Original Article

Combined general and regional anesthesia and effects on immune function in patients with benign ovarian tumors treated by laparoscopic therapy

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Received August 1, 2013; Accepted August 19, 2013; Epub September 1, 2013; Published September 15, 2013

Abstract: Objective: Anesthesia has been shown to suppress immune function, which can negatively affect the treatment of patients with various tumors. Here, we assessed two different anesthesia methods, general versus combined regional/general, in treatment of benign ovarian tumor by laparoscopic therapy. Methods: Out of 160 patients with benign ovarian tumors treated by laparoscopic therapy, 80 received general anesthesia combined with thoracic epidural anesthesia during surgery, and 80 received general anesthesia only. Venous blood samples were obtained at the following time points: before induction of anesthesia (T0), 2 hours after anesthesia, during operation, 3 days (d) after operation, 5 d after operation, and 7 d after operation. Percentages of CD3⁺, CD4⁺, and CD4⁺/CD8⁺ T lymphocytes were determined at these time points by flow cytometry to assess immune function. Results: For both groups, percentages of CD3⁺, CD4⁺, and CD4⁺/CD8⁺ T cells decreased significantly from T0 to 2 hr after anesthesia (P < 0.05). These percentages decreased again during surgery. However, T cell percentages in patients receiving combined anesthesia returned to normal levels 5 d after surgery, and those receiving only intravenous anesthesia returned to normal by 7 d after surgery. There were no significant differences in CD3⁺, CD4⁺, or CD4⁺/CD8⁺ T cell percentages between the two anesthesia groups at T0 and 7 d. However, significant differences in these percentages were observed between the two groups at all other time points. Interestingly, the decrease observed within the combined group was less dramatic than those observed within the intravenous-only group (P < 0.05). Conclusions: These findings indicate that, while any anesthesia may suppress immune function of patients treated by laparoscopic therapy, the effect of general anesthesia combined with thoracic epidural anesthesia on immune function was less than that produced by general anesthesia alone.

Keywords: Epidural anesthesia, general anesthesia, ovarian tumor, laparoscopy, immune function

Introduction

Ovarian tumor detachment under laparoscope is less traumatic than traditional treatment methods, and patients can recover rapidly after surgery; therefore, this procedure has increasingly wide application [1]. However, surgical procedures and the accompanying anesthesia that is administered are generally believed to induce a stress response that can suppress immune function. Reduced immune function may have negative impacts on outcomes for woman with ovarian cancer in the perioperative period [2]. Importantly, the selection of appropriate anesthesia and the administration of timely and effective analgesia post-procedure can not only reduce a patient’s stress response, but can also reduce the impact on perioperative immune function. Indeed, regional anesthesia, rather than general anesthesia, has been shown to have less dramatic effects on immune response. Laparoscopy is typically performed under general anesthesia, but can be done successfully under regional anesthesia. In this study, ovarian tumor detachment was performed under laparoscope with administration of a combined general-epidural anesthesia or intravenous anesthesia. Changes in perioperative T lymphocyte subsets were evaluated in patients to investigate the influences of these two different anesthesia methods on patient immune function.
Effects of anesthesia on immune function

Materials and methods

Participants

160 women with benign ovarian tumors received laparoscopic surgery in Third Hospital of the Chinese Peoples Liberation Army January 2010 and December 2012. Their median age was 34.9 ± 7.5 years and ages ranged from 22 to 48 years. Participants had varied tumor pathologies: 94 were cases of ovarian teratoma, 22 were cases of ovarian serous cystadenoma, 19 were cases of mucinous cystadenoma, and 25 were cases of simple ovarian cysts. All patients had normal hepatic and renal functions were free of infection and immune, endocrine, and circulatory disease before the operation, and no blood transfusion was given during the preoperation period. Patients were divided randomly into combined general-epidural anesthesia group (“Combined”) and intravenous anesthesia group (“IV”) in accordance with admission order, 80 cases in each group.

Surgical methods

Thirty minutes before operation, patients in both groups were administered 0.5 mg atropine and 0.1 g phenobarbital sodium by intramuscular injection and sodium lactate Ringer’s solution by intravenous infusion. Patients in the IV group were given 0.5 mg/kg midazolam, 5 mg/kg fentanyl, 0.8 mg/kg atracurium, and 1.5 mg/kg propofol by intravenous infusion; they also received tracheal intubation after induction of anesthesia. During the operation, 6-10 mg/(kg • h) propofol was continuously given by intravenous infusion, while fentanyl and atracurium were intermittently given by intravenous infusion. Patients in the Combined group received epidural puncture between the T12 and L1 gap under 3 ml 2% lidocaine; induction of anesthesia was performed after the block plane is determined, and patients received tracheal intubation similar to the IV group. Before the operation, 3-6 mg/(kg • h) propofol was continuously given by intravenous infusion and 0.75% ropivacaine of 6-8 mL/h was injected at the epidural site.

Outcomes measurement

Venous blood samples were extracted from patients in both groups at the following six time points: pre-anesthesia (T0), 2 hr after anesthesia (2 hr), during operation (During), 3 days post-procedure (3 d), 5 days post-procedure (5 d), and 7 days post-procedure (7 d). The extracted

Table 1. Percentages of CD3+ T cells in patients following anesthesia administration

<table>
<thead>
<tr>
<th>Groups</th>
<th>T0</th>
<th>2 hr</th>
<th>During</th>
<th>3 d</th>
<th>5 d</th>
<th>7 d</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined</td>
<td>61.57 ± 8.73</td>
<td>60.25 ± 8.40</td>
<td>54.07 ± 8.81</td>
<td>58.60 ± 8.34</td>
<td>60.60 ± 8.29</td>
<td>61.21 ± 7.92</td>
<td>8.837</td>
<td>0.001</td>
</tr>
<tr>
<td>IV</td>
<td>61.91 ± 8.39</td>
<td>55.96 ± 9.09</td>
<td>50.25 ± 8.71</td>
<td>54.97 ± 8.15</td>
<td>57.42 ± 8.47</td>
<td>60.41 ± 8.36</td>
<td>18.967</td>
<td>0.001</td>
</tr>
<tr>
<td>t</td>
<td>0.246</td>
<td>3.100</td>
<td>2.759</td>
<td>2.780</td>
<td>2.402</td>
<td>0.627</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.806</td>
<td>0.002</td>
<td>0.006</td>
<td>0.006</td>
<td>0.017</td>
<td>0.531</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05 vs. T0.

Table 2. Percentages of CD4+ T cells in patients following anesthesia administration (%)

<table>
<thead>
<tr>
<th>Groups</th>
<th>T0</th>
<th>2 hr</th>
<th>During</th>
<th>3 d</th>
<th>5 d</th>
<th>7 d</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined</td>
<td>39.68 ± 7.91</td>
<td>36.46 ± 8.47</td>
<td>32.29 ± 8.71</td>
<td>36.34 ± 8.65</td>
<td>39.25 ± 8.33</td>
<td>39.31 ± 7.93</td>
<td>9.254</td>
<td>0.001</td>
</tr>
<tr>
<td>IV</td>
<td>39.51 ± 9.13</td>
<td>32.87 ± 5.43</td>
<td>26.91 ± 6.03</td>
<td>33.49 ± 5.76</td>
<td>36.81 ± 5.44</td>
<td>39.93 ± 5.48</td>
<td>47.687</td>
<td>0.001</td>
</tr>
<tr>
<td>t</td>
<td>0.119</td>
<td>3.191</td>
<td>4.540</td>
<td>2.450</td>
<td>2.182</td>
<td>0.578</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.905</td>
<td>0.002</td>
<td>0.001</td>
<td>0.015</td>
<td>0.031</td>
<td>0.564</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05 vs. T0.

Table 3. Percentages of CD4+/CD8+ T cells in patients following anesthesia administration (%)

<table>
<thead>
<tr>
<th>Groups</th>
<th>T0</th>
<th>2 hr</th>
<th>During</th>
<th>3 d</th>
<th>5 d</th>
<th>7 d</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combined</td>
<td>1.63 ± 0.30</td>
<td>1.41 ± 0.30</td>
<td>1.37 ± 0.27</td>
<td>1.48 ± 0.28</td>
<td>1.59 ± 0.21</td>
<td>1.61 ± 0.24</td>
<td>13.315</td>
<td>0.001</td>
</tr>
<tr>
<td>IV</td>
<td>1.63 ± 0.28</td>
<td>1.29 ± 0.29</td>
<td>1.14 ± 0.32</td>
<td>1.39 ± 0.30</td>
<td>1.49 ± 0.30</td>
<td>1.61 ± 0.28</td>
<td>33.274</td>
<td>0.001</td>
</tr>
<tr>
<td>t</td>
<td>0.109</td>
<td>2.552</td>
<td>5.036</td>
<td>2.056</td>
<td>2.482</td>
<td>0.119</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.914</td>
<td>0.012</td>
<td>0.001</td>
<td>0.041</td>
<td>0.014</td>
<td>0.906</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*P < 0.05 vs. T0.
venous blood samples were mixed evenly in a special anti-coagulation test-tube and stored in a refrigerator (at 4°C). Flow cytometer was used to detect the level of CD3\(^+\) and CD4\(^+\) and CD4\(^+\)/CD8\(^-\).

**Statistical methods**

SPSS17.0 statistical software was used for statistical analysis. ANOVA analysis and pairwise comparison method (SNK method) were adopted for intra-group analysis. Two-tailed Student’s t test was used to compare groups. \( p < 0.05 \) was considered as statistically significant.

**Results**

Prior to and within the week following ovarian tumor removal by laparoscopy, patients’ blood samples were evaluated for immune function changes as indicated by differences in the presence of subsets of T lymphocytes. Flow cytometry was used to count CD3\(^+\), CD4\(^+\) and CD4\(^+\)/CD8\(^-\) T cells at various time points: prior to anesthesia (T0), 2 hours after anesthesia (2 hr), during surgery (During), and 3, 5 and 7 days after surgery (3 d, 5 d, 7 d, respectively). The percentages of cells expressing CD3 (Table 1), CD4 (Table 2), and CD4/CD8 (Table 3) were compared between patients receiving combined epidural and intravenous (Combined) anesthesia and those receiving intravenous (IV) anesthesia alone. Percentages of CD3\(^+\), CD4\(^+\), and CD4\(^+\)/CD8\(^-\) began to decline in both groups at 2 hr following anesthesia administration, differences that were significantly different from T0 for both groups (\( p < 0.05 \)). Percentages of each of these cells fell to the lowest levels during surgery. Moreover, percentages of T cells had returned to normal for both groups of patients by 7 d after surgery. While there were no significant differences between anesthesia groups in percentages of CD3\(^+\), CD4\(^+\), or CD4\(^+\)/CD8\(^-\) cells at T0 or T5, significant differences were observed between anesthesia groups for all three subsets of T cells at 2 hr, During, and 3 d (\( p < 0.05 \) for each). Further, patients receiving IV anesthesia alone exhibited more dramatic decreases in CD3\(^+\), CD4\(^+\) and CD4\(^+\)/CD8\(^-\) T cells (\( p < 0.05 \) for each).

**Discussion**

Ovarian cancer occurs frequently and is becoming more commonly treated by ovarian detachment under laparoscope. This procedure is less traumatic than traditional surgery, allowing patients to recover rapidly after surgery [1]. However, anesthesia administration has been shown to affect immune function, mainly by influencing the function and structural integrity of the immune barrier, the number and activity of phagocytes, and the content of anti-microbial substances in normal body fluids and tissues [2]. Further, cancer patients can undergo a series of neuroendocrine and other physiological changes in the body when they are suffering surgical trauma and other external noxious stimulation, and, additionally, there is a close association and mutual influence between neuroendocrine and immune systems [3]. Interestingly, studies have shown that general anesthesia can inhibit cortisol production caused by intubation, but does not inhibit catecholamines and reduce IL-2 caused by surgical stimulation [4-6]. Further, neuroendocrine responses caused by surgical stress response can suppress cellular immune function and increase the tumor cell transfer probability in the perioperative period. However, regional anesthesia administered, for example, in the spine, rather than systemic anesthesia, can reduce the risk of tumor cell metastases during operation [2]. Furthermore, pain stimulation after operation can directly transmit to the central nervous system, and thus stimulate the neuro-immune endocrine system. Simultaneously, the increase of endogenous catecholamine levels of cortico-steroids and prostaglandin caused by the stress response can change the mechanism of immunity [7, 8]. Therefore, anesthesia and analgesia in the perioperative period can greatly affect the patient’s immune system. Recent studies compared the effects of anesthesia in cervical cancer and abdominal cancer patients using general anesthesia and epidural anesthesia, then measuring the number of T lymphocytes and NK cells during different time periods before and after anesthesia [9, 10]. These studies found that epidural anesthesia conferred greater protection of immune function in the perioperative period.

Here, we compared the effects of different anesthesia methods on immune function of patients with ovarian tumors treated by laparoscopic therapy. We found that, while immune function decreased significantly after anesthesia and surgery for patients treated with IV anesthesia alone and combined IV/epidural anesthesia, those patients treated with com-
Effects of anesthesia on immune function

Combined anesthesia exhibited less dramatic declines and recovered immune function more quickly. Therefore, anesthesia and surgery, in general, suppress immune functions, but intravenous anesthesia combined with epidural anesthesia produces a smaller effect on immune function compared to intravenous anesthesia alone. These findings suggest that intravenous anesthesia combined with epidural anesthesia is more advantageous than intravenous anesthesia in the treatment of ovarian tumor by ovarian detachment under laparoscope.

An additional finding of this study is that the immune functions of patients in both groups recovered to the pre-anesthetic level, indicating that effects of anesthesia on immune function are reversible.

In summary, anesthesia can damage the immune function of patients undergoing ovarian detachment under laparoscope. However, general (intravenous) anesthesia combined with regional (epidural) anesthesia results in relatively smaller effects on immune function.

Disclosure of conflict of interest

None.

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References


