A Randomized Trial of Respiratory Status during Airway Stenting under General Anesthesia Spontaneous Respiration vs. Controlled Ventilation with Muscle Relaxants

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Summary: Airway stenting is a procedure in which a stent is inserted into a stenotic site in the airway. However, the optimal ventilation for airway stenting remains controversial. We have planned a randomized, unblinded controlled study to compare intraoperative respiratory status by dividing patients, who underwent airway stenting, into spontaneous respiration (SP) and controlled ventilation with muscle relaxants (MR) groups. This study started in April 2016. The subjects, patients aged ≥20 years with airway stenosis caused by malignant neoplasms for which airway stenting was scheduled, are randomly allocated to SP and MR groups. Anesthesia management is performed in accordance with the anesthetic methods established in each group to compare parameters of the intraoperative respiratory status. The primary endpoint is the incidence of intraoperative oxygen desaturation events (SpO₂<95). Secondary endpoints are the mean intraoperative P/F ratio, pH, PaCO₂, adverse events, and proportion of protocol treatment achievement. Currently, there is no evidence of anesthetic methods affecting airway stenting. Some studies have claimed that muscle relaxants worsen airway stenosis, while others have reported stable anesthetic management of controlled ventilation with muscle relaxants in airway stenting. This study may aid in clarifying anesthetic methods for airway stenting.

Key words airway stenting, spontaneous respiration, muscle relaxants, randomized trial, anesthesiology

INTRODUCTION

Airway stenting is a procedure in which a stent is inserted into a stenotic site in the airway in order to relieve dyspnea. Underlying diseases include the infiltration of lung or esophageal cancer. Rigid bronchoscopes are used in some procedures, whereas flexible bronchoscopes are used in others. General anesthesia is essential when inserting a rigid bronchoscope. As the operating field is the airway, total intravenous anesthesia with propofol and remifentanil is commonly used. At our hospital a rigid bronchoscope is generally used. During surgery, an anesthesia apparatus is connected to the side of a rigid bronchoscope. Ventilation mode is generally divided into two methods, spontaneous respiration or controlled ventilation with muscle relaxants.

Some studies have reported that the administration of muscle relaxants to patients with airway stenosis may worsen airway obstruction, causing hypoxemia [1]. Furthermore, ventilation disorder was observed after administration of a muscle relaxant in a child...
with a giant anterior mediastinal tumor [2]. On the other
hand, other studies demonstrated stable anesthetic
management of controlled ventilation with muscle re-
 laxants in airway stenting [3]. A small-scale retrospec-
tive study found no significant difference in the respira-
tory state in the presence or absence of muscle relaxants
[4].

This study may help clarify whether spontaneous
respiration or controlled ventilation is optimal for gen-
eral anesthesia in airway stenting.

METHODS

This study is designed to investigate whether con-
trolled ventilation with a muscle relaxant during airway
stenting decreases the incidence of hypoxemic events
in comparison with spontaneous respiration.

Study design

This is a randomized, unblinded, single-center, par-
allel group controlled trial.

Anesthetic protocol

Spontaneous respiration (SP) group

After local laryngeal anesthesia with 4% lidocaine,
anesthesia is induced with propofol TCI at 1.0 mg/mL
and remifentanil at 0.1 mg/kg/min. The depth of anes-
thesia is titrated to maintain spontaneous respiration.
After superior laryngeal nerve blocking with 4 mL of
1% lidocaine, a rigid bronchoscope is inserted, and
connected to an anesthesia apparatus. Oxygen admin-
istration (FiO2 1.0) is started. For maintenance, the
doses of propofol TCI and remifentanil are increased
or decreased depending on the invasiveness of the op-
eration to maintain a bispectral index (BIS) level of 60
or less and spontaneous respiration. After the opera-
tion is completed, the rigid bronchoscope is removed.
The jaw thrust maneuver is conducted and a face mask
with 100% O2 at 6 L/min is applied until the patient
wakes.

Controlled ventilation with muscle relaxants group
(MR group)

Anesthesia is induced with propofol TCI at 3.0
mg/mL and remifentanil at 0.5 mg/kg/min. After loss
of consciousness and confirmation of successful mask
ventilation, rocuronium at 0.6 mg/kg is administered.
Two minutes later, a rigid bronchoscope is inserted
and connected to an anesthesia apparatus. Pressure-
limited controlled ventilation with FiO2 1.0 is started.
The initial frequency of 20 cmH2O ventilation is 12 times
per min and is changed in accordance with the pa-
tient’s thoracic movement. Additional rocuronium at
0.1 to 0.2 mg/kg is administered if twitch reactions on
TOF stimulation are observed on a muscle relaxation
monitor, or body movement, bucking or coughing are
observed. For maintenance, the doses of propofol TCI
and remifentanil are increased or decreased to maintain
a BIS value of 60 or less. After the operation is com-
pleted, the rigid bronchoscope is removed. Patients
are ventilated with a face mask with 100% O2 at 6 L/
min until awakening and appearance of spontaneous
respiration. After confirming two twitches on TOF,
sugammadex at 2 mg/kg is administered, and TOF re-
covery to \( \geq 90\% \) is confirmed.

Participants

Eligibility criteria

1) For whom airway stenting is scheduled for airway
stenosis caused by malignant neoplasms.
2) Those aged 20 years or older at the time of regis-
tration (no upper limit)
3) Those from whom written informed consent has
been obtained.

Exclusion criteria

1) Obese patients with a body mass index (BMI) of
\( \geq 30 \).
2) With esophagobronchial fistulae.
3) With SpO2 of <95% despite oxygen administra-
tion with a mask or cannula.
4) Patients intubated before surgery.
5) With anterior compression of the trachea caused
by a giant mass.
6) Pregnant.
7) With hypersensitivity to rocuronium, sugamma-
dex or other anesthetics.
8) With myasthenia gravis or myasthenic syndrome.
9) With cerebral disease and an unreliable BIS value.
10) Having a history of serious allergy.
11) Patients undergoing dialysis, as it may be impos-
sible to remove the sugammadex-rocuronium com-
plex by dialysis.
12) With dysfunction of one lung not due to the under-
lying disease for airway stenting.
13) Others who were considered ineligible by the at-
tending physicians in this study.

Randomization and blinding

The subjects are registered to an electronic data
capture system and randomly allocated to each group
automatically by a computer program. For randomiza-
tion, the minimization method, using the preoperative
respiratory state (P/F ratio \( \leq 250 \) on arterial blood gas
analysis) and stenotic site of the airway (whether the site involves the main trachea) as allocation adjustment factors, is adopted. To calculate the P/F ratio, a conversion table is referred to for FiO₂ administration with a facemask, nasal cannula or a reservoir mask. This study is unblinded.

Endpoints

The primary endpoint is the incidence of desaturation events (SpO₂<95).

Secondary endpoints are the mean intraoperative pH, PaCO₂, and P/F ratio on blood gas analysis, incidence of adverse events, and proportion of protocol completion. The mean values are calculated from all intraoperative blood gas analyses for each patient.

Data management

Regular monitoring is performed for all registered patients to confirm safety, observance of protocol and accuracy of data.

Central monitoring is performed for all data collected at the data center from the case report forms (CRF).

Source document verification for site monitoring is performed to assure consistency between anesthetic records and CRF.

Safety reporting is performed for adverse events. Adverse events are recorded in detail.

Sample size

The target number of patients is 66.

According to our previous data on 91 patients who underwent airway stenting in 2013, desaturation events (SpO₂:<95%) occurred in 6 (7.4%) of 81 patients in the MR group and in 5 (50%) of 10 patients in the SP group. Based on this, the incidence of desaturation events in the MR group was 8%. As the SP group consisted of a small number of patients, the point estimation of the incidence is 37% based on the lower limit of the confidence interval (0.70), 37.3%. To detect a difference in the incidence between the two groups at a significance level of α = 0.05 (one-sided) and detection power of 80%, 30 patients per group are required (both groups: n = 60). Taking into account dropout, the number of patients per group is 33 (both groups: n = 66).

Statistical analysis

For the primary outcome, patients with an SpO₂ of <95% are regarded as having desaturation events, and the incidence in each group is calculated. Logistic regression analysis with a model of the groups and allocation adjustment factors is performed to calculate the MR/SP odds ratio and 90% confidence interval. For the secondary outcomes, the mean intraoperative pH, PaCO₂, and P/F ratio in each group are calculated. The results are compared between the two groups using a general linear model with allocation adjustment factors. The proportion of protocol completion is calculated for each group. Logistic regression analysis with allocation adjustment factors is performed to calculate the MR/SP odds ratio and 90% confidence interval. The incidences of adverse events in each group are calculated.

DISCUSSION

The optimal anesthetic method for airway stenting is controversial. Many anesthesiologists in Japan have been educated to avoid administration of muscle relaxants and maintain spontaneous respiration for patients with airway stenosis.

Recently, however, the use of muscle relaxants was reconsidered for difficult airways. In April 2014, the JSA Airway Management Guidelines 2014 was published [5]. It was prepared by 26 respiratory experts and shows the proportion of experts who support each approach. The guidelines state the following:

- There is no evidence supporting administration of muscle relaxants after confirming mask ventilation (88%).
- If mask ventilation is impossible, a muscle relaxant should be administered to facilitate it (92%).

Many experts support administration of muscle relaxants for difficult airways. However, these guidelines assume upper airway obstruction, not central airway stenosis or obstruction.

The new antagonist sugammadex for the muscle relaxant rocuronium may have influenced this change in difficult airway management. Neostigmine has been used to antagonize muscle relaxants, but it is a competitive antagonist of receptors for muscle relaxants and risks recurarization. Sugammadex binds with the muscle relaxant, eliminating its activity if necessary. However, several studies reported risks in patients with anterior tumor-related compression of the trachea, and such patients were excluded from this study.

Sugammadex has been used in all patients treated with muscle relaxants during airway stenting at our hospital, and there has been no residual muscle relaxation in any patient. Residual muscle relaxation after using sugammadex was noted in 5 (4.5%) of 117 patients in a previous study [6]. A TOF ratio of ≤0.9 was considered residual muscle relaxation in this study.
patients demonstrated recovery of spontaneous respiration.

At our hospital, airway stenting is performed for approximately 100 patients per year. Our retrospective study involving 20 patients in 2013 found that respiratory status in the controlled ventilation with MR group was more favorable than in the SP group. The incidences of desaturation events (SpO$_2$: $<95\%$) in the SP and MR groups were 50 and 0%, respectively (n=5/10 and 0/10, respectively; 95%CI: 23 to 76% and 0 to 28%, respectively) (P=0.016). There was no patient with an SpO$_2$ of $<90\%$ in either group [7].

Respiratory status is influenced by several factors, and a study involving 350 patients with difficulty in mask ventilation reported that various factors were associated with this problem [8]. To avoid any bias when selecting anesthetic methods, we have designed a prospective randomized comparative study.

DECLARATION

Competing interests
The authors declare that they have no competing interests.

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Authors’ contributions
AK participated in the design of the study and performed the statistical analysis. SO, HS, MO, NS, SY, YM and AT conceived of the study, and participated in its design and coordination, and helped to draft the manuscript.

All authors read and approved the final manuscript.

Ethics approval and consent to participate
The study received approval from the Clinical Research Ethics committee of Nagoya Medical Center on March 4, 2016. This study was registered on the University Hospital Medical Information Network (UMIN) Trial Registry (No. UMIN000024079) on May 4, 2016. The study is conducted in accordance with the protocol, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the guidelines of the declaration of Helsinki.

Written informed consent is obtained from every patient participating in the study.

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