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The Multi-Strategy Intervention to Enhance Quality of Anesthesia Care for Obese Patients: A Factorial Randomized Controlled Trial

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Background

Obesity is a significant global epidemic, affecting approximately 650 million people worldwide in 2016.[1] The prevalence of obesity has risen in the recent decades and exerted a heavy burden on healthcare system.[2] Obesity substantially increases the risk of metabolic, cardiovascular, respiratory diseases, and several types of cancers, which impairs quality of life and shortens life expectancy.[2]

Patients with obesity represent a challenge in perioperative and anesthetic management because of the altered anatomy and physiology associated with obesity. The obesity-related pathology in the setting of surgery includes gastroesophageal reflux[3], poor visualization of vocal cord during tracheal intubation[4], abnormal cardiovascular hemodynamics[5], and postoperative nausea and vomiting (PONV)[6], which contribute to higher perioperative risk and negatively affect patient's recovery after surgery.[7] (Figure 1)

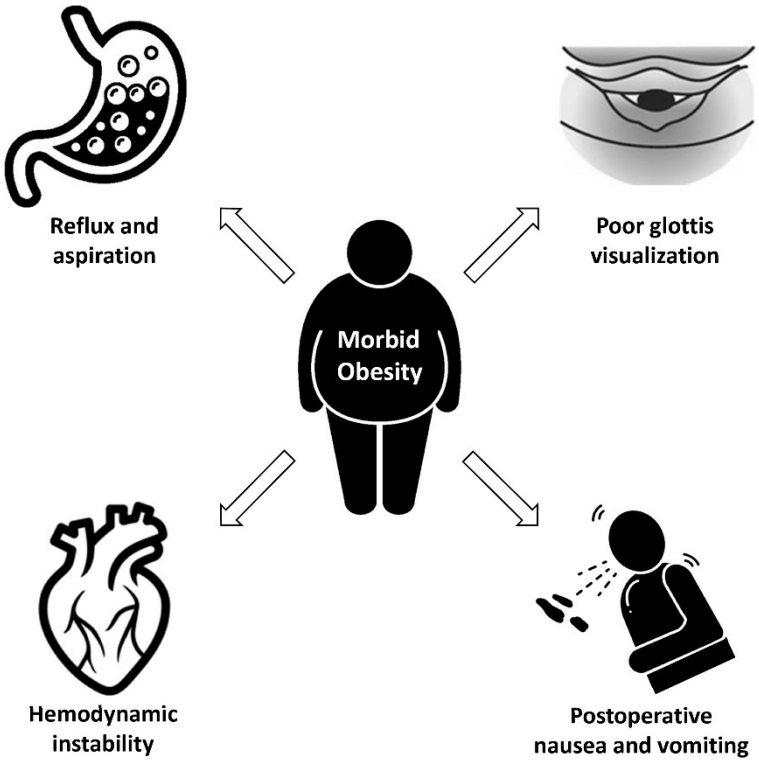

Figure 1: Anesthesia challenges for obese patients

Gastroesophageal reflux and aspiration risk during positive ventilation

Obesity is a risk factor for the development of gastroesophageal reflux disease.[3] Several physiologic abnormalities associated with obesity prolong esophageal acid exposure, including lower esophageal sphincter abnormalities, susceptibility to the development of hiatal hernia, higher intragastric pressure and gastric capacity.[3,8] Study has showed that obese people are prone to a hypotensive lower esophageal sphincter, defined as a basal pressure < 10 mmHg or 13.6 cmH_2O.[8] In addition, transient relaxations of the lower esophageal sphincter are more common in obese patients.[9] Study has also reported that almost half obese patients are comorbid

with hiatal hernia, which is clearly a predisposing factor for gastroesophageal reflux.[10] Obese patients were also found to have increased intra-abdominal pressure, resulted from the gravitational force of the adipose tissue on the abdominal cavity.[11] These pathologies may contribute to the risk of pulmonary aspiration when protective airway reflexes are depressed in general anesthesia.[12]

Aspiration is the most significant etiology of airway complications and anesthesia death.[13] To prevent pulmonary aspiration during anesthesia, it is important to determine the level of inspiratory pressure minimizing gastric insufflation during pulmonary ventilation. A randomized trial has showed that inspiratory pressure of 15 cmH_2O can decrease the occurrence of gastric insufflation during induction of anesthesia for non-paralyzed non-obese patients.[14] Although morbid obesity predisposes to the development of pulmonary aspiration during anesthesia[13], there is still little evidence regarding the safe inspiratory pressure to prevent the occurrence of gastric insufflation during positive ventilation.

Poor glottis visualization during tracheal intubation

Obese patients present a unique challenge to airway management for anesthesia providers. Obesity-related obstructive sleep apnea and reduced neck movement contribute to a higher risk of difficulty intubation.[15] Previous study has showed that video laryngoscopy provides better glottis visualization and reduces the time to successful intubation with similar intubation success rates compared to Macintosh direct laryngoscopy in morbidly obese patients.[4,16] However, video or direct laryngoscopy may be inappropriate for patients with limited mouth opening, loose teeth or dental prosthesis. It remains unclear for the utility of other video intubating devices used in obese population.

Video intubating stylet is a useful tool for the placement of tracheal tubes. For tracheal intubation, a tracheal tube is preloaded over the video stylet, which is passed through the oral cavity to visualize the epiglottis and guided to glottic opening via a monitor.[17] Video intubating stylet has been reported to be more effective and safer than Macintosh laryngoscope in the placement of double-lumen tubes in thoracic surgery.[18-20] Video intubating stylet has also been demonstrated useful in tracheal intubation for cervical spine-immobilized patients.[21,22] Nevertheless, previous work in obese patients was limited.

Hemodynamic instability in bariatric surgery

Obesity is commonly associated with a variety of neurohormonal, metabolic, and hemodynamic alterations that potentially change cardiac structure and functions.[5] The dysregulations of hemodynamics may contribute to left and right ventricular dysfunction and even predispose to heart failure in severely obese patients.[5] The cardiovascular abnormality may precipitate the occurrence of hemodynamic instability when obese patients with preoperative fasting experience pneumoperitoneum and reverse Trendelenburg positioning in bariatric surgery.[7,23]

Obese patients have a higher cardiovascular risk after noncardiac surgery due to their

comorbid cardiovascular and metabolic diseases, including cardiac arrest and myocardial infarction.[24] In addition, obesity negatively affects respiratory system and significantly alters lung function, which is characterized by a reduction in vital capacity and total lung capacity with a restrictive pattern.[25] Study has showed that patients undergoing bariatric surgery have an increased risk of major respiratory complications.[26] However, there are still few effective strategies in reducing postoperative complications after bariatric surgery.

There are commercial devices for measuring cardiac output (CO) through minimal invasive approaches.[27] The major principles and techniques of CO measurement include the Fick principle, arterial waveform analysis techniques, and the Doppler principle.[28] ProAQT® device (Pulsion Medical Systems, Munich, Germany) is a modular platform on the basis of PiCCO™ pulse contour algorithm.[28] ProAQT® allows the continuous evaluation and real-time visualization for hemodynamic status and supports goal-directed hemodynamic therapy (GDHT) in surgical patients. Meta-analysis of randomized trials suggests that the application of perioperative GDHT may facilitate recovery in patients following major abdominal surgery.[29] Regardless of the broad use of minimally invasive CO monitoring in anesthesia and critical care, the evidence for its benefits in obese patients is limited. It is unclear whether application of minimally invasive CO monitoring in guiding intraoperative administration of fluid, inotrope, and vasopressor improves patient outcomes after bariatric surgery. Strong clinical data support the use of minimally invasive CO monitors in patients undergoing abdominal surgery although these studies generally did not focus on obese patients.[29]

Postoperative nausea and vomiting in obese patients

PONV is a common adverse event among patients following bariatric procedures with a reported rate of 18% to 82%.[30-32] PONV may increase the risk of wound dehiscence and prolong the length of stay in the post-anesthesia recovery room.[33] Besides, PONV represents one of the frequent reasons for unanticipated re-hospitalization after bariatric surgery.[34] In particular, morbidly obese people have a greater risk of PONV compared to those with body mass index $< 35\ kg \cdot m^{-2}$ after bariatric surgery.[35]

Current practice guidelines recommend the use of single or multiple types of antiemetics as PONV prophylaxis according to Apfel risk prediction score.[36] However, these guidelines are primarily based on evidence derived from general population.[7,23] There are few studies investigating the clinical strategy to mitigate PONV risk pertinent to obese patients. In addition, it remains unclear whether intravenous dexamethasone, a common prophylactic agent for PONV, is associated with potential adverse effects in obese people, such as hyperglycemic response, wound infection and delayed healing.[7,23,37] Since obese patients are susceptible to the injury of hyperglycemia and associated wound infection[38,39], it is of great importance to elucidate the risk and benefits of dexamethasone in the prevention of PONV.

Research Objective

The main objective of this study is to investigate the optimal anesthesia for obese patients undergoing bariatric surgery in the strategies of positive pulmonary ventilation, tracheal intubation technique, hemodynamic monitoring, and PONV prophylaxis, as the followed:

1. To evaluate the effectiveness and adverse effect of intravenous dexamethasone for PONV prophylaxis
2. To determine the safe inspiratory pressure to prevent the occurrence of gastric insufflation during facemask ventilation using point-of-care ultrasonography of antrum
3. To compare the effectiveness and safety between video intubating stylet and video laryngoscope in the placement of tracheal tubes
4. To apply minimally invasive CO monitors in guiding goal-directed hemodynamic therapy and assess its impact on major complications and postoperative recovery

Novelty and Implication

1. Considering the growing prevalence of obesity and its potential impact on perioperative care, the optimal anesthesia strategy for obese patients should be further explored.
2. Investigation of perioperative use of dexamethasone will enrich the current literature of PONV prophylaxis for obese patients.
3. The study will determine the airway pressure threshold to prompt gastric insufflation during positive ventilation, providing a practical guidance in the airway management of anesthesia and cardiopulmonary resuscitation.
4. This study will evaluate the application of video intubating stylet in the tracheal intubation of obese patients, offering another evidence-based intubation technique.
5. This research will also provide valuable evidence regarding the treatment effect of intraoperative GDHT in obese patients, which may offer an important implication for precision hemodynamic management in the obese people.
6. The study will provide important evidence for an Enhanced Recovery After Surgery (ERAS) protocol of bariatric surgery.

Materials and Methods

We will conduct a factorial parallel randomized controlled trial using permuted block randomization and stratified randomization and conforming to the CONSORT Statement to investigate multiple clinical outcomes in obese patients undergoing laparoscopic sleeve gastrectomy (LSG) at Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan.[40-42] Four randomizations will be conducted, including intravenous dexamethasone for PONV, various inspiratory pressure of mask ventilation, three tracheal intubation techniques, and goal-directed hemodynamic therapy using minimally invasive cardiac output monitoring. (Figure 2) A computer-generated list of randomizations will be applied for these group allocations. Each patient will be randomly assigned a specific study number and group in four randomizations, and these assignments will be then enclosed in envelopes and sealed.

Inclusion criteria are patients aged ≥ 20 years with body mass index ≥ 30 $kg \cdot m^{-2}$ undergoing LSG at Shuang Ho Hospital. Exclusion criteria are as the following:

1. Pregnant or lactating women
2. Severe cardiopulmonary distress, including left ventricular ejection fraction < 40%, double or triple vessel disease, New York Heart Association functional classification ≥ 3, peripheral oxygen saturation by pulse oximetry (SpO_2) < 90% in room air, and moderate to severe pulmonary hypertension.
3. Previous esophageal, gastric, or duodenal surgery.
4. Previous head and neck surgery or radiation therapy
5. Previous cervical spine injury
6. High-degree cardiac arrythmia, including atrial fibrillation and severe atrioventricular block
7. Use of cardiac pacemaker or automated implantable cardioverter defibrillator
8. Chronic kidney disease, stage ≥ 4 (estimated glomerular filtration rate < 30 $ml \cdot min^{-1}$)
9. Planned transferal to intensive care unit for mechanical ventilation
10. QTc prolongation determined by a standard 12-lead electrocardiogram
11. Patients using emetogenic or antiemetic drugs within 24 hours before surgery
12. Patients requiring rapid sequence induction or fiberoptic awake intubation
13. Patient refusal to participate

The flow diagram for research conduction is shown in Figure 2. Before surgery, all paticipants will be evaluated for morphometric and airway characteristics regarding difficult airway, including interincisor distance (< 3 cm or not)[43], mentohyoid distance (< 4 cm or not), thyromental distance (< 6.5 cm or not)[44], neck movement (< 80 degrees or not)[45], neck circumference measured at the thyroid cartilage (> 43 cm or not)[46], modified Mallampati score[47], upper lip bite test[48], and mandibular prognathism test[49].

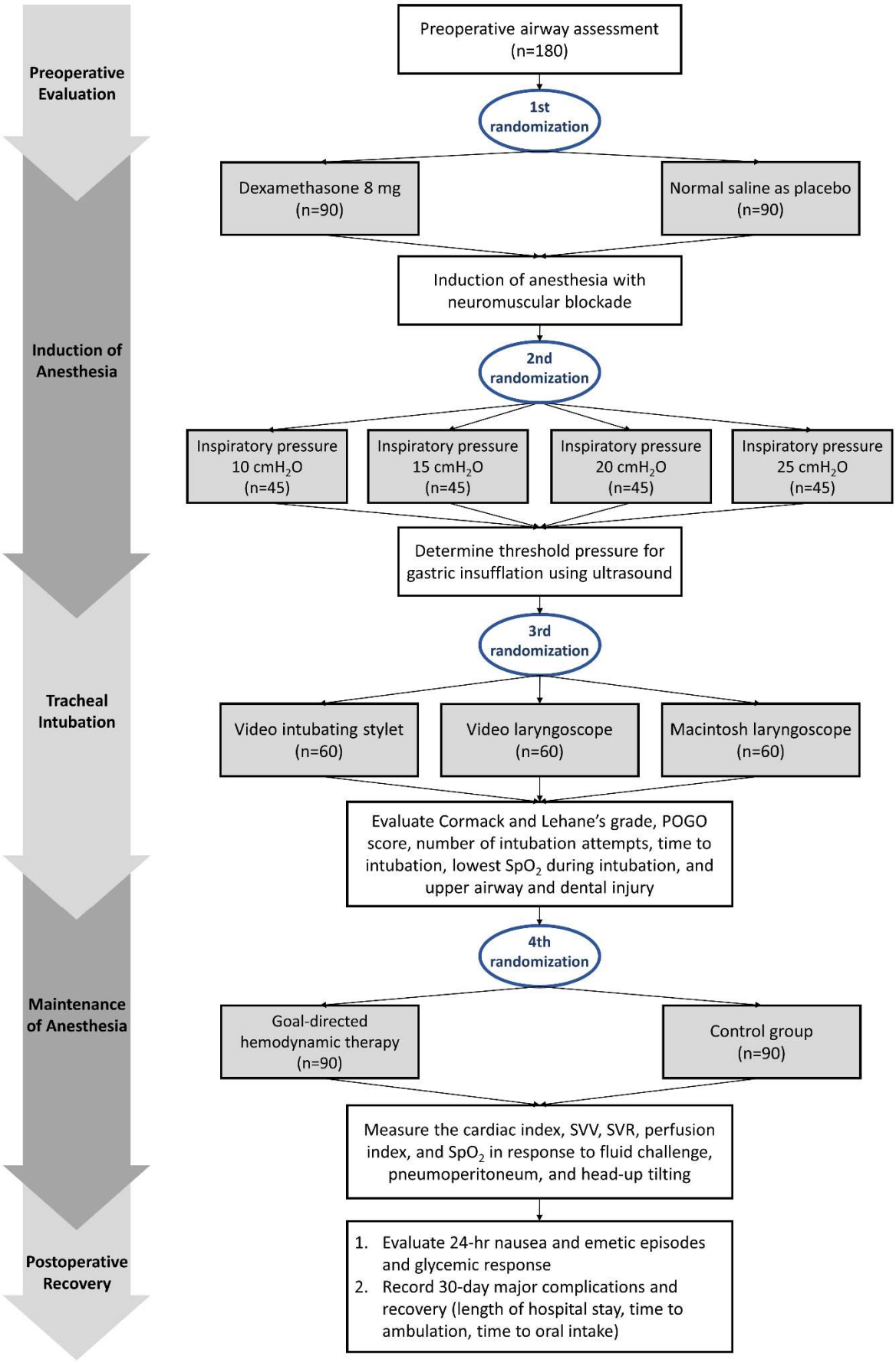

Figure 2: Flow diagram for research conduction

Substudy 1: An evaluation of the effect of intravenous dexamethasone on postoperative nausea and vomiting: a double-blind, placebo-controlled trial

At the operating room, patients will be initially placed in a ramped position and then moved into a reverse Trendelenburg position to achieve a 30-degree incline of the thorax before preoxygenation. Each patient will be randomly assigned 1:1, stratified by presence of diabetes mellitus, to one of each of the following two interventions: dexamethasone (8 mg intravenously) and placebo (0.9% sodium chloride). The envelopes of group allocation will be opened just before the induction of general anesthesia.

After preoxygenation using facemask with pure oxygen 10 $l \cdot min^{-1}$ until end-tidal fractional oxygen concentration in the expired air (EtO_2) ≥ 80%, general anesthesia will be induced with propofol 1.5–2.0 $mg \cdot kg^{-1}$ ideal body weight and fentanyl 1–2 $\mu g \cdot kg^{-1}$ total body weight. Tracheal intubation will be facilitated with rocuronium 0.8–1.0 $mg \cdot kg^{-1}$ ideal body weight. After induction, a radial artery catheterization will be performed for continuous monitoring of arterial pressure and measurement of serum glucose. In the designated patients, 8 mg of dexamethasone or placebo will be given intravenously within 10 minutes after the induction of anesthesia. Anesthesia will be maintained with 2–3 vol% sevoflurane and 60% oxygen in nitrogen, whereas the fraction of inspired oxygen (FiO_2) 0.8–1.0 will be used during pneumoperitoneum to ensure oxygen saturation higher than 92%. If the value of surgical pleth index (CARESCAPE B650 Monitor, GE Healthcare, Chicago, IL, USA) is more than 50 or heart rate or blood pressure increases by more than 20% from baseline values during surgery, an intravenous bolus of fentanyl 25 or 50 μg will be given. Besides, the concentration of sevoflurane can be adjusted as clinically appropriate.

After surgery, all patients will receive supplemental oxygen, and pain will be relieved with ketorolac 15 to 30 mg. The need for postoperative opioids will be at the discretion of the anesthesiologist, and the dose will be adjusted according to clinical needs. Patients who request rescue antiemetic therapy or who have an emetic episode will be given droperidol 1.25 mg. If symptoms persist, metoclopramide 10 mg will be administered.

Primary outcome is the incidence of PONV, which includes any nausea, emetic episodes (retching or vomiting), or both during the first 24 postoperative hour. At the 2nd and 24th postoperative hours, trained investigators who are blinded to the group allocation will record the number of emetic episodes, the time each one occurs, and self-reported worst nausea episode during the preceding duration on an 11-point scale (0: no nausea and 10: the most severe nausea). Secondary outcomes are serum glucose levels of post-induction, end of surgery, and the 24th postoperative hour. We will also evaluate risk factors for PONV according to Apfel risk prediction model, including age, sex, smoking status, body mass index, history of PONV or motion sickness, duration of anesthesia, and the use of intraoperative and postoperative intravenous opioids. Research staff blinded to group allocation will determine and document any episodes of surgical site infection and delayed wound healing within 30 days after surgery.

Substudy 2: An investigation of the threshold inspiratory pressure for gastric insufflation using ultrasonography of gastric antrum: a double-blind randomized controlled trial

We will measure the antral area of each participant lying in supine position on the operating table, using a portable ultrasound device (LOGIQ™, GE Healthcare, Chicago, IL, USA, fitted with a 1.5 to 5.0 MHz convex transducer). We will determine the longitudinal (D_1) and anteroposterior (D_2) diameters of the cross-section of antrum in the sagittal plane passing through abdominal aorta.[50] To obtain a standardized scanning level, the aorta and left lobe of the liver are employed as internal landmarks. The relaxed diameters of the antrum are measured between antral contractions. The area of gastric antrum is calculated using the formula: antral area = $D_1 \times D_2 \times \pi / 4$. In addition, the gastric fluid volume will be calculated with a validated model based on the cross-sectional area of the gastric antrum, described previously.[51]

Patients will be randomized into one of the four groups defined by the applied inspiratory pressure (10, 15, 20, or 25 cmH_2O) using blocked randomization. During induction of anesthesia, normal saline 20 ml will be immediately infused after the administration of rocuronium 0.8–1.0 $mg \cdot kg^{-1}$ ideal body weight.[52] After loss of eyelash reflex, a Guedel oropharyngeal airway (Biçakcilar, Istanbul, Turkey) will be placed into the oral cavity to assure adequate mouth opening. A facemask will be applied firmly to the patient's face to ensure an adequate seal. A two-handed head-tilt jaw-thrust maneuver will be performed to establish an open airway. Once apnea determined by end-tidal capnography occurs, a mechanical ventilation with the assigned peak inspiratory pressure will be initiated. The pressure-controlled mode will be used with an inspiratory-to-expiratory ratio of 1:2 and no positive end-expiratory pressure (PEEP), at a frequency of 15 $breath \cdot min^{-1}$ and with 100% oxygen, by the ventilator (Carestation 620, Datex-Ohmeda, Inc., Madison, WI, USA).[53]

Real-time ultrasonography of the antrum will be performed by the same anesthesiologist who performs the preoperative ultrasonography. Another anesthetist will perform continuous auscultation over epigastric area. Researchers performing ultrasonography and auscultation are blinded one to another regarding the detection of gastric insufflation and the inspiratory pressure of pressure-controlled ventilation. The ultrasonography screen will be concealed from the anesthetist performing the auscultation. Facemask ventilation will be continued for 2 min. The trachea will be thereafter intubated, and the antral area will be measured again.

Primary outcome is the episode of gastric insufflation. The ultrasonographic diagnosis of gastric insufflation is defined as the presence of an acoustic shadow phenomenon and/or a comet-tail artifact into the antrum.[14] A typical whoosh sound with gurgling while auscultating over the epigastrium defines the diagnosis of gastric insufflation by auscultation method.[54] Secondary outcomes are specific respiratory parameters of anesthesia monitoring, recorded at time 30, 60, 90, and 120 s during facemask ventilation and after tracheal intubation, including SpO_2, EtO_2, the end-tidal carbon dioxide concentration in the expired air ($EtCO_2$), minute leak volume ($ml \cdot min^{-1}$), measured peak airway pressure, and tidal volume.

Substudy 3: A comparison of video intubation stylet and video laryngoscope in tracheal intubation: an open-label randomized controlled trial

Eligible patients will be randomly allocated 1:1:1, stratified by body mass index > 50 $kg \cdot m^{-2}$, to group 1 (video intubating stylet), group 2 (video laryngoscopy), or group 3 (direct laryngoscopy). Tracheal intubation will be performed by experienced attending anesthesiologists who have performed at least 100 cases each with Trachway® video intubating stylet, GlideScope® video laryngoscopy, and Macintosh direct laryngoscopy. The anesthesiologist performing tracheal intubation is blinded to all preoperative evaluations.

In group 1, a tracheal tube (ConvaTec, Berkshire, England, UK) in appropriate sizes is preloaded over the Trachway® video intubating stylet (TVI-4050, Markstein Sichtec Medical Corp, Taichung, Taiwan), which is introduced into oral cavity to visualize the epiglottis and guided to glottis via a monitor after full neuromuscular blockade is achieved. In group 2, a tracheal tube is preloaded over a GlideRite® stylet, which is specifically designed to work with GlideScope® video laryngoscope (Verathon Medical, Bothell, WA, USA). GlideScope® blade size 3 (GS-3) or 4 (GS-4) is used in all patients. In group 3, tracheal tubes are prepared with a hockey stick-shaped stylet, and direct laryngoscopy is performed using a size-3 or -4 Macintosh blade (Rüsch Inc., Duluth, GA, USA). In all patients, backward, upward, and rightward pressure on the larynx and Sellick maneuvers are allowable to obtain the best glottic view.[55,56] If the initial intubation attempt fails or is terminated for desaturation (defined as $SpO_2 < 92\%$) or need to change the patient's position, the intubation device will be removed, and manual bag mask ventilation will be performed. Intubation failure is defined as more than three intubation attempts or need to change intubation devices. Any intubation rescue techniques will be used at the discretion of the staff anesthesiologist.

Primary outcome is the best glottis visualization, graded according to Cormack and Lehane's classification with external laryngeal pressure applied.[57] Glottic views graded as III or IV are regarded as difficult. Secondary outcomes are number of intubation attempts, the percentage of glottic opening (POGO) score, time to intubation, lowest SpO_2 during intubation, and ease of intubation. Each video stylet or laryngoscope blade insertion is defined as an intubation attempt. Minor adjustments of patient's position or tube stylet are not considered separate attempts. The POGO score is defined by the best glottis visualization (0%, 25%, 50%, 75%, or 100%).[58] Time to intubation is defined as the interval between intubating stylet or laryngoscope insertion into oral cavity and $EtCO_2$ detected. Ease of intubation is a subjective assessment of anesthesiologists, rated as (1) very easy, (2) easy, (3) moderate, (4) difficult, and (5) impossible.[59] Safety outcomes are upper airway injury (bleeding, abrasion or laceration), dental injury (bleeding, trauma, fracture), respiratory complications (laryngospasm, bronchospasm, aspiration), cough (mild, moderate, severe), sore throat (mild, moderate, severe), and hoarseness (noticed by the patient only, apparent to an observer). Research staff blinded to group allocation will evaluate the complications at the 2nd and 24th postoperative hours.

Substudy 4: An investigation of the putative benefits of goal-directed hemodynamic therapy targeting cardiac index in obese patients undergoing laparoscopic sleeve gastrectomy: an open-label randomized controlled trial

At the operation room, we will apply the Masimo Radical 7 pulse oximetry (Masimo Corp., Irvine, CA, USA) to the fingers of all enrolled patients to measure perfusion index and SpO_2 throughout the surgery. After the placement of a tracheal tube, patients will receive ventilator support with the tidal volume 6–8 $ml \cdot kg^{-1}$ ideal body weight, a respiratory rate of 10–15 min^{-1} and PEEP 5 cmH_2O applied by the ventilator.[60] The FiO_2 will be set at 0.3–0.7 to maintain SpO_2 ≥ 98% throughout the surgery. Each patient will be randomly allocated to one of each of the following two groups: goal-directed hemodynamic therapy and control.

In both groups, intraoperative maintenance rate of crystalloid fluids is 3 $ml \cdot kg^{-1} \cdot hr^{-1}$ ideal body weight. ProAQT®-derived hemodynamic data and peripheral perfusion index and SpO_2 will be acquired at the following time points: 5 min after induction of anesthesia, 5 min after start of pneumoperitoneum and head-up tilting, 5 min after end of pneumoperitoneum, cessation of volatile anesthetics, and 5 min after extubation. Subjects of the GDHT group will be managed according to the ERAS algorithm utilizing ProAQT® parameters to maintain the cardiac index ≥ 2.5 $l \cdot min^{-1} \cdot m^{-2}$.[61] In brief, if cardiac index < 2.5 $l \cdot min^{-1} \cdot m^{-2}$, a bolus of 150 ml of crystalloid fluid will be given until the stroke volume variation is < 10%. If cardiac index < 2.5 $l \cdot min^{-1} \cdot m^{-2}$ despite the stroke volume variation of ≥ 10% following fluid challenge, continuous intravenous infusion of dopamine 5–10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ will be administered. If mean arterial pressure is < 70 mmHg despite cardiac index ≥ 2.5 $l \cdot min^{-1} \cdot m^{-2}$, intravenous infusion of norepinephrine 2–10 $\mu g \cdot min^{-1}$ will be used. (Figure 3)

Subjects allocated to the control group are hemodynamically managed as per anesthesiologist preference. Typically, isolated hypotension (20% decrease in mean arterial pressure below baseline or < 60 mmHg) is treated by single or consecutive boluses of norepinephrine 5 or 10 μg. If hypotension persists, repeat boluses of ephedrine 4 mg will be administered until mean arterial pressure is above 60 mmHg. If hypotension is accompanied by signs of hypovolemia (urine output < 0.5 $ml \cdot kg^{-1} \cdot hr^{-1}$ and/or an increase in heart rate > 20% above baseline), crystalloid or colloid fluids will be given until urine output and/or heart rate are normalized. If hypotension persists despite volume challenge, norepinephrine will be used.

In both groups, the fluid, inotrope, and vasopressor responsiveness, ProAQT® parameters (cardiac index, stroke volume variation, systemic vascular resistance, and mean arterial pressure), and the signals of pulse oximetry (perfusion index and SpO_2) will be evaluated and recorded for each 15-min interval throughout the surgery. In control group, the ProAQT® monitoring will be concealed from the anesthetist in charge. Artifact-free signals are considered valid for statistical analysis. At the end of surgery, all participants will receive a manual recruitment maneuver of 30 to 40 cmH_2O for 10 s three times. In all patients, cessation of volatile anesthetics will be timed to facilitate early awakening after wound closure. All patients

will be decurarized from rocuronium-induced neuromuscular blockade with sugammadex dosed at 2 mg·kg^{-1} ideal body weight + 40%.[62]

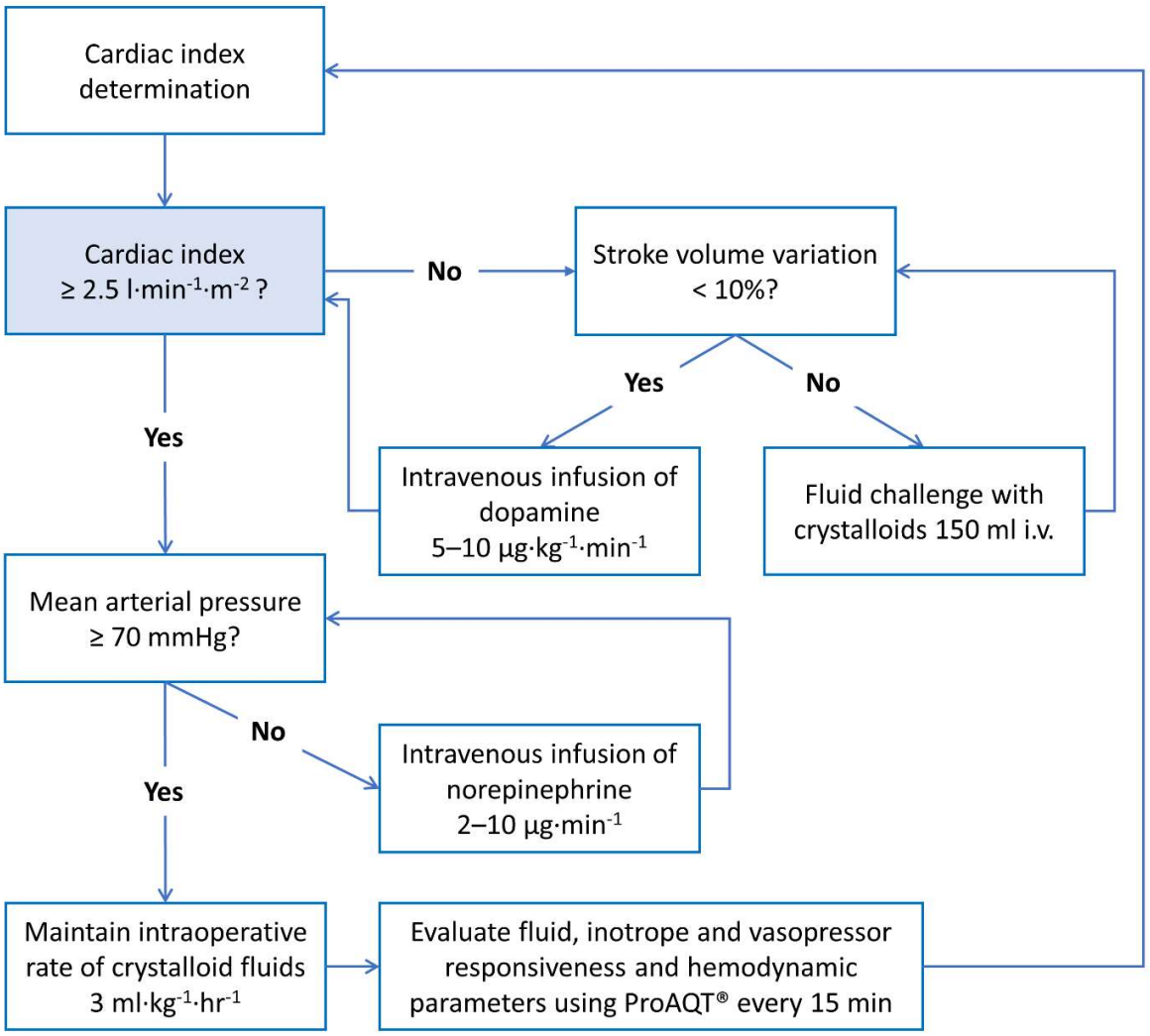

Figure 3: Goal-directed hemodynamic algorithm to guide intraoperative fluid therapy and the use of inotrope and vasopressor

Primary outcome is a composite of major complications according to the European Perioperative Clinical Outcome definitions within 30 days after surgery, including myocardial ischemia or infarction, arrhythmia, acute kidney injury, gastrointestinal bleeding, anastomotic breakdown, surgical site infection, and hospital-acquired pneumonia.[63] Secondary outcomes comprise longitudinal changes of ProAQT® parameters (cardiac index, stroke volume variation, systemic vascular resistance, and mean arterial pressure) and signals of pulse oximetry (peripheral perfusion index and SpO_2), relative change of arterial partial pressure of oxygen (PaO_2)/FiO_2, PaO_2/FiO_2, serum glucose, base excess values after induction of anesthesia and at the end of surgery, clinically relevant hypotensive episodes (decrease in mean arterial pressure > 20% for more than 15 min requiring vasopressors), need for intensive care, time to ambulation, time to first oral intake, and length of hospital stay. Episodes of major complications will be evaluated by research staff blinded to group assignment.

Sample Size Estimation

According to prior study[64], at least 80 patients in each group of GDHT and control are needed to detect a significant difference, accepting a type I error of 5% and type II error of 10% with anticipated incidence of postoperative major complications 30% in GDHT group and 55% in control group in Substudy 4.[65] To allocate 60 subjects to each group of video intubating stylet, video laryngoscopy, and direct laryngoscopy in Substudy 3, a total of 180 subjects are needed for the factorial trial. There are about 120 obese people undergoing LSG at our hospital per year. Considering the patient selection criteria and possible patient refusal, an estimated sample of 90 patients will be recruited per year in this trial. Therefore, it will take about 2 years for patient recruitment.

Statistical Analysis

Baseline patient characteristics and outcome variables will be compared between two groups using chi-square tests or Fisher's exact tests for categorical variables and either t tests or Wilcoxon rank sum tests for continuous variables, as appropriate. For three and four group comparisons, chi-square tests or Fisher's exact tests will be used for categorical variables and either one-way ANOVA or Kruskal-Wallis rank test for continuous variables, as appropriate. *Post hoc* pairwise comparisons will be performed using the Bonferroni correction. For longitudinal data, generalized linear mixed models or generalized estimating equations models will be used to analyze the association between exposure variables and outcomes of interest. For time to event data, Kaplan-Meier method and log-rank test will be applied for group comparisons. Multivariable logistic regression, simple linear regression, or Cox proportional hazards regression analyses will be used to identify potential influential factors of outcomes. A two-sided significance level of 0.05 will be used to define statistically significant difference. All the statistical analyses will be conducted using Statistics Analysis System (SAS), Version 9.4 (SAS Institute Inc., Cary, NC, USA).

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