Comparative study between intravenous anesthesia (propofol) and inhalational anesthesia (sevoflurane) on the cytokine’s response to abdominal operation

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ORIGINAL STUDY

Comparative study between intravenous anesthesia (propofol) and inhalational anesthesia (sevoflurane) on the cytokine's response to abdominal operation

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Abstract

Introduction: These days, the need for more information and familiarity with the inflammatory response to different anesthetic drugs increase. Not only some patients suffering from immune reactions against some anesthetic drugs, but all surgical patients are liable to decrease in immunity postoperatively. This may increase the postoperative morbidity and mortality, affects healing, and spread of tumors postoperatively. This decrease in immunity is due to surgery trauma causing imbalance in cytokine response.

Patients and methods: This article was written on 40 patients, and patients were randomly classified into four equal classes. Class A: inhalational anesthesia on major operation. Class B: intravenous anesthesia on major operation. Class C: inhalational anesthesia on minor operation. Class D: intravenous anesthesia on minor operation.

Results: The authors found that proinflammatory cytokine [interleukin (IL)-6] levels increase postoperatively in all classes but with higher levels in inhalational anesthesia more than intravenous anesthesia and in major operation than in minor operation. Anti-inflammatory cytokine (IL-10) increases slightly in intravenous anesthesia more in major operation and was higher in inhalational anesthesia, especially after 24 h postoperatively, more in major operation. We also noticed a correlation between cortisol level with IL-6 levels, this means an increase more in major operation than in minor operation and with higher levels in inhalational anesthesia than intravenous anesthesia, which shows slight increase in cortisol level.

Conclusion: Inhalational anesthesia had the highest effect to induce inflammatory cytokine response to operations than the intravenous anesthesia, whether on major or minor operations.

Keywords: Inflammatory cytokine, Inhalational anesthesia, Intravenous anesthesia

1. Introduction

Operative injury stimulates both proinflammatory and anti-inflammatory cytokine responses and the severity of the response, as well as the balance between proinflammatory and anti-inflammatory cytokines is determined by severity of operative injury and related to mortality and morbidity and operative outcome. Severe dysregulation of cytokine response may induce mortality and morbidity, such as impairing healing of the wound, infection, organ dysfunction, and spreading of the tumor postoperatively. The balance between anti-inflammatory and proinflammatory cytokines is affected by preoperative physical status of the patient, time of operation, and intensity of pain. General anesthesia may disturb the cytokine responses, either by impair functions of production cell or indirectly by modulation of cytokine response.
Total intravenous anesthesia might have a considerable influence on the balance between proinflammatory and anti-inflammatory cytokine response to operative injury. This effect may be mediated through their effect on the stress response to operative injury [1]. Operative injury induces an inflammatory state characterized by release of anti-inflammatory and proinflammatory cytokines. The extent of these effects is proportional to the time of the operative procedure [2]. The inflammatory phase of wound healing is characterized by the infiltration of inflammatory cells, which participate by releasing proinflammatory cytokines and anti-inflammatory cytokines. Proinflammatory and anti-inflammatory cytokines are involved in the initiation, control, and termination of all stages of wound healing [3]. Cytokines are protein mediators that exert their effect by binding to cell-surface protein to regulate immune response. They are produced from activated leukocytes such as polymorphs and monocytes, as well as endothelial cells. Most cytokines are proinflammatory [tumor necrosis factor (TNF), interleukin (IL)-6, and IL-8], while some cytokines have anti-inflammatory effects (IL-10, IL-1ra, and interferon) [4]. The response of cortisol and cytokines is increased after operative injury. Cortisol and cytokines are important indicators of operative injury, and several attempts have been made to control this response [5]. There is a graded cortisol response to the degree of stress, such as the type of surgery. Cortisol level also correlates with the severity of injury [6].

2. Aim

The aim was to compare between intravenous anesthesia and inhalational anesthesia on the cytokines’ (IL-6) and (IL-10) production during minor and major abdominal operation and to correlate this effect with the stress response to operation.

3. Patients and methods

The institutional committee’s ethical criteria were followed during all proceedings. The Local Medical Ethics Committee approved the study. Following an explanation of the purpose, procedures, and nature of the study to all participants, signed informed consent was obtained from each participant.

This article was done on 40 patients arranged for abdominal operation and were arranged into one of 4 equal classes of patients’

Class A: Inhalational anesthesia class arranged for exploratory (major operation).

Class B: Intravenous anesthesia class arranged for laparotomy (major operation).

Class C: Inhalational anesthesia class arranged for hernia (minor operation).

Class D: Intravenous anesthesia class arranged for hernia (minor operation).

3.1. Inclusion criteria

Both sexes were studied with age range from 20 to 40 years, average weight according to age, and American Society of Anesthesiologists (ASA) physical status I–II, in abdominal operation.

3.2. Exclusion criteria

Patients with immune disorders, endocrine disorders, morbid obesity, renal or hepatic disorders, fever, bronchial asthma, and leukocytosis.

Anesthetic management: patients were fasting for at least 8 h before surgery.

3.3. Preoperative assessment

Careful history taking, clinical examination (vital data, chest, and cardiac examination), laboratory studies (fasting plasma glucose, creatinine, urea level, SGPT, SGOT, PT, PTT, INR, and complete blood picture), chest radiography, and the results of ECG and echocardiograph were reviewed.

3.4. Premedication

A peripheral intravenous (IV) line is inserted and secured. All patients received Midazolam 0.05 mg/kg IV 15 min before induction of anesthesia.

Monitoring: ECG, noninvasive blood pressure, O2 saturation, and end-tidal CO2 were monitored, duration of operation and anesthesia, and the time between discontinuation of anesthetics and extubation.

Induction: patients in intravenous class were induced by IV injection of 2–3 mg/kg propofol and fentanyl 1–2 μg/kg, with 100% O2. Patients in inhalational anesthesia were induced by fentanyl 1–2 μg/kg with sevoflurane 6–8% and 100% O2. Endotracheal intubation was facilitated in both classes with atracurium 0.08–0.1 mg/kg. After endotracheal intubation, all patients were mechanically ventilated where the tidal volume and respiratory rate were adjusted to maintain end-tidal CO2 within normal level.
3.5. Maintenance

Anesthesia was maintained with either sevoflurane 2–3% in inhalational anesthesia or continuous-infusion propofol 4–8 mg/kg/h in intravenous class with atracurium and fentanyl boluses guided by the hemodynamics and clinical situation.

3.6. Time of operation

Time of operation about 1 h in minor operative classes and about 3 h in major operative classes.

3.7. Blood sampling

In total, three blood samples, 10 ml each, were withdrawn from every patient, the first sample before induction of anesthesia as control, the second sample 4 h postoperatively, and the third 24 h postoperatively. The plasma level of the cytokines IL-6 and IL-10 as well as cortisol level were measured.

3.8. Statistical analysis

Descriptive statistics is presented as mean and standard deviations, statistical tests used included paired Students’ t-test for comparing values within the same group and unpaired Student’s t-test for comparing values within two groups, and analysis of variance for more than two groups. Correlation and regression analysis are to be performed wherever applicable. Significance level is only when P value is less than 0.05.

4. Results

This article was written on 40 patients who were classified into four classes:

Class A: Inhalational anesthesia arranged for exploratory (major operation).
Class B: Intravenous anesthesia arranged for laparotomy (major operation).
Class C: Inhalational anesthesia arranged for hernia (minor operation).
Class D: Intravenous anesthesia arranged for hernia (minor operation).

Table 1. Demographic data.

<table>
<thead>
<tr>
<th>Class</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>26.1 ± 2.8</td>
<td>25.5 ± 4.4</td>
<td>24.5 ± 3.1</td>
<td>23.6 ± 2.5</td>
</tr>
</tbody>
</table>
| Sex (male/female) | 6
4 | 7
3 | 6
4 | 7
3 |
| Weight (kg) | 69.5 ± 6.9 | 72.4 ± 5.9 | 69.5 ± 6.8 | 69.4 ± 6.4 |
| Height (cm) | 168.5 ± 6.1 | 166.7 ± 8.9 | 169 ± 6.3 | 169 ± 6 |

Data are expressed as mean ± SD. P < 0.05, significance.

The results of the four classes are illustrated in the following tables and figures.

4.1. Demographic and operative data

According to age, sex, weight, and height, there was no significant variation between the four studied classes (Table 1).

4.2. Operative data

There was no significant variation between the four classes as regards time of operation and the recovery time (Table 2).

As regards preoperative IL-6, no statistically significant variation was found between class A and class B. Also, no significant variation was found between class C and class D. There was a statistically significance increase in class A compared with class D, also, a significant variation in class B compared with class D. Four-hour IL-6 levels within the same class; A statistically significant increase in IL-6 level values at 4 h postoperatively compared with the preoperative values in the four groups was detected. In-between classes: A highly significant increase was shown between class A and class B, also, a highly significant difference was found between class C and class D. There was a significant difference in class A in relation to class C and a statistically significant difference in class B in relation to class D, was found. Twenty-four hours IL-6 level: within the same class. IL-6 values at 24 h postoperatively and preoperatively showed a significant increase when compared with the 4-h and preoperative values in four groups. In-between classes: there was a highly statistically significant variation in IL-6 values in class A—class B, also, a highly significant variation was found in class C compared with class D, and a highly significant variation in class A—class C, also, there was a significant variation in class B—class C (Tables 3 and 4).

As regards IL-10 level preoperatively, no significant variation was found in class A and class B, also, no significant variation was found between class C and class D. There was significant variation in class A compared with class C, also, a significant variation in class B in relation to class D was found. As regards 4-h IL-10 within the same class: a statistically significant increase in IL-10 values at 4 h
postoperatively compared with the preoperative value in the four classes was detected. In-between classes: A highly statistically significant increase was shown between class A and class B, also, a highly significant variation was found in class C and class D. There was a significant variation in class A in relation to class C and a highly significant variation in class B in relation to class D was shown. As regards 24 h IL-10 levels within the same class: IL-10 values at 24 h postoperatively showed a statistically significant increase compared with the procedure and 4 h after procedure values in the four classes. In-between classes: there was a highly significant variation in IL-10 values in class A in relation to class B, also, a highly significant variation was found in class D in relation to class C, also, a highly significant variation in class A in relation to class D, also, there was a highly significant variation in class B in relation to class D.

As regards cortisol levels, preoperative cortisol levels, in-between classes: No significant variation was found in class A compared with class B, also, no significant variation was found in class C compared with class D. There was a highly significant variation in class A compared with class C, and a highly significant variation in class B compared with class D. As regards 4-h cortisol level, within the same class: A highly significant variation in cortisol value at 4 h postoperatively compared with the preoperative value in the four groups was detected. In-between classes: a highly significant variation was in class A against class B, also, a significant variation was found in class C compared with class D. There was a highly significant variation in class A compared with class D, also, a significant variation in class B in relation to class D. As regards 24-h cortisol levels, within the same group: Cortisol values at 24 h postoperatively showed a statistically significant increase when compared with the procedure and 4 h after procedure values in the four classes. In-between groups: there was a statistically significant variation in cortisol values in class A compared with class B, also, a statistically significant difference was found in class C in relation to class D. There was a highly significant variation in class A compared with class C, and there was a statistically significant difference in class B in relation to class D (Table 5).

### 5. Discussion

This article represents the effect of inhalational anesthesia and intravenous anesthesia on the cytokine production to major and minor operation by measuring the level of IL-6, IL-10, and cortisol before the procedure, 4 h, and 24 h after the procedure. In the present article, as regards the recovery time, there was no significant variation when comparing inhalational anesthesia in major operative classes against intravenous anesthesia in major operative classes, also, there was no statistically significant difference when comparing inhalational anesthesia in minor operative classes against intravenous anesthesia in minor operative classes. This comes in agreement with the results of [7], who found no significant difference in recovery endpoints when comparing inhalational anesthesia with intravenous anesthesia. On the other side [8], found that early recovery was longer in the inhalational anesthesia.

When comparing the preoperative values of IL-6 in-between groups, no significant variation was found between class A and class B, also, no significant variation was found between class C and class D. But there was a significant variation in major operative classes in relation to minor operative classes for both inhalational anesthesia and intravenous anesthesia classes with higher values in major operative classes, most probably due to more stress response in major operative classes. As regards IL-6 values at 4 h postoperatively, it was represented with significant increase in all classes in

### Table 3. Interleukin-6 values in the four classes (ng/ml).

<table>
<thead>
<tr>
<th>Class</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before operation</td>
<td>3.9 ± 0.6</td>
<td>3.9 ± 0.8</td>
<td>3 ± 0.7</td>
<td>3 ± 0.3</td>
</tr>
<tr>
<td>4 h after operation</td>
<td>13.4 ± 1.1a</td>
<td>8 ± 0.8b</td>
<td>10.1 ± 1.4a</td>
<td>5.6 ± 1.1b</td>
</tr>
<tr>
<td>24 h after operation</td>
<td>23.5 ± 1.3a</td>
<td>10.8 ± 0.9b</td>
<td>19.9 ± 1.2a</td>
<td>9.2 ± 0.6b</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.

* Significance within the same group with P < 0.05.

* Significance in-between groups with P < 0.05.

### Table 4. Interleukin-10 values in the four classes (ng/ml).

<table>
<thead>
<tr>
<th>Class</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before operation</td>
<td>4.9 ± 0.7</td>
<td>4.8 ± 1</td>
<td>3.6 ± 0.9</td>
<td>3.3 ± 1</td>
</tr>
<tr>
<td>4 h after operation</td>
<td>10.8 ± 0.8a</td>
<td>7.6 ± 0.4b</td>
<td>8.2 ± 1a</td>
<td>6.6 ± 0.5c</td>
</tr>
<tr>
<td>24 h after operation</td>
<td>11.4 ± 0.9a</td>
<td>8.2 ± 0.4b</td>
<td>8.5 ± 1.6a</td>
<td>7.3 ± 0.4c</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.

* Significance within the same group with P < 0.05.

* Significance in-between groups with P < 0.05.

### Table 5. Cortisol values in the four classes (µg/dl).

<table>
<thead>
<tr>
<th>Class</th>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before operation</td>
<td>17.4 ± 1.3</td>
<td>17.8 ± 1.3</td>
<td>12 ± 1.5</td>
<td>11.7 ± 1.2</td>
</tr>
<tr>
<td>4 h after operation</td>
<td>33.5 ± 1.4a</td>
<td>22.8 ± 1.4a</td>
<td>28.5 ± 2.1a</td>
<td>20.7 ± 1.6c</td>
</tr>
<tr>
<td>24 h after operation</td>
<td>35.8 ± 1.5a</td>
<td>24.4 ± 1.4a</td>
<td>30.4 ± 1.4a</td>
<td>21.3 ± 1.4a</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± SD.

* Significance within the same group with P < 0.05.

* Significance in-between groups with P < 0.05.
relation to preoperative levels. This is due to activation of the inflammatory response by operative stimulation. Values of 4-h postoperative IL-6 were significantly lower in intravenous classes compared with inhalational classes in minor and major operation, which indicated suppression of inflammatory response by intravenous anesthesia. The values of IL-6 at 4 h were significantly higher in major operative classes compared with minor operative classes, most probably due to longer operative stress time. IL-6 values at 24 h postoperatively were significantly higher in all classes compared with preoperative and 4-h postoperative levels, indicating continuous inflammatory response postoperatively. When comparing 24-h IL-10 levels in-between classes, it was found that in inhalational anesthesia classes, the IL-6 value was still significantly increased more than intravenous classes in minor and major operation, this indicates continued suppression of inflammation with intravenous anesthesia. Also, the values of IL-6 at 24 h continued to be higher in major operative classes, compared with minor operative classes, most probably due to longer operative stress time. Our results come in agreement with Schneemilch et al. [1]. They found that IL-10 increases slightly after induction in propofol group, but decreases postoperatively and significantly increases in sevoflurane group mainly postoperatively, more after one day of surgery [11]. They also found that pre-induction levels of IL-10 were negligible in both classes but still low levels intraoperatively. IL-10 production increases postoperatively with high levels of IL-10 occurring at 4 h. IL-10 increase in intravenous anesthesia class at 4 h was more than that in the inhalational anesthesia class, the level of IL-10 starts to decrease over the postoperative period, but still above baseline at 24 h in inhalational and IV classes, respectively. Both classes represent a postoperative high level of IL-10 that was more in classes B and C. In the present study, when comparing the preoperative values of cortisol inbetween groups, no statistically significant difference was found between inhalational anesthesia and intravenous anesthesia in major operation and minor operation as regards the preoperative values. But there was a statistically significant variation in major operation classes in relation to minor operation classes for both inhalational anesthesia classes and intravenous anesthesia classes with higher values in major operative classes, due to more stress in major operative classes. As regards cortisol values at 4 h postoperatively, it was found to be significantly higher in all classes compared with the preoperative levels. This is due to activation of the inflammatory response by surgical stimulation. Values of 4-h postoperative cortisol were significantly lower in intravenous anesthesia classes compared with inhalational anesthesia classes in minor and major operation, which indicates suppression of inflammatory response by intravenous anesthesia. The values of cortisol at 4 h were significantly higher in major operative classes compared with minor operative classes, most probably due to longer operative stress time.
operative stress time. Cortisol values at 24 h postoperatively were significantly higher in all classes compared with preoperative and 4-h postoperative levels, indicating continuous inflammatory response postoperatively. When comparing 24-h cortisol levels in-between classes, it was found that in inhalational anesthesia classes, the cortisol level was still significantly higher than intravenous anesthesia classes in minor and major operation, this indicates continued suppression of inflammation with intravenous anesthesia. Also, the values of cortisol at 24 h continued to be higher in major operative classes, compared with minor operative classes, most probably due to longer operative stress time. These results come in agreement with Schneemilch et al. [1], who showed a positive relation between IL-6 and cortisol. Also, Crozier et al. [12] found that cortisol increased promptly after start of operation in inhalational group, the increase in concentration was delayed in intravenous anesthesia and concentration was also significantly smaller than those in inhalational anesthesia classes. Sheeran and Hall [13] showed that IL-6 stimulates adrenocorticotrophic hormone production, with subsequent secretion of cortisol. As steroids inhibit cytokine gene expression, a negative feedback mechanism operates. This indicates that use of intravenous anesthesia in operation has minimal effect on the inflammatory response to operation compared with inhalational anesthesia. This comes in agreement with Gilliland Helene and Marily [11], who found that intravenous anesthesia had the higher effect to produce anti-inflammatory cytokine production.

5.1. Conclusion

Inhalational anesthesia had the higher effect to induce inflammatory cytokine response to operations than the intravenous anesthesia, whether on major or minor operations.

Conflicts of interest

None declared.

References