Penehyclidine hydrochloride on postoperatively cognitive function

X. Hongyu\textsuperscript{a,1}, W. Qingting\textsuperscript{a,1}, S. Xiaoling\textsuperscript{a}, Z. Liwu\textsuperscript{a}, Y. Ailing\textsuperscript{a}, L. Xin\textsuperscript{b,∗}

\textsuperscript{a} Department of Anesthesiology, Central Hospital of Zibo City, Zibo 255036, Shandong Province, China
\textsuperscript{b} Department of Anesthesiology, Maternal and Child Health Hospital of Zibo City, Zibo 255029, Shandong Province, China

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ABSTRACT

There are many drugs that affect postoperative cognitive function in patients under general anesthesia. Penehyclidine 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 decrease 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 remains 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,
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 thorascopes 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) score ≤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 CO₂ 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 intraperative 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 (x ± 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 χ² 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, χ² = 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, χ² = 18.926; p = 0.008, χ² = 25.838) compared to groups B and C. The incidence of POCD was higher in group B compared to group C (p = 0.027, χ² = 17.647). At the 7th day after operation, the MMSE scores in group A were significantly decreased (p = 0.004, F = 25.757; p < 0.001, F = 28.538), and the POCD incidence was significantly increased (p = 0.003, χ² = 25.258; p < 0.001, χ² = 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, χ² = 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, χ² = 24.783; p < 0.001, χ² = 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, χ² = 3.689) on the 1st day after surgery. At the 4th day after surgery, the delirium rate of group A increased significantly compared to groups B and C (p = 0.005, χ² = 24.685; p = 0.002, χ² = 25.567), and was maintained at the 7th day (p < 0.001, χ² = 31.458; p < 0.001, χ² = 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, χ² = 17.678; p = 0.003, χ² = 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, χ² = 15.799; p = 0.016, χ² = 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, χ² = 16.467; p < 0.001, χ² = 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, χ² = 4.578; p = 0.689, χ² = 3.699; p = 0.854, χ² = 2.848). The incidence of postoperative PPC was significantly lower in group A compared to groups B and C (p = 0.003, χ² = 14.368; p = 0.001, χ² = 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, F = 20.638), and were not significantly different among the three groups (p = 0.756, F = 4.578;
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 cytokines, 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.

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 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 surgery.

**Table 1**

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years old)</th>
<th>BMI</th>
<th>Gender (case)</th>
<th>ASA grade (case)</th>
<th>Surgical site (case)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>I</td>
<td>II</td>
<td>III</td>
</tr>
<tr>
<td>Group A</td>
<td>72.43 ± 5.75</td>
<td>20.65 ± 1.92</td>
<td>16</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Group B</td>
<td>71.82 ± 6.53</td>
<td>21.05 ± 1.57</td>
<td>14</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Group C</td>
<td>69.10 ± 8.29</td>
<td>19.88 ± 2.16</td>
<td>17</td>
<td>13</td>
<td>7</td>
</tr>
<tr>
<td>p</td>
<td>0.638</td>
<td>0.594</td>
<td>0.721</td>
<td>0.492</td>
<td>0.821</td>
</tr>
</tbody>
</table>

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

**Table 2**

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

<table>
<thead>
<tr>
<th>Group</th>
<th>Operation time (min)</th>
<th>Single lung ventilation time (min)</th>
<th>Intraoperative blood loss (ml)</th>
<th>Extubation time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>118.51 ± 37.72</td>
<td>76.84 ± 15.43</td>
<td>215.74 ± 32.85</td>
<td>24.73 ± 5.49</td>
</tr>
<tr>
<td>Group B</td>
<td>125.71 ± 32.86</td>
<td>77.93 ± 14.58</td>
<td>227.82 ± 27.56</td>
<td>22.91 ± 6.32</td>
</tr>
<tr>
<td>Group C</td>
<td>122.82 ± 35.74</td>
<td>75.22 ± 18.63</td>
<td>219.51 ± 31.28</td>
<td>24.50 ± 4.21</td>
</tr>
<tr>
<td>p</td>
<td>0.827</td>
<td>0.935</td>
<td>0.046</td>
<td>0.473</td>
</tr>
<tr>
<td>F/H</td>
<td>5.357</td>
<td>5.176</td>
<td>8.925</td>
<td></td>
</tr>
</tbody>
</table>

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

**Table 3**

Comparison of education degree among three groups (n).

<table>
<thead>
<tr>
<th>Group</th>
<th>Illiterate</th>
<th>Primary education</th>
<th>Middle school education and above</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group A</td>
<td>4</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>Group B</td>
<td>5</td>
<td>18</td>
<td>7</td>
</tr>
<tr>
<td>Group C</td>
<td>3</td>
<td>16</td>
<td>11</td>
</tr>
<tr>
<td>p</td>
<td>0.621</td>
<td>0.746</td>
<td>0.375</td>
</tr>
<tr>
<td>H</td>
<td>5.357</td>
<td>5.176</td>
<td>8.925</td>
</tr>
</tbody>
</table>

Note: Group A – penehyclidine hydrochloride group; Group B – atropine group; Group C – normal saline control group.
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.
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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 < 0.01; Group A vs. Group B and Group C, \( p < 0.05; Group A vs. Groups B and C, \( * * * p < 0.001. (C) T1 vs. T0 of all three groups, \( * * * p < 0.001; T4 vs. T3 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


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.

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.