THE EFFECTS OF PROVISION OF ANESTHESIA ON ONE-YEAR MORTALITY IN PATIENTS WITH SEVERE COMPLICATIONS

JUNKO USHIRODA*, SATOKI INOUE**, YU TANAKA** AND MASAHIKO KAWAGUCHI**

Abstract

**Background:** General anesthesia in patients with comorbid conditions may affect their intermediate or long-term outcomes. In this study, we evaluated the effects of provision of anesthesia on mortality in critical patients with comorbid conditions by retrospectively investigating one-year mortality in patients with ASA physical status more than III who underwent minor surgery for relative indications and nonfatal reasons.

**Methods:** Data were collected during the period between January 2006 and December 2011. Eligible patients were those with ASA physical status more than III who underwent minor surgery under general anesthesia for relative indications and nonfatal reasons. Preoperative clinical information was collected from the patient’s clinical charts. Comorbidity was quantified using the Charlson comorbidity index. All the patients were evaluated for in-hospital mortality and were followed-up for mortality at one-year.

**Results:** During the study period, 14,979 patients underwent general anesthesia. Thirty six patients satisfied the eligibility for enrollment. Charlson comorbidity index of the patients ranged from one to five. No patients died during their hospital-stay; however, 4 patients were lost to follow up. Therefore, one-year mortality rates for each Charlson index category were 0%.

**Conclusion:** The postoperative one-year mortality in patients with ASA physical status more than III undergoing minor surgery under general anesthesia for relative indications and nonfatal reasons was expected to be considerably small regardless of the Charlson index category.

**Key words:** Comorbidity, Charlson comorbidity index, Anesthesia, Mortality.

Introduction

Modern anesthesia management allows us to provide surgical interventions for considerably critical patients with comorbid conditions although it is still challenging. On the other hand, it has been discussed that deep anesthesia was associated with mortality among middle-aged and elderly surgical patients1,2,3. Therefore, it is very likely that provision of anesthesia itself for critical patients with comorbid conditions may affect their intermediate or long-term outcomes. However, little is known about the effects of provision of anesthesia on mortality in critical patients with comorbid conditions because it is practically impossible to provide only anesthesia without surgery just for
the sake of answering this question.

To answer the above question as much as possible, we arbitrarily assumed that the situations of patients with ASA physical status more than III undergoing minor surgery for relative indications and nonfatal reasons resemble the situations of providing only anesthesia without surgery for critical patients with comorbid conditions. It is not unreasonable to suppose that drugs including anesthetics, analgesics and muscle relaxants, endotracheal intubation, positive pressure ventilation and fluid infusion associated with general anesthesia would have more effect on patients’ outcome than minor surgical procedure.

In this study, we evaluated the effects of provision of anesthesia on mortality in critical patients with comorbid conditions by retrospectively investigating one-year mortality in patients with ASA physical status more than III who underwent minor surgery for relative indications and nonfatal reasons.

**Materials and Methods**

Approval for review of patient’s clinical charts was obtained from the Nara Medical University Institutional Review Board (Approval No.533). Data were collected during the period between January 2006 and December 2011. Eligible patients were those with ASA physical status more than III who underwent minor surgery under general anesthesia for relative indications and nonfatal reasons. Therefore, patients who underwent cardiovascular surgery, neurosurgery, oncological surgery, trauma surgery, debridement, drainage or amputation, and any emergency surgery were excluded.

Preoperative clinical information was collected from the patient’s clinical charts. Comorbidity was quantified using the Charlson Comorbidity Index. Additional data including type of surgery, anesthesia and operation time, intraoperative fluid balance were also collected. All the patients were evaluated for in-hospital mortality and were followed-up for mortality at one-year using the clinical charts, telephone interviews, or postal questionnaires. If the patient had died in the follow-up period, the date of death was recorded.

The Charlson comorbidity index originally can predict one-year mortality for a patient who may have a range of comorbid conditions. Each condition is assigned a score of 1, 2, 3, or 6, proportional to the relative risk of death (at one-year) associated with that disease (Table 1). The sum of the integers makes up the Charlson score, and the Charlson score was prospectively consolidated into four previously defined groups known as the Charlson Index: 0 points (none), 1–2 points (low), 3–4 points (moderate), and ≥5 points (high) as originally described. It has been reported that the Charlson index at the hospital admission due to a specific medical condition has a good correlation with 1-year mortality rates. In addition, illness severity, which was rated as “not to mildly ill”, “moderately ill”, or “severely ill” as previously described, within the same Charlson index category also has a good correlation with 1-year mortality rates. We assumed that the “not to mildly ill” conditions were similar to the situations that patients with ASA physical status more than III undergo minor surgery for relative indications and nonfatal reasons. It is reasonable to suppose that specific illness conditions providing minor surgery for relative indications and nonfatal reasons are not so severe. The original mortality rates from the work of Charlson and colleagues are presented in the Table 2.

### Table 1

<table>
<thead>
<tr>
<th>Comorbid conditions</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>1</td>
</tr>
<tr>
<td>Dementia</td>
<td>1</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>1</td>
</tr>
<tr>
<td>Connective tissue disease</td>
<td>1</td>
</tr>
<tr>
<td>Ulcer disease</td>
<td>1</td>
</tr>
<tr>
<td>Mild liver disease</td>
<td>1</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1</td>
</tr>
<tr>
<td>Hemiplegia</td>
<td>2</td>
</tr>
<tr>
<td>Renal disease</td>
<td>2</td>
</tr>
<tr>
<td>Any tumor</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes with end-organ damage</td>
<td>2</td>
</tr>
<tr>
<td>Leukemia</td>
<td>2</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>2</td>
</tr>
<tr>
<td>Moderate/severe liver disease</td>
<td>3</td>
</tr>
<tr>
<td>Metastatic solid tumor</td>
<td>6</td>
</tr>
<tr>
<td>AIDS</td>
<td>6</td>
</tr>
</tbody>
</table>
Table 2

<table>
<thead>
<tr>
<th>Charlson comorbidity index category</th>
<th>Illness Severity 0</th>
<th>1-2</th>
<th>3-4</th>
<th>&gt;5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not to mildly ill</td>
<td>7%</td>
<td>16%</td>
<td>41%</td>
<td>64%</td>
</tr>
<tr>
<td>Moderately ill</td>
<td>6%</td>
<td>17%</td>
<td>39%</td>
<td>76%</td>
</tr>
<tr>
<td>Severely ill</td>
<td>12%</td>
<td>30%</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>Total</td>
<td>7%</td>
<td>21%</td>
<td>43%</td>
<td>78%</td>
</tr>
</tbody>
</table>

The gray zone shows the one-year mortality rates of the “not to mildly ill” conditions in patients with each Charlson comorbidity index category. We referred these values as predicted mortality in our patients.

Descriptive statistics were used to summarize the demographics and intraoperative data. Categorical variables were reported as percentages. The continuous variables were described using the mean and standard deviation. One-year mortality rates with 95% confidence intervals were calculated for each Charlson Index category. If necessary, to determine correlation of the Charlson Index category with one-year mortality, the Spearman’s rank correlation coefficient was calculated. In addition, the Kaplan–Meier estimation method was used to obtain the survival distribution estimates for each Charlson Index category. The statistical difference of survival distributions among the categories was examined using the log-rank test. Statistical significance was defined as P<0.05.

Results

During the study period, 14,979 patients underwent general anesthesia. Of those, 36 patients with ASA physical status more than III underwent minor surgery under general anesthesia for relative indications and nonfatal reasons (Table 3). Of the eligible 36 patients, no patients died during their hospital stay; however, 4 patients were lost to follow up after discharge.

Patients characteristics are presented in the Table 3. The majority of the performed operations was
orthopedics. There was no patient with Charlson Index of 0. There were 6 patients with Carlson Index point ≥5, who were categorized in Carlson index category ≥5; however, there was no patient with Carlson index point ≥6. Carlson comorbid conditions are presented in the Table 4. All 32 patients survived one-year postoperatively. The one-year mortality rates with 95% confidence intervals for each Carlson Index category were 0% (95% confidence interval = 0% to 0%). Because all patients in any Carlson Index categories survived one-year, correlation of the Carlson Index category with one-year mortality and the survival distribution could not be determined from our data. In this regard, looking at the one-year mortality rates of illness severity at “not to mildly ill” conditions from the original work of Carlson’s, which we referred, the one-year mortality rate increased as Carlson Index severity increased (See the gray zone in Table 2).

Discussion

Our results revealed that the postoperative one-year mortality in patients with ASA physical status more than III undergoing minor surgery under general anesthesia for relative indications and nonfatal reasons was expected to be considerably small regardless of the Carlson Index category. As mentioned before, we assumed that the situations that patients with ASA physical status more than III undergo minor surgery for relative indications and nonfatal reasons resemble the situations that we provide only anesthesia without surgery for critical patients with comorbid conditions. Therefore, it might be postulated that the effects of provision of anesthesia on mortality in critical patients with comorbid conditions are not significant. However, a prerequisite may be necessary that the comorbid condition should be stable because the scheduled surgery should be canceled if the comorbid condition itself is life-threatening.

There is a lack of definition of “comorbidity”, but it seems that the following concept is widely accepted; a medical condition existing simultaneously but independently with another condition in a patient. In addition, a newer concept has been also proposed that a medical condition in a patient that causes, is caused by, or is otherwise related to another condition in the same patient⁸. According to these concepts of “comorbidity”, development of another medical condition is required whenever the term “comorbidity” is intended to use. Otherwise, the term “comorbidity” could not be used if development of another medical condition were not observed in patients with specific medical conditions. Nevertheless, another medical condition indicates significant events including acute injuries and illness. It has been recognized that the Carlson Index is strongly associated with mortality rates in emergency patients as well as in medical inpatients⁴⁻⁷,⁹,¹⁰. We could not simply apply the absolute mortality rates observed in the specific medical conditions to the others even with the identical Carlson index; however, it is safe to say that the patients with higher Carlson Index category will have higher mortality rates after sustaining any significant events including acute injuries and illness. On the contrary, the Carlson index in our patients who underwent minor surgery under general anesthesia showed no association with one-year mortality. As mentioned before, we need to consider comorbid medical conditions when significant medical events occur. Therefore, it may be concluded that no significant medical events consequently occurred in our patients. In other words, it can be said that minor surgery under general anesthesia is not a condition that can deteriorate comorbid diseases. The effects of provision of anesthesia itself on comorbid conditions should be less significant than the combined effects of anesthetic and minor surgical procedures. Thus, it is reasonable to suppose that provision of anesthesia itself does not fulfill the medical events that can threaten comorbid conditions.

In clinical settings, there seems to be no objection that the effects of surgical reason with absolute indication or major surgical procedures on mortality exceeds provision of anesthesia in most cases. Therefore, the effects of provision of anesthesia itself on comorbid conditions can be negligible in such cases. However, anesthesiologists frequently encounter situations where they need to consider the effects of provision of anesthesia on mortality in critical patients with comorbid conditions. As mentioned above, it is when critical patients with comorbid conditions undergo a minor surgery for relative indication and nonfatal reasons. With our results, we could come to the postulation that there is no need to refuse to
provide anesthesia management, for the concern about significant effects of anesthesia on patient’s outcome. However, as mentioned before, this proposal may be rejected when the comorbid condition is unstable and life-threatening in itself.

There are several limitations in this study. First, we did not see the effects of provision of anesthesia itself on mortality in critical patients with comorbid conditions in the true meaning. It is difficult to make a real answer; however, there is a laboratory report giving a clue to this question. Culley and colleagues investigated whether general anesthesia with isoflurane-nitrous oxide shortens life expectancy in aged rats. They reported that general anesthesia does not reduce life expectancy in aged rats\textsuperscript{11}. We need to consider a discrepancy of human and animal studies and the hypothesis regarding old age as a comorbid condition; however, it is not unreasonable to think that this study supports our opinion. Second, we recruited for our study surgical patients who had actually undergone scheduled operations. However, critical patients with comorbid conditions, should have existed, would most likely have their scheduled surgeries canceled after considering their comorbid conditions, relative indications, and nonfatal reasons. The mortality rates might have been affected if these patients had undergone scheduled operations. One of the reasons for this concern might be on account of the retrospective nature of this study design. However, such a selection bias is thought to be difficult to avoid in clinical settings even in a prospective study because there must be cases where patient selection is completed before anesthesia consultation. Therefore, a necessary prerequisite might be that the comorbid condition should be stable when deriving any conclusion based on the obtained results in this study. Third, 4 patients were lost to follow up (10%). It has been suggested that plausible assumptions regarding outcomes of patients lost to follow-up could change the interpretation of results even with the median percentage of participants lost to follow-up is 6\%\textsuperscript{12}. Therefore, we might need to be careful to interpret our study results while taking it into consideration that 10\% patients were lost to follow up. Lastly, we extracted only 36 eligible patients from our study population. In addition, no patient died within one year after anesthesia possibly due to the small population. The conclusion drawn from this study might exceed the capability of the present data. Accordingly, much larger data base would be required to confirm our results.

In conclusion, the postoperative one-year mortality in patients with ASA physical status more than III undergoing minor surgery under general anesthesia for relative indications and nonfatal reasons is considerably small regardless of the Charlson Index category. With this finding, we might postulate that the effects of provision of anesthesia on mortality in critical patients with comorbid conditions are not significant. However, to derive this conclusion, we need at least a prerequisite that the comorbid condition should be stable.

\textbf{Study funding}  
Departmental financial source only supported this study.

\textbf{Conflicts of Interest}  
None.

\textbf{Acknowledgement}  
None.
References


The key to

Lock-up

Postoperative Pain

**STEP I**
Initial bolus
- Inject 1 ampoule Tramal® 100 mg I.V. or I.M. slowly over 2-3 minutes

**Ways of administration after initial bolus**

- **Infusion**
- **PCA**
- **Injection**

**STEP II**
Inject 3 ampoules Tramal®, each 100 mg, in 500 ml of infusion solution.
- Subsequent increments of 25 mg with a lock-out time of 5 minutes.
- Usual dose is 50 mg or 100 mg 12 hourly up to a total daily dose of 400 mg except in special clinical circumstances which might necessitate daily doses up to 400 mg.
- Further treatment with Tramal® boluses on demand.

- If needed further doses of Tramal® 50 mg up to a total of 200 mg (including the initial bolus) within the first 60 min.

**STEP III**
Follow-up
- 1-2 capsules every 4-6 hours
- 100 mg
- 20-40 drops every 4-6 hours
- 1 suppository every 4-6 hours
- 1 tablet every 12 hours

**Loading Dose**
- 2.5 – 3 mg/kg** at wound closure

**An intra-operative loading dose of Tramal® will reduce PONV rates**

**Loading Dose**
- If intra-operative dose not given then: BOLUS I.V.*
  - 100 mg over 2-3 mins**

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- 97% of BRIDION patients recovered to a TOF ratio of 0.9 from 1 to 2 PTCs within 5 minutes

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- BRIDION rapidly reversed patients from 1 to 2 PTCs in 2.7 minutes

BRIDION is indicated for the reversal of neuromuscular blockade induced by rocuronium or vecuronium. In children and adolescents (aged 2-17 years), BRIDION is only recommended for routine reversal of moderate rocuronium-induced neuromuscular blockade.

Important safety information

BRIDION is not recommended in patients with severe renal impairment. Studies in patients with hepatic impairment have not been conducted and, therefore, patients with severe hepatic impairment should be treated with great caution. Caution should be exercised when administering BRIDION to pregnant women as no clinical data on exposed pregnancies are available.

BRIDION has not been investigated in patients receiving non-racemic or racemic in the intensive care unit (ICU) setting.

If neuromuscular blockade is required within 24 hours of BRIDION administration, a non-racemic neuro muscular blocking agent should be used instead of rocuronium or vecuronium. The most commonly reported adverse reactions were dyspepsia (oral or bitter taste) and asthenic complications (tiredness, feeling of weakness, or feeling of coldness in extremities). In patients treated with BRIDION, a few cases of awareness were reported. The relation to BRIDION is uncertain. In a few isolated cases, allergic-like reactions (e., flushing, urticaria rash) following BRIDION were reported. Physicians should be prepared for the possibility of allergic reactions and take appropriate precautions. No fatal cases of anaphylactic complications, severe anaphylaxis, were reported in 2 patients and a causal relationship could not be fully excluded.

Volunteer studies have demonstrated a slight (10%–25%) and transient (0–30 minutes) prolongation of the recovery time achieved partial thromboplastin time (PTT) with BRIDION, however, clinical studies have demonstrated no clinically relevant effect on postoperative bleeding complications with BRIDION alone or in combination with propofol, sufentanil, and/or remifentanil. In BRIDION has demonstrated an in vitro pharmacodynamic interaction with anticoagulants; caution should be exercised in patients on anticoagulants for preoperative or intraoperative administration. This pharmacodynamic interaction is not clinically relevant for patients receiving routine prophylactic anticoagulation. Although formal interaction studies have not been conducted, no drug interactions were observed in clinical trials. Preclinical data suggest that clinically significant drug interactions are unlikely with the possible exceptions of benzodiazepines, furosemide, and hormonal contraceptives.

* Pain of four
* Preoperative setting
* Second study


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