primary education	Middle school education and above
Group A	4	17	9
Group B	5	18	7
Group C	3	16	11
p	0.621	0.746	0.375
H	5.357	5.176	8.925

Note: Group A – penehyclidine hydrochloride group; Group B – atropine group; Group C – normal saline control group.

IL-6, IL-8, and TNF-α are common inflammatory factors that play important roles in trauma-mediated and immune-mediated inflammation [32]. IL-6 and IL-8 are mainly produced in monocytes/macrophages, and their levels significantly increase during inflammation [32]. IL-6 can cause edema, and damage endothelial cells to reduce the volume of circulating blood. A study has also confirmed that the continuous increase of IL-6 in the blood is closely related to postoperative complications. It is an important factor determining the degree of inflammation and prognosis, and is an important acute phase response factor [33]. IL-8 is recognized as a specific inflammatory factor leading to lung injury and has a strong chemotactic effect on leukocytes, and high IL-8 level are positively correlated with lung injury [34]. TNF-α is produced by monocytes and initiates inflammatory reactions by promoting the release of other inflammatory factors and cytokines. Upon binding to TNF-α receptors in the lung tissue, it causes lysosomal destruction and lung injury, and can also stimulate vascular endothelial cells and promote the migration of inflammatory factors to the injured sites. It also acts directly on vascular endothelial cells, causing increased permeability and pulmonary edema [35,36]. Finally, TNF-α stimulates the monocytes and macrophages to produce and secrete IL-6 and IL-8, and then acts synergistically with IL-6 and IL-8 [37]. Therefore, IL-6, IL-8 and TNF-α are closely involved in lung injury.

Both PHC and atropine caused a decrease in the MMSE scores and an increase in the incidence of POCD and PD. There was no significant difference in these indicators between the two drugs at the 1st day after surgery. However, at the 4th and 7th day post-surgery, they increased significantly in the PHC group compared to the atropine group. Therefore, the incidence of POCD and PD increased with time after PHC

Table 2
Comparison of operation time, single lung ventilation time, intraoperative blood loss and extubation time among the three groups.

Group	Operation time (min)	Single lung ventilation time (min)	Intraoperative blood loss (ml)	Extubation time (min)
Group A	118.51 ± 37.72	76.84 ± 15.43	215.74 ± 32.85	24.73 ± 5.49
Group B	125.71 ± 32.86	77.93 ± 14.58	227.82 ± 27.56	22.91 ± 6.32
Group C	122.82 ± 35.74	75.22 ± 18.63	219.51 ± 31.28	24.50 ± 4.21
p	0.827	0.746	0.935	0.473
F	4.336	5.821	3.867	7.815

Note: Group A – penehyclidine hydrochloride group; Group B – atropine group; Group C – normal saline control group.

Table 4
Comparison of MMSE scores among three groups.

Group	One day before surgery	The 1st day after surgery	The 4th day after surgery	The 7th day after surgery
Group A	27.82 ± 2.15	24.72 ± 3.74*	16.70 ± 4.58	14.83 ± 4.12
Group B	26.51 ± 3.21	24.64 ± 3.43*	19.82 ± 3.95$^{\#\&}$	17.72 ± 4.21$^{\$\$\&}$
Group C	27.11 ± 2.64	23.83 ± 4.33*	23.51 ± 4.56$^{\#\#}$	24.11 ± 4.11$^{\$\$\$}$

Note: MMSE – mini-mental state scale; Group A – penehyclidine hydrochloride group; Group B – atropine group; Group C – normal saline control group; the score on the 1st day after surgery compared with that on one day before surgery, $^{*}p < 0.05$; the score of Group B compared with that of Group A on the 4th day after surgery, $^{\#}p < 0.05$; the score of Group C compared with that of Group A on the 4th day after surgery, $^{\#\#}p < 0.01$; the score of Group B compared with that of Group A on the 7th day after surgery, $^{\$\$}p < 0.01$; the score of Group C compared with that of Group A on the 7th day after surgery, $^{\$\$\$}p < 0.001$; the score of Group B compared with that of Group C, $^{\&}p < 0.05$.

Table 5
Comparison of POCD incidence rate among three groups (%).

Group	The 1st day after surgery	The 4th day after surgery	The 7th day after surgery
Group A	10.0	36.7$^{\#\#}$	53.3$^{\#\#\#}$
Group B	6.7	20.0$^{*\$}$	26.7$^{\&\&\$\$}$
Group C	10.0	13.3**	13.3$^{\&\&\&}$

Note: POCD – postoperative cognitive dysfunction; Group A – penehyclidine hydrochloride group; Group B – atropine group; Group C – normal saline control group; the rate of Group B compared with that of Group A, $^{*}p < 0.05$; the rate of Group C compared with that of Group A, $^{**}p < 0.01$; the rate of Group B compared with that of Group A, $^{\&\&}p < 0.01$; the rate of Group C compared with that of Group A, $^{\&\&\&}p < 0.001$; the rate of Group A on the 4th day compared with that on the 1st day after surgery, $^{\#\#}p < 0.01$; the rate of Group A on the 7th day compared with that on the 1st day after surgery, $^{\#\#\#}p < 0.001$; the rate of Group B compared with that of Group C, $^{\$}p < 0.05$; the rate of Group B compared with that of Group C, $^{\$\$}p < 0.01$.

Table 6
Comparison of the postoperative delirium rates in the three groups (%).

Group	The 1st day after surgery	The 4th day after surgery	The 7th day after surgery
Group A	10	26.7$^{\#}$	53.3$^{\#\#}$
Group B	13.3	20.0$^{**\$}$	23.3$^{\&\&\&\$}$
Group C	13.3	13.3**	16.7$^{\&\&\&}$

Note: Group A – penehyclidine hydrochloride group; Group B – atropine group; Group C – normal saline control group; the rate of Group B or Group C compared with that of Group A, $^{**}p < 0.01$; the rate of Group B or Group C compared with that of Group A, $^{\&\&\&}p < 0.001$; the rate of Group A on the 4th day compared with that on the 1st day after surgery, $^{\#}p < 0.05$; the rate of Group A on the 7th day compared with that on the 1st day after surgery, $^{\#\#}p < 0.001$; the rate of Group B compared with that of Group C, $^{\$}p < 0.05$.

administration, and the increase was greater than with the currently used atropine. PHC significantly increased the instances of blurred vision, but did not differ from atropine on other adverse reactions such as dry mouth, facial flushing etc. Therefore, in terms of postoperative cognitive function and adverse reactions, atropine performed better than PHC. The incidence of PPCs was significantly lower in the PHC group compared to the atropine and control groups. Serum levels of IL-6, IL-8, and TNF-α significantly increased after surgery in the control and atropine groups but in the PHC group, only increased significantly on the 1st day after operation and then decreased markedly on the 4th and 7th day post-surgery. This confirmed that the decrease in the incidence of PPCs by penehyclidine was likely due to a decrease in the levels of pro-inflammatory cytokines, and that PHC was a better option than atropine in reducing pulmonary complications. The length of hospital stay was significantly shorter in the PHC group, indicating that a lower incidence of pulmonary complications had a greater effect on the recuperative period of elderly patients than on the incidence of POCD and PD. To summarize, PHC increased the incidence of POCD and PD, and reduced the incidence of PPC and shortened the length of hospital stay in elderly lung cancer patients who received surgery. We surmise that since the advantages outweigh the disadvantages, PHC is a good anticholinergic drug that can be used in elderly patients. We only examined the incidence of POCD, PD and PPC within the 7-day post-operation, and therefore can only confirm the short-term effect of PHC. Further experimental studies are needed to study its long-term effects. In addition, we only confirmed the beneficial role of PHC in lung surgery and cannot state whether these benefits also extend to other surgeries.

In conclusion, PHC can increase postoperative cognitive impairment and incidence of postoperative delirium in elderly thoracoscopic lung cancer patients under general anesthesia. However, it can reduce the incidence of PPCs, most likely by lowering the serum levels of IL-6, IL-8, and TNF-α in patients. PHC has the potential of clinical use in elderly patients.

Table 7
Comparison of the adverse reactions, postoperative PPC incidence rate, and the duration of hospital stay were compared among the three groups.

Group	Adverse reactions (case)				Postoperative PPC incidence rate (%)	Duration of hospital stay (day)
	Blurred vision	Dry mouth	Skin flushing	Dizziness		
Group A	12$^{\&\&\&}$	16$^{\&\&\&}$	14$^{\&\&\&}$	7$^{\&}$	16.7%	11.62 ± 3.28
Group B	6$^{*\&\&}$	15$^{\&\&\&}$	13$^{\&\&\&}$	8$^{\&}$	40.0%$^{\#\#}$	17.71 ± 4.54$^{\$\$}$
Group C	1	4	2	4	46.7%$^{\#\#}$	16.83 ± 4.74$^{\$\$}$

Note: PPC – postoperative pulmonary complication; Group A – penehyclidine hydrochloride group; Group B – atropine group; Group C – normal saline control group; Group B compared with Group A, $^{*}p < 0.05$; Group A and Group B compared with Group C, $^{\&}p < 0.05$; Group B compared with Group C, $^{\&\&}p < 0.01$; Group A and Group B compared with Group C, $^{\&\&\&}p < 0.001$; Group B and Group C compared with Group A, $^{\#\#}p < 0.01$; Group B and Group C compared with Group A, $^{\$\$}p < 0.01$.

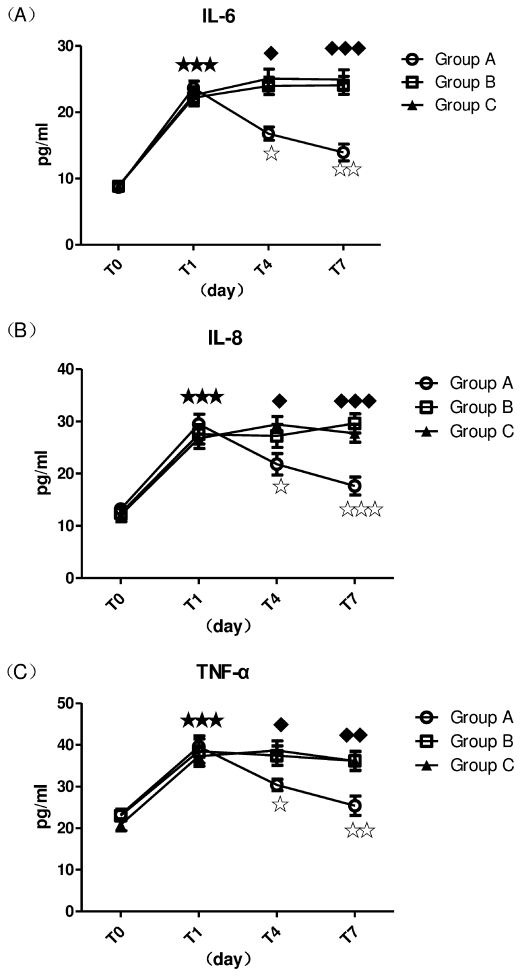

Fig. 1. Comparison of IL-6, IL-8 and TNF-α among the three groups. The abscissas T0, T1, T4, and T7 indicate 1 day before surgery, and day 1, 4 and 7 post-surgery respectively. The ordinate shows the concentration of inflammatory cytokines in the blood. (A) T1 vs. T0 of all three groups, ★★★$p < 0.001$; T4 vs. T1 of Group A, ☆$p < 0.05$; T7 vs. T1 of Group A, ☆☆$p < 0.01$; Group A vs. Group B and Group C, ◆$p < 0.05$; Group A vs. Groups B and C, ◆◆◆$p < 0.001$. (B) T1 vs. T0 of all three groups, ★★★$p < 0.001$; T4 vs. T1 of Group A, ☆$p < 0.05$; T7 vs. T1 of Group A, ☆☆☆$p < 0.001$; Group A vs. Group B and Group C, ◆$p < 0.05$; Group A vs. Group B and Group C, ◆◆◆$p < 0.001$. (C) T1 vs. T0 of all three groups, ★★★$p < 0.001$; T4 vs. T1 of Group A, ☆$p < 0.05$, T7 vs. T1 of Group A, ☆☆$p < 0.01$; Group A vs. Group B and Group C, ◆$p < 0.05$, Group A vs. Groups B and C, ◆◆$p < 0.01$. IL-6 – interleukin-6; IL-8 – interleukin-8; TNF-α – tumor necrosis factor-alpha.

Declaration of Competing Interest

The authors confirm that this manuscript has no conflict of interest.

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References

[1] Kratz T, Diefenbacher A. Delirium as a risk factor for POCD. Dtsch Arztebl Int 2017;114(20):362.
[2] Bi J, Shan W, Luo A, Zuo Z. Critical role of matrix metallopeptidase 9 in postoperative cognitive dysfunction and age-dependent cognitive decline. Oncotarget 2017;8(31):51817–29.
[3] Cao YH, Chi P, Zhao YX, Dong XC. Effect of bispectral index-guided anesthesia on consumption of anesthetics and early postoperative cognitive dysfunction after liver transplantation: an observational study. Medicine (Baltimore) 2017;96(35):e7966.
[4] Valentin LS, Pereira VF, Pietrobon RS, et al. Effects of single low dose of dexamethasone before noncardiac and nonneurologic surgery and general anesthesia on postoperative cognitive dysfunction-a phase III double blind, randomized clinical trial. PLoS One 2016;11(5):e0152308.
[5] Xie H, Huang D, Zhang S, et al. Relationships between adiponectin and matrix metalloproteinase-9 (MMP-9) serum levels and postoperative cognitive dysfunction in elderly patients after general anesthesia. Aging Clin Exp Res 2016;28(6):1075–9.
[6] Chi YL, Li ZS, Lin CS, Wang Q, Zhou YK. Evaluation of the postoperative cognitive dysfunction in elderly patients with general anesthesia. Eur Rev Med Pharmacol Sci 2017;21(6):1346–54.
[7] Qiao Y, Feng H, Zhao T, Yan H, Zhang H, Zhao X. Postoperative cognitive dysfunction after inhalational anesthesia in elderly patients undergoing major surgery: the influence of anesthetic technique, cerebral injury and systemic inflammation. BMC Anesthesiol 2015;15:154.
[8] Drews T, Franck M, Radtke FM, et al. Postoperative delirium is an independent risk factor for posttraumatic stress disorder in the elderly patient: a prospective observational study. Eur J Anaesthesiol 2015;32(3):147–51.
[9] Kazmierski J, Banys A, Latek J, et al. Mild cognitive impairment with associated inflammatory and cortisol alterations as independent risk factor for postoperative delirium. Dement Geriatr Cogn Disord 2014;38(1–2):65–78.
[10] Xiang D, Xing H, Tai H, Xie G. Preoperative C-reactive protein as a risk factor for postoperative delirium in elderly patients undergoing laparoscopic surgery for colon carcinoma. Biomed Res Int 2017;2017:5635640.
[11] Smulter N, Lingehall HC, Gustafson Y, et al. Disturbances in oxygen balance during cardiopulmonary bypass: a risk factor for postoperative delirium. J Cardiothorac Vasc Anesth 2018;32(2):684–90.
[12] Kalisvaart KJ, Vreeswijk R, de Jonghe JF, van der Ploeg T, van Gool WA, Eikelenboom P. Risk factors and prediction of postoperative delirium in elderly hip-surgery patients: implementation and validation of a medical risk factor model. J Am Geriatr Soc 2010;54(5):817–22.
[13] Cascella M, Muzio MR, Bimonte S, Cuomo A, Jakobsson JG. Postoperative delirium and postoperative cognitive dysfunction: updates in pathophysiology, potential translational approaches to clinical practice and further research perspectives. Minerva Anestesiol 2018;84(2):246–60.
[14] Saito H, Hatakeyama K, Konno H, Matsunaga T, Shimada Y, Minamiya Y. Impact of pulmonary rehabilitation on postoperative complications in patients with lung cancer and chronic obstructive pulmonary disease. Thorac Cancer 2017;8(5):451–60.
[15] Canizares Carretero MA, Garcia Fontan EM, Blanco Ramos M, et al. Is age a predisposing factor of postoperative complications after lung resection for primary pulmonary neoplasms? Cir Esp 2017;95(3):160–6.
[16] Wang S, Li X, Li Y, et al. The long-term impact of postoperative pulmonary complications after video-assisted thoracic surgery lobectomy for lung cancer. J Thorac Dis 2017;9(12):5143–52.
[17] Yang Y, Zhao L, Ma J. Penehyclidine hydrochloride preconditioning provides cardiac protection in a rat model of myocardial ischemia/reperfusion injury via the mechanism of mitochondrial dynamics mechanism. Eur J Pharmacol 2017;813:130–9.
[18] Staff PO. Correction: penehyclidine hydrochloride pretreatment ameliorates rhabdomyolysis-induced AKI by activating the Nrf2/HO-1 pathway and allevi-ating endoplasmic reticulum stress in rats. PLoS One 2016;11(4):e0154138.
[19] Guo Y, Wei M, Yan Z, Wang G. Penehyclidine hydrochloride attenuates LPS-induced acute lung injury in rats. Chinese J Cell Mole Immunol 2017;33(11):1486.
[20] Kannan T. ASA grading: a step forward. J Perioper Pract 2017;27(3):54–8.
[21] Orozco Arbelaez E, Banegas JR, Rodriguez Artalejo F, Lopez Garcia E. Influence of habitual chocolate consumption over the mini-mental state examination in Spanish older adults. Nutr Hosp 2017;34(4):841–6.
[22] Zarbo C, Brivio M, Brugnera A, et al. Post-operative cognitive decline (POCD) after gynaecologic surgery: current opinions and future applications. Arch Gynecol Obstet 2018;297(4):1073.
[23] Gonfiotti A, Bongiolatti S, Bertolaccini L, et al. Thoracoscopic lobectomy for locally advanced-stage non-small cell lung cancer is a feasible and safe approach: analysis from multi-institutional national database. J Vis Surg 2017;3:160.
[24] Abah U, Casali G, Batchelor TJP, et al. Pathological lymph node involvement is not a predictor of adverse outcomes in patients undergoing thoracoscopic lobectomy for lung cancer. Eur J Cardiothorac Surg 2017;44(11):S12–3.
[25] Ericsson MC, Gatz M, Kareholt I, Parker MG, Fors S. Validation of abridged mini-mental state examination scales using population-based data from Sweden and USA. Eur J Age 2017;14(2):199–205.
[26] Liebert AD, Chow RT, Bicknell BT, Varigos E. Neuroprotective effects against POCD by photobiomodulation: evidence from assembly/disassembly of the cytoskeleton. J Exp Neurosci 2016;10:1–19.
[27] Vasunilashorn SM, Guess J, Ngo L, et al. Derivation and validation of a severity scoring method for the 3-minute diagnostic interview for confusion assessment method-defined delirium. J Am Geriatr Soc 2016;64(8):1684–9.
[28] Rasoulinejad S, Gargari SLM. Aptamer-nanobody based ELASA for specific detection of Acinetobacter baumannii isolates. J Biotechnol 2016;231:46–54.
[29] Shu Y, Yang Y, Zhang P. Neuroprotective effects of penehyclidine hydrochloride against cerebral ischemia/reperfusion injury in mice. Brain Res Bull 2016;121:115–23.
[30] Zhao W, Huang X, Zhang L, et al. Penehyclidine hydrochloride pretreatment ameliorates rhabdomyolysis-induced AKI by activating the Nrf2/HO-1 pathway and alleviating endoplasmic reticulum stress in rats. PLoS One 2016;11(3):e0151158.
[31] Serpa NA, Campos PP, Hemmes SN, et al. Kinetics of plasma biomarkers of inflammation and lung injury in surgical patients with or without postoperative pulmonary

complications. Eur J Anaesthesiol 2017;34(4):229–38.
[32] Tang SC, Liao PY, Hung SJ, et al. Topical application of glycolic acid suppresses the UVB induced IL-6, IL-8, MCP-1 and COX-2 inflammation by modulating NF-kappaB signaling pathway in keratinocytes and mice skin. J Dermatol Sci 2017;86(3):238–48.
[33] Mullol J, Callejas FB, Mendez-Arancibia E, et al. Montelukast reduces eosinophilic inflammation by inhibiting both epithelial cell cytokine secretion (GM-CSF, IL-6, IL-8) and eosinophil survival. J Biol Regul Homeost Agents 2010;24(4):403–11.
[34] Rodriguez E, Guevara J, Paez A, et al. The altered expression of inflammation-related molecules and secretion of IL-6 and IL-8 by HUVEC from newborns with maternal inactive systemic lupus erythematosus is modified by estrogens. Lupus 2008;17(12):1086–95.
[35] Xu Q, Choksi S, Liu Z. Switching from TNF-induced inflammation to death signaling. Mol Cell Oncol 2017;5(1):e1392402.
[36] Zelazowska-Rutkowska B, Mrugacz M, Cylwik B. Comparison of the diagnostic power of Serum IL-6, IL-8 and TNF-alpha for the idiopathic anterior uveitis in children. Clin Lab 2017;63(11):1889–95.
[37] Bahramabadi R, Fathollahi MS, Hashemi SM, et al. Serum levels of IL-6, IL-8, TNF-alpha, and TGF-beta in chronic HBV-infected patients: effect of depression and anxiety. Lab Med 2017;7(1):3757.