ANESTHESIOLOGY

Muscular Tissue Oxygen Saturation and Posthysterectomy Nausea and Vomiting

The iMODIPONV Randomized Controlled Trial

Gang Li, M.D., Ph.D., Dan-Dan Tian, M.D., Xu Wang, M.D., Xiaoxian Feng, M.D., Wenyu Zhang, M.D., Ju Bao, M.D., Dong-Xin Wang, M.D., Ph.D., Yan-Qiu Ai, M.D., Ya Liu, M.D., Mengyuan Zhang, M.D., Mingjun Xu, M.D., Dong-Liang Mu, M.D., Ph.D., Xu Zhao, M.D., Feng Dai, Ph.D., Jian-Jun Yang, M.D., Ph.D., Xiangming Che, M.D., David Yanez, Ph.D., Xiangyang Guo, M.D., Ph.D., Lingzhong Meng, M.D., on behalf of the iMODIPONV Research Group

ANESTHESIOLOGY 2020; 133:318–31

ABSTRACT

Background: Suboptimal tissue perfusion and oxygenation during surgery may be responsible for postoperative nausea and vomiting in some patients. This trial tested the hypothesis that muscular tissue oxygen saturation–guided intraoperative care reduces postoperative nausea and vomiting.

Methods: This multicenter, pragmatic, patient- and assessor-blinded randomized controlled (1:1 ratio) trial was conducted from September 2018 to June 2019 at six teaching hospitals in four different cities in China. Nonsmoking women, 18 to 65 yr old, and having elective laparoscopic surgery involving hysterectomy (n = 800) were randomly assigned to receive either intraoperative muscular tissue oxygen saturation–guided care or usual care. The goal was to maintain muscular tissue oxygen saturation, measured at flank and on forearm, greater than baseline or 70%, whichever was higher. The primary outcome was 24-h postoperative nausea and vomiting. Secondary outcomes included nausea severity, quality of recovery, and 30-day morbidity and mortality.

Results: Of the 800 randomized patients (median age, 50 yr [range, 27 to 65]), 799 were assessed for the primary outcome. The below-goal muscular tissue oxygen saturation area under the curve was significantly smaller in patients receiving muscular tissue oxygen saturation–guided care (n = 400) than in those receiving usual care (n = 399; flank, 50 *vs.* 140% · min, $P < 0.001$; forearm, 53 *vs.* 245% · min, $P < 0.001$). The incidences of 24-h postoperative nausea and vomiting were 32% (127 of 400) in the muscular tissue oxygen saturation–guided care group and 36% (142 of 399) in the usual care group, which were not significantly different (risk ratio, 0.89; 95% CI, 0.73 to 1.08; $P = 0.251$). There were no significant between-group differences for secondary outcomes. No harm was observed throughout the study.

Conclusions: In a relatively young and healthy female patient population, personalized, goal-directed, muscular tissue oxygen saturation–guided intraoperative care is effective in treating decreased muscular tissue oxygen saturation but does not reduce the incidence of 24-h posthysterectomy nausea and vomiting.

(ANESTHESIOLOGY 2020; 133:318–31)

EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Suboptimal tissue perfusion and oxygenation may provoke nausea and vomiting

What This Article Tells Us That Is New

- Eight hundred relatively young women having laparoscopic hysterectomies were randomized to routine care or to muscle tissue oxygenation maintained at greater than baseline or 70%, whichever was higher
- Guided management improved tissue oxygenation but did not reduce nausea and vomiting

Among adverse events and complications after surgery, the occurrence of postoperative nausea and vomiting is frequently listed by patients as one of their most disturbing concerns.[1] Postoperative nausea and vomiting can occur in more than 50% of at-risk patients, despite the use of various prophylactic measures.[2] Nausea and vomiting can lead to patient discomfort, complications, prolonged hospitalization, and increased healthcare costs.[3] Suboptimal perfusion and oxygenation of gastrointestinal tissue beds may be responsible for postoperative nausea and vomiting in some patients[4–6]; however, this speculation has not been investigated.

Supplemental Digital Content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

Submitted for publication October 22, 2019. Accepted for publication March 10, 2020. Published online first on April 20, 2020. From the Department of Anesthesiology, Peking University Third Hospital, Beijing, China (G.L., X.G.); the Department of Anesthesiology, Pain and Perioperative Medicine, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan Province, China (D.-D.T., Y.-Q.A., J.-J.Y.); the Department of Anesthesiology, Shandong Provincial Hospital Affiliated to Shandong First Medical University, Jinan, Shandong Province, China (X.W., M.Z.); the Department of Anesthesiology, The Second Hospital of Hebei Medical University, Shijiazhuang, Hebei Province, China (X.F., Y.L.); the Department of Anesthesiology, Beijing Obstetrics and Gynecology Hospital, Capital Medical University, Beijing, China (W.Z., M.X., X.C.); the Department of Anesthesiology, Peking University First Hospital, Beijing, China (J.B., D.-X.W., D.-L.M.); the Department of Biostatistics, Yale University School of Public Health, Yale Center for Analytical Sciences, New Haven, Connecticut (F.D.); and the Department of Anesthesiology, Yale University School of Medicine, New Haven, Connecticut (X.Z., D.Y., L.M.).

 Anesthesiology 2020; 133:318–31. DOI: 10.1097/ALN.0000000000003305

At present, gastrointestinal perfusion and oxygenation cannot be directly monitored in patients. The question is whether there is a tissue bed whose perfusion and oxygenation can not only be monitored but also be used as a surrogate of gastrointestinal perfusion and oxygenation. Skeletal muscle is a potential candidate because its superficial location allows interrogation using a noninvasive biophotonic sensor. Moreover, the flow-regulatory mechanism of the gastrointestinal system appears to be more similar to that of skeletal muscles compared with that of vital organs, as suggested by the plots of organ blood flow against organ perfusion pressure (*i.e.*, pressure autoregulation).[7]

Technologic advancement has now enabled continuous and noninvasive bedside measurement of muscular tissue oxygen saturation using a near-infrared spectroscopy tissue oximeter.[8–10] Muscular tissue oxygen saturation is essentially a measurement of the balance between the rates of oxygen consumption and supply in the skeletal muscle.[11] A recent observational study showed an association between lower intraoperative muscular tissue oxygen saturation monitored on the forearm and higher risk of postoperative nausea and vomiting in patients having robotic laparoscopic hysterectomy, suggesting a potential similarity of tissue perfusion and oxygenation between gastrointestinal and muscular tissue beds.[9] However, whether an intervention protocol aimed at maintaining muscular tissue oxygen saturation at a predetermined range reduces postoperative nausea and vomiting has not been studied.

We hypothesized that the intraoperative care aimed at maintaining muscular tissue oxygen saturation at a predetermined range reduces postoperative nausea and vomiting. We conducted a randomized trial in which patients were randomly assigned to receive either muscular tissue oxygen saturation–guided care or usual care during laparoscopic hysterectomy. Our aim was to investigate whether intraoperative muscular tissue oxygen saturation–guided care, compared with usual care, can significantly reduce the incidence of postoperative nausea and vomiting.

Materials and Methods

Trial Design

The intervention guided by Muscular Oxygenation to Decrease the Incidence of PostOperative Nausea and Vomiting (iMODIPONV) was a multicenter, pragmatic, superiority, patient- and assessor-blinded randomized controlled (1:1 ratio) trial comparing the effects of intraoperative muscular tissue oxygen saturation–guided care and usual care on postoperative nausea and vomiting in patients having laparoscopic hysterectomy. The trial was designed and overseen by a steering committee (Supplemental Digital Content, http://links.lww.com/ALN/C353), organized at Yale University School of Medicine (New Haven, Connecticut), supported by institutional and departmental sources of the participating institutions, and conducted at six teaching hospitals located in four different cities in China after approval by the institutional review board at each participating hospital. This trial (identifier NCT03641625) was registered at ClinicalTrials.gov by the principal investigator, Lingzhong Meng, on August 22, 2018. The trial was conducted in accordance with the principles of the Declaration of Helsinki and the original protocol. The authors assume responsibility for the accuracy and completeness of the data and analyses, as well as the fidelity of the trial and this report.

Participants

We studied patients who had three or more risk factors for postoperative nausea and vomiting, *i.e.*, female sex, nonsmoking status, and expected opioid analgesia use.[12,13] The inclusion criteria were age 18 to 65 yr, nonsmoker status, American Society of Anesthesiologists (Schaumberg, Illinois) Physical Status classification of I to III, and an elective laparoscopic procedure involving hysterectomy. We excluded those patients who were scheduled for vaginal or open hysterectomy, urgent or emergent surgery, or a procedure involving bowel resection. We also excluded patients who had major systemic comorbidities or had undergone chemotherapy or radiotherapy within 3 months before surgery.

Randomization

The participants were identified and consented on the day before surgery. Both verbal and written informed consent was obtained. On the day of surgery (approximately 30 to 60 min preoperatively), the participants were randomly assigned in a 1:1 ratio based on block randomization (size = 4), using a statistical package (version 9.3; SAS Institute Inc., USA), to the muscular tissue oxygen saturation–guided care group or the usual care group. Each study sequence number (from 1 to 800) and its corresponding group assignment were printed on paper, which was then concealed in a sequentially numbered envelope. The sequence number of the envelope was the same as the study sequence number printed on the paper. All envelopes were kept at the study headquarters and distributed, sequentially and in multiples of four, to each study site based on the speed of patient recruitment. The study envelopes were secured in a dedicated container and managed by the study coordinator at each participating hospital. An envelope was allocated to a participant sequentially.

Blinding and Data Quality

The study coordinator at each participating hospital and the anesthesia team taking care of the patients were not blinded to group assignment. Other care providers, patients, and outcome assessors were blinded to group assignment. Outcome assessors were not allowed to participate in other aspects of the study and recorded outcome data independently. The study coordinators and investigators participating in intraoperative care were not allowed to participate in outcome

assessment. Research laptops used for data capturing were password-secured. All data were first recorded on a predesigned paper case report form and later transferred to a web-based REDCap database (https://projectredcap.org/). Members of the quality committee conducted regular study site visits to reinforce the execution of the study protocol, monitor the accuracy of research data, and ensure the adherence to timely and accurate data recording and transfer. An independent three-member data safety monitoring board was established to monitor patient safety for the trial.

Monitoring

In addition to routine monitoring, including electrocardiography, pulse oximetry, and noninvasive blood pressure, patients from both groups were also monitored using a tissue oximeter (FORE-SIGHT Elite, CAS Medical Systems Inc., acquired by Edwards Lifesciences, USA) and a hemodynamic monitor (LiDCOrapid; LiDCO, United Kingdom). One biophotonic sensor was placed on the left paraspinal muscle (perpendicularly aligned to the spine at the L2–3 level) to monitor the flank muscular tissue oxygen saturation, while another biophotonic sensor was placed on the brachioradialis muscle of the left forearm (approximately two fingers below the antecubital crease) to monitor the forearm muscular tissue oxygen saturation. The finger cuff of the LiDCOrapid monitor was placed on the left hand to monitor systemic hemodynamics, while the cuff used for noninvasive blood pressure measurement as part of the routine care was placed on the right upper arm. The real-time muscular tissue oxygen saturation and hemodynamic data were captured by a research laptop at a frequency of 0.5 Hz. The monitoring and data recording were started before anesthesia induction and stopped immediately before moving the patient from the operating table to the transporting bed.

Anesthetic Care

The anesthetic care was standardized. After facemask preoxygenation, anesthesia was induced using lidocaine, sufentanil, and propofol. All patients were endotracheally intubated and mechanically ventilated with a tidal volume of approximately 6 ml/kg and respiratory rate of 10 to 16 breaths/min to maintain the end-tidal carbon dioxide at 30 to 40 mmHg. The inspired fraction of oxygen was 50%. Anesthesia was maintained using propofol and remifentanil infusion. Dexamethasone and 5-HT3 antagonists were used for postoperative nausea and vomiting prophylaxis. Sufentanil was the drug of choice for intraoperative analgesia.

Intervention Guided by a Tissue Oximeter and Hemodynamic Monitor

After patient arrival in the operating room, we first performed baseline measurements, including flank and forearm muscular tissue oxygen saturation, cardiac output, stroke volume, heart rate, systemic vascular resistance, and blood pressure, before anesthesia induction and with the patient awake, calm, and breathing room air. Patients received light sedation if they appeared anxious. Anesthesia was induced after baseline measurements. In the usual care group, the screens of both the tissue oximeter and hemodynamic monitor were covered by an opaque cloth, and the patients were managed per the usual care. In the muscular tissue oxygen saturation–guided care group, both monitors were open to anesthesiologists, and the patients were managed per the muscular tissue oxygen saturation–guided care (fig. 1).

The goal of the muscular tissue oxygen saturation–guided care was to maintain the flank and forearm muscular tissue oxygen saturation equal to or greater than the baseline measurement or 70%, whichever was higher, based on the results of a previous observational study.[9] Interventions were initiated whenever muscular tissue oxygen saturation was lower than the goal for 60 s at either the flank or forearm location. The first step was to check cardiac output. If cardiac output was lower than the baseline level, stroke volume and heart rate were assessed to determine the cause of cardiac output reduction (cardiac output = stroke volume × heart rate). If stroke volume was lower than baseline, preload augmentation, myocardial contractility enhancement, and/or afterload reduction were considered. If heart rate decrement was the cause, measures to increase heart rate were instituted. The second step was to check systemic vascular resistance if the cardiac output was greater than or equal to baseline. Measures to decrease systemic vascular resistance were considered if the systemic vascular resistance was higher than 80% of baseline. We recommended nicardipine if a vasodilatory agent was deemed necessary (based on unpublished data). The third step was to check blood pressure if both cardiac output and systemic vascular resistance were acceptable while muscular tissue oxygen saturation remained low. Measures to increase blood pressure were considered if it was lower than 80% of baseline.[14] Because blood pressure is proportional to cardiac output and systemic vascular resistance, the differential diagnosis and therapeutic options for hypotension revolved around the first and second steps aforementioned. The following interventions dealt with arterial blood oxygen content, muscular tissue metabolic activity, and other potential causes. We maintained pulse oxygen saturation at 95% or above and hemoglobin at 7 to 9 g/dl depending on the patient's comorbidities. The intraabdominal pressure was decreased if it was deemed unnecessarily high. Muscle relaxants could be considered when all other measures failed.

The intervention protocol was thoroughly explained to all investigators. Two formal mandatory trainings, 8 h each, were conducted in August 2018 and January 2019. Members of the quality committee (Supplemental Digital Content, http://links.lww.com/ALN/C353) visited all participating hospitals during the first 3 months of the study to resolve outstanding issues and reinforce protocol execution.

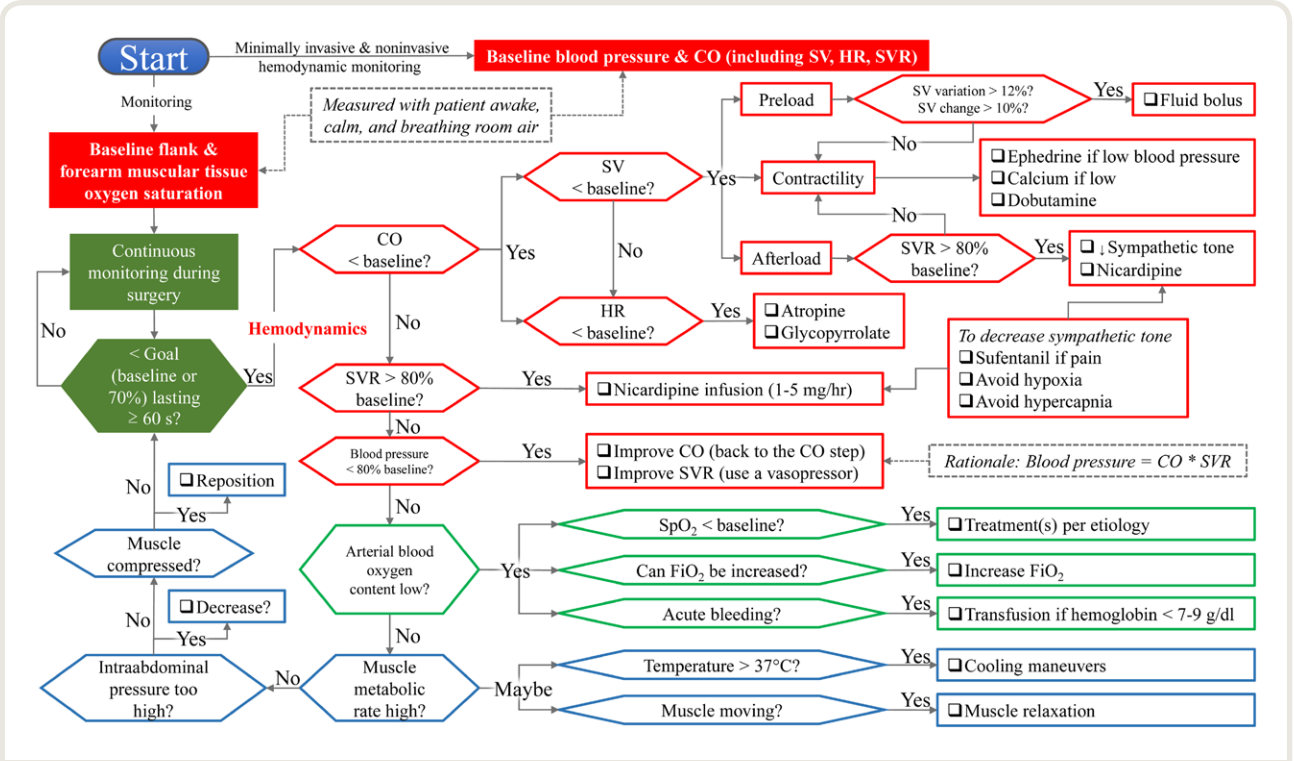

Fig. 1. Protocol of muscular tissue oxygen saturation–guided care. Refer to the text for detailed explanations. CO, cardiac output; FIO_2, inspired oxygen fraction; HR, heart rate; SpO_2, pulse oxygen saturation; SV, stroke volume; SVR, systemic vascular resistance.

Remote research meetings were conducted weekly to discuss various issues and coordinate research efforts.

The effectiveness of the intervention protocol in maintaining muscular tissue oxygen saturation in the predetermined ranges was assessed using the below-goal area under the curve, which is the accumulative product of the difference between the goal and the actual muscular tissue oxygen saturation times the duration over which muscular tissue oxygen saturation was below the goal. A smaller area under the curve indicated better intervention effectiveness and better adherence to the intervention protocol, whereas a large area under the curve indicated the opposite (fig. S1A and S1B in Supplemental Digital Content, http://links.lww.com/ALN/C353). Similarly, the degree of hemodynamic changes below the baseline measurement was assessed using the below-baseline area under the curve. A smaller area under the curve indicated a smaller hemodynamic deviation from the baseline and *vice versa*.

Outcomes

The primary outcome was the incidence of 24-h postoperative nausea and vomiting, defined as the development of nausea, retching, or vomiting within 24 h after surgery.[12,15] The secondary outcomes were the incidence of postoperative nausea and vomiting and the severity of nausea and pain at very early (0 to 2 h), early (2 to 6 h), and late (6 to 24 h) postoperative stages. Patients used an 11-grade numerical rating scale ranging from 0 (none) to 10 (the worst) to rate the severity of their nausea and pain. Patients were considered to experience moderate to severe nausea or pain if the numerical rating scale score was greater than or equal to 5. Other secondary outcomes included (1) the quality of recovery over the first 24 h after surgery as measured by the 15-item quality-of-recovery scale[16]; (2) the quality of the first night's sleep after surgery; (3) the time from the end of surgery to the first out-of-bed ambulation; (4) the time from the end of surgery to the first tolerated meal; (5) the length of the patient's hospital stay; (6) admission to the intensive care unit; (7) hospital readmission; and (8) 30-day morbidity and mortality.

Statistical Analysis

We assumed that muscular tissue oxygen saturation–guided care could reduce the incidence of 24-h postoperative nausea and vomiting from 50%[2,13,17] to 40% in patients having laparoscopic hysterectomy. With two-sided significance and power set at 0.05 and 80%, respectively, the sample size required to detect the projected reduction is 388 patients/group. We planned to enroll 400 patients in each group, assuming a drop-out rate of approximately 3%.

Descriptive statistics were calculated for demographic, baseline, and perioperative characteristics and outcomes. Categorical variables are presented as frequencies and

percentages, whereas continuous variables are presented as means and standard deviations or medians and interquartile ranges depending on the data distribution assessed using histograms and Q–Q plots. Absolute standardized differences between the intervention and control groups were calculated using the method described by Yang and Dalton.[18]

The primary analyses were performed based on the modified intention-to-treat population, which included all patients who had undergone randomization and surgery. The primary outcome was evaluated by the chi-square test, and other binary variables were evaluated by the chi-square test or Fisher's exact test as appropriate. The effect between two groups was quantified by the risk ratio and 95% CI. CIs for the difference of two proportions were calculated using Newcombe's method with continuity correction.[19] The two-sample *t* test or nonparametric Wilcoxon rank-sum test was used to compare continuous variables. CIs for median differences were calculated using Hodges–Lehmann estimates.[20]

A series of sensitivity analyses were performed for the primary outcome. First, a per-protocol analysis was performed based on the modified intention-to-treat population with the exclusion of those patients in whom the study protocol was not followed, including randomization errors, ineligible surgery, nonadherence to the intervention protocol, monitor malfunctioning, and postoperative intubation of the patient. Second, a multiple logistic regression model for the incidence of 24-h postoperative nausea and vomiting was fit in which hospital was adjusted for to assess the impact of between-hospital heterogeneity on risk estimates. Third, another logistic regression model was fit in which hospital, postoperative nausea, and vomiting risk factors and variables having between-group imbalance ($P < 0.100$) were adjusted for as covariates. The odds ratios from logistic regression analyses were converted into risk ratios using the method of Zhang and Yu.[21]

Subgroup analyses of the primary outcome were performed by the following prespecified criteria: participating hospital, age ranges (18 to 39, 40 to 49, 50 to 65 yr), body mass index (less than 25 *vs.* 25 or more), education level (lower than college *vs.* college or higher), diagnosis (benign *vs.* malignant), American Society of Anesthesiologists Physical Status classification (I *vs.* II to III), baseline hemoglobin level (less than median *vs.* median or higher), baseline creatinine level (less than median *vs.* median or higher), history of hypertension, postoperative nausea and vomiting and motion sickness, intraoperative drugs (propofol, remifentanil, sufentanil, and muscle relaxant), anesthesia time (less than 120 min *vs.* 120 min or more), crystalloid administered (less than median *vs.* median or higher), estimated blood loss (less than median *vs.* median or higher), and urine output (less than median *vs.* median or higher). The heterogeneity of effects across subgroups was assessed by testing the significance of the treatment-by-group interaction in the multivariable logistic regression models of the postoperative nausea and vomiting incidence.

The statistical analyses were performed with R (version 3.5.2) packages including arsenal,[22] stddiff,[23] fmsb,[24] and sjstats.[25] A two-sided *P* value of less than 0.050 was considered statistically significant for the primary outcome. The Holm–Bonferroni method[26] was applied to adjust for multiple testing for secondary outcomes, subgroup analyses, and sensitivity analysis of the primary outcome.

Results

Patient Enrollment and Characteristics

From September 2018 to June 2019, a total of 1,049 patients scheduled for an elective procedure involving hysterectomy were evaluated, with 800 patients randomly assigned to receive either muscular tissue oxygen saturation–guided care (n = 400) or usual care (n = 400). The treatment groups had reasonably balanced baseline characteristics (table 1) and balanced baseline tissue oxygenation and hemodynamic measurements (table 2). Because of the cancellation of surgery after randomization for one patient from the usual care group, the modified intention-to-treat population had a total of 799 patients, with 400 in the muscular tissue oxygen saturation–guided care group and 399 in the usual care group (fig. 2).

Effectiveness of Muscular Tissue Oxygen Saturation–guided Care

Muscular tissue oxygen saturation–guided care yielded a lower below-goal flank muscular tissue oxygen saturation area under the curve (50 *vs.* 140% · min; $P < 0.001$; fig. S1C and S1D in Supplemental Digital Content, http://links.lww.com/ALN/C353) and forearm muscular tissue oxygen saturation area under the curve (53 *vs.* 245% · min; $P < 0.001$; fig. S1E and S1F in Supplemental Digital Content, http://links.lww.com/ALN/C353) compared with usual care; it also yielded a lower below-baseline heart rate area under the curve (849 *vs.* 1,180 beats; $P < 0.001$), received more crystalloids (1,600 *vs.* 1,250 ml; $P < 0.001$), and produced more urine (300 *vs.* 250 ml; $P < 0.001$) compared with usual care; these between-group differences remained significant after adjustment of multiple testing (table 2). Patients in the muscular tissue oxygen saturation–guided care group had lower below-baseline cardiac index area under the curve (71 *vs.* 91 ml/m^2; $P = 0.004$), systolic blood pressure area under the curve (1,617 *vs.* 1,976 mmHg · min; $P = 0.014$), and diastolic blood pressure area under the curve (1,086 *vs.* 1,376 mmHg · min; $P = 0.015$); however, these between-group differences were not significant after adjustment for multiple testing (table 2).

Table 1. Demographic and Perioperative Characteristics of the Patients at Baseline

Characteristic	Muscular Tissue Oxygen Saturation-guided Care (N = 400)	Usual Care (N = 399)	Absolute Standardized Difference*
Mean age ± SD, yr	50 ± 8	50 ± 7	0.01
Median height (interquartile range), cm	160 (157–164)	160 (157–163)	0.05
Median body weight (interquartile range), kg	63 (58–70)	63 (57–69)	0.11
Mean body mass index ± SD	25 ± 4	25 ± 3	0.10
ASA Physical Status, no. (%)†			
I	114 (28.5)	128 (32.1)	0.08
II	283 (70.8)	267 (66.9)	
III	3 (0.8)	4 (1.0)	
Marital status, no. (%)			
Married	386 (96.5)	379 (95.0)	0.08
Other (never married, divorced, or widow)	14 (3.5)	20 (5.0)	
Education, no. (%)			
No school	12 (3.0)	22 (5.5)	0.13
Elementary school	60 (15.0)	55 (13.8)	
Middle school	129 (32.2)	131 (32.8)	
High school	94 (23.5)	92 (23.1)	
College	95 (23.8)	89 (22.3)	
Master's degree	7 (1.8)	7 (1.8)	
Doctorate degree	3 (0.8)	3 (0.8)	
Median education (interquartile range), yr	10 (9–15)	9 (9–12)	0.05
Surgical diagnosis, no. (%)			
Dysfunctional uterine bleeding	13 (3.2)	17 (4.3)	0.26
Uterine pain, bleeding, and enlargement	9 (2.2)	16 (4.0)	
Uterine descensus and prolapse	24 (6.0)	11 (2.8)	
Uterine leiomyomas	147 (36.8)	143 (35.8)	
Pelvic inflammatory disease	1 (0.2)	2 (0.5)	
Pelvic endometriosis	12 (3.0)	12 (3.0)	
Cervical stenosis with recurring pyometra after unsuccessful attempts to keep the cervix open	0 (0.0)	1 (0.3)	
Cervical intraepithelial carcinomas	42 (10.5)	60 (15.0)	
Early invasive cervical cancer	48 (12.0)	41 (10.3)	
Endometrial adenocarcinoma and sarcoma	80 (20.0)	75 (18.8)	
Trophoblastic disease	1 (0.2)	0 (0.0)	
Ovarian and fallopian tube neoplasms	21 (5.2)	19 (4.8)	
Malignant disease of other adjacent organs	2 (0.5)	2 (0.5)	
Coexisting medical condition, no. (%)			
Psychiatric disease	0 (0.0)	3 (0.8)	0.12
Neurologic disease	10 (2.4)	5 (1.3)	0.09
Hypertension	93 (23.3)	80 (20.0)	0.08
Cardiovascular disease	12 (3.0)	18 (4.6)	0.08
Pulmonary disease	6 (1.5)	4 (1.0)	0.05
Endocrinologic disease	35 (8.7)	42 (10.6)	0.06
Renal insufficiency	1 (0.2)	1 (0.2)	0.00
Digestive disease	13 (3.2)	10 (2.5)	0.04
History of alcohol consumption, no. (%)			
Never	378 (94.5)	376 (94.2)	0.05
Occasional drinker	20 (5.0)	22 (5.5)	
≥ 3 drinks per week	2 (0.5)	1 (0.3)	
History of anesthesia, no. (%)			
Never	158 (39.5)	152 (38.1)	0.03
General anesthesia	126 (31.5)	128 (32.1)	0.01
Spinal anesthesia	99 (24.8)	99 (24.8)	0.00
Nerve block	0 (0.0)	2 (0.5)	0.10
Local anesthesia	33 (8.2)	31 (7.8)	0.02
History of postoperative nausea and vomiting, no. (%)			
Never had surgery	153 (38.2)	150 (37.6)	0.10
Surgery without postoperative nausea and vomiting	223 (55.8)	215 (53.9)	
Surgery with postoperative nausea and vomiting	24 (6.0)	34 (8.5)	
History of motion sickness, no. (%)	95 (23.8)	80 (20.1)	0.09
Preoperative lab results and bowel preparation			
Median hemoglobin (interquartile range), g/l	128 (116–137)	126 (111–136)	0.14
Median creatinine (interquartile range), μmol/l‡	57 (50–65)	57 (51–64)	0.01

(*Continued*)

Table 1. (Continued)

Characteristic	Muscular Tissue Oxygen Saturation-guided Care (N = 400)	Usual Care (N = 399)	Absolute Standardized Difference*
Bowel preparation before surgery, no. (%)	378 (94.5)	375 (94.0)	0.02
Patients recruited at each hospital, no. (%)			
Peking University First Hospital	30 (7.5)	30 (7.5)	0.01
Peking University Third Hospital	122 (30.5)	122 (30.5)	
Shandong Provincial Hospital	68 (17.0)	68 (17.0)	
Zhengzhou University First Hospital	76 (19.0)	76 (19.0)	
Hebei Medical University Second Hospital	64 (16.0)	63 (15.8)	
Beijing Obstetrics Gynecology Hospital	40 (10.0)	40 (10.0)	

*Absolute standardized differences were calculated using the method described by Yang and Dalton.[18] †The ASA criteria for physical status include a classification for normal health (I), mild systemic disease (II), and severe systemic disease (III). ‡Data regarding the preoperative creatinine were missing for one patient in the muscular tissue oxygen saturation-guided care group.

ASA, American Society of Anesthesiologists.

Table 2. Perioperative Interventions and Measurements

Variable	Muscular Tissue Oxygen Saturation-guided Care (N = 400)	Usual Care (N = 399)	Median or Proportion Difference (95% CI)*	*P* Value	*P* Value (Adjusted)†
Median duration of anesthesia (interquartile range), min	158 (116–204)	153 (117–214)	−1.0 (−10.0–8.0)	0.878	> 0.999
Median duration of surgery (interquartile range), min	120 (84–168)	115 (88–169)	−1.0 (−9.0–7.0)	0.864	> 0.999
Medication administered during surgery					
Median propofol (interquartile range), mg	866 (613–1,150)	830 (620–1,145)	−20.0 (−30.0–70.0)	0.456	> 0.999
Median remifentanil (interquartile range), mg	1.1 (0.7–1.7)	1.0 (0.7–1.5)	0.0 (0.0–0.1)	0.298	> 0.999
Median sufentanil (interquartile range), μg	30 (20–41)	30 (20–40)	0.0 (0.0–5.0)	0.053	> 0.999
Dexamethasone, no. (%)	399 (99.8)	398 (99.7)	0.0 (−0.7–0.7)	0.999	> 0.999
5-HT3 antagonist, no. (%)	397 (99.2)	396 (99.2)	0.0 (−1.2–1.2)	0.998	> 0.999
Cisatracurium, no. (%)	201 (50.3)	206 (51.6)	−1.4 (−8.6–5.8)	0.697	> 0.999
Rocuronium, no. (%)	190 (47.5)	182 (45.6)	1.9 (−5.3–9.1)	0.593	> 0.999
Cisatracurium and rocuronium, no. (%)	9 (2.2)	11 (2.8)	−0.5 (−2.9–1.9)	0.647	> 0.999
Input and output during surgery					
Median crystalloid (interquartile range), ml	1,600 (1,200–2,000)	1,250 (1,000–1,600)	300.0 (200.0–400.0)	**< 0.001**	**< 0.001**
Colloid, no. (%)	113 (28.3)	92 (23.1)	5.2 (−1.1–11.5)	0.093	> 0.999
Packed erythrocyte, no. (%)	6 (1.5)	12 (3.0)	−1.5 (−3.8–0.8)	0.151	> 0.999
Median estimated blood loss (interquartile range), ml	50 (20–100)	50 (20–100)	0.0 (0.0–0.0)	0.217	> 0.999
Median urine output (interquartile range), ml	300 (200–500)	250 (150–400)	100.0 (50.0–100.0)	**< 0.001**	**< 0.001**
Baseline tissue oxygenation, median measurement (interquartile range), %					
Flank muscular tissue oxygen saturation‡	76 (73–79)	76 (73–79)	0.0 (−1.0–1.0)	0.815	> 0.999
Forearm muscular tissue oxygen saturation‡	81 (76–86)	81 (76–87)	0.0 (−1.0–1.0)	0.978	> 0.999
Intraoperative tissue oxygenation, median AUC (interquartile range), % · min§					
Flank muscular tissue oxygen saturation AUC < baseline‖	43 (3–179)	119 (14–403)	−38.0 (−64.5 to −19.5)	**< 0.001**	**< 0.001**
Flank muscular tissue oxygen saturation AUC < 70%#	0 (0–3)	0 (0–32)	0.0 (0.0–0.0)	**< 0.001**	**< 0.001**
Flank muscular tissue oxygen saturation AUC < goal (baseline or 70%, whichever is higher)‖	50 (4–187)	140 (15–423)	−48.0 (−72.0 to −25.5)	**< 0.001**	**< 0.001**
Forearm muscular tissue oxygen saturation AUC < baseline**	48 (5–227)	231 (20– 931)	−105.0 (−170.7–58.0)	**< 0.001**	**< 0.001**
Forearm muscular tissue oxygen saturation AUC < 70%††	0 (0–3)	0 (0–43)	0.0 (0.0–0.0)	**< 0.001**	**< 0.001**
Forearm muscular tissue oxygen saturation AUC < goal (baseline or 70%, whichever is higher)**	53 (6–241)	245 (24– 954)	−124.5 (−180.5 to −69.5)	**< 0.001**	**< 0.001**
Baseline hemodynamics, median measurement (interquartile range)					
Cardiac index, ml · min^{-1} · m^{-2}‡‡	3.4 (2.8–4.0)	3.3 (2.7–3.9)	0.0 (0.0–0.2)	0.151	> 0.999
Stroke volume, ml‡‡	75 (63–90)	75 (61–88)	1.0 (−2.0–4.0)	0.435	> 0.999
Heart rate, beats/min§§	74 (67–82)	73 (67–81)	0.0 (−1.0–2.0)	0.563	> 0.999
Systemic vascular resistance, mmHg · min^{-1} · ml^{-1}‡‡	1,310 (1,111–1,618)	1,380 (1,150–1,659)	−46.0 (−99.0–6.0)	0.080	> 0.999
Systolic blood pressure, mmHg§§	131 (118–143)	132 (120–145)	−1.0 (−3.0–2.0)	0.586	> 0.999
Diastolic blood pressure, mmHg§§	77 (70–85)	79 (71–85)	−1.0 (−3.0–0.0)	0.166	> 0.999
Mean blood pressure, mmHg§§	95 (86–103)	95 (87–104)	0.0 (−2.0–1.0)	0.609	> 0.999

(*Continued*)

Table 2. (Continued)

Variable	Muscular Tissue Oxygen Saturation-guided Care (N = 400)	Usual Care (N = 399)	Median or Proportion Difference (95% CI)*	*P* Value	*P* Value (Adjusted)†
Intraoperative hemodynamics, median AUC < baseline (interquartile range)§					
Cardiac index, ml/m²‖‖	71 (36–136)	91 (42–172)	−15.0 (−26.0 to −4.6)	**0.004**	0.128
Stroke volume, ml · min##	1,014 (495–2,224)	1,301 (550–2,522)	−142.0 (−305.5–7.4)	0.064	> 0.999
Heart rate, beats***	849 (326–1,586)	1,180 (629–2,033)	−294.4 (−428.9 to −163.6)	**< 0.001**	**< 0.001**
Systemic vascular resistance, mmHg · min²/ml##	9,398 (2,356–26,038)	8,364 (2,122–23,897)	616.3 (−397.5–1,800.3)	0.224	> 0.999
Systolic blood pressure, mmHg · min***	1,617 (804–3,042)	1,976 (955–3,600)	−267.8 (−492.5– -53.5)	**0.014**	0.434
Diastolic blood pressure, mmHg · min***	1,086 (528–1,974)	1,376 (669–2,363)	−182.3 (−341.0– -34.3)	**0.015**	0.450
Mean blood pressure, mmHg · min***	920 (396–1,922)	1,102 (431–2,245)	−125.3 (−268.5–3.5)	0.058	> 0.999
Postoperative nausea and vomiting prophylaxis					
5-HT3 antagonist, no. (%)	93 (23.2)	87 (21.8)	1.4 (−4.6–7.5)	0.625	> 0.999
Droperidol, no. (%)	3 (0.8)	4 (1.0)	−0.3 (−1.8–1.3)	0.702	> 0.999
Postoperative nausea and vomiting treatment					
5-HT3 antagonist, no. (%)	25 (6.2)	30 (7.5)	−1.3 (−5.0–2.5)	0.479	> 0.999
Metoclopramide, no. (%)	25 (6.2)	22 (5.5)	0.7 (−2.8–4.2)	0.658	> 0.999

Bold text indicates $P < 0.05$.

*The between-median or between-proportion differences and 95% CIs calculated using Hodges–Lehmann estimates and Newcombe's method with continuity correction, respectively, were used to characterize the between-group difference. †The *P* value was adjusted for multiple comparisons based on the Holm–Bonferroni method. All 41 hypotheses in this table were regarded as a family during calculation. ‡Data regarding the baseline flank or forearm muscular tissue oxygen saturation measurement were missing for one patient in the muscular tissue oxygen saturation-guided care group. §Patients with more than 50% missing data or less than 20 min of data recording time were excluded from the analysis. ‖Data regarding the flank muscular tissue oxygen saturation AUC lower than baseline and goal (baseline or 70%) were missing for six patients in the muscular tissue oxygen saturation-guided care group and nine patients in the usual care group. #Data regarding the flank muscular tissue oxygen saturation AUC lower than 70% were missing for five patients in the muscular tissue oxygen saturation-guided care group and 9 patients in the usual care group. In total, 127 of 395 (32%) patients in the muscular tissue oxygen saturation-guided care group and 172 of 390 (44%) patients in the usual care group had an AUC that was greater than 0. **Data regarding the forearm muscular tissue oxygen saturation AUC lower than baseline and goal (baseline or 70%) were missing for six patients in the muscular tissue oxygen saturation-guided care group and eight patients in the usual care group. ††Data regarding the forearm muscular tissue oxygen saturation AUC less than 70% were missing for five patients in the muscular tissue oxygen saturation-guided care group and eight patients in the usual care group. In total, 128 of 395 (32%) patients in the muscular tissue oxygen saturation-guided care group and 189 of 391 (48%) patients in the usual care group had an AUC that was greater than 0. ‡‡Data regarding the baseline cardiac index, stroke volume, and systemic vascular resistance were missing for one patient in the muscular tissue oxygen saturation-guided care group and two patients in the usual care group. §§Data regarding the baseline heart rate, systolic, diastolic, and mean blood pressure were missing for one patient in the muscular tissue oxygen saturation-guided care group. ‖‖Data regarding the cardiac index AUC lower than baseline were missing for 21 patients in the muscular tissue oxygen saturation-guided care group and 31 patients in the usual care group. ##Data regarding the stroke volume and systemic vascular resistance AUC lower than baseline were missing for 20 patients in the muscular tissue oxygen saturation-guided care group and 30 patients in the usual care group. ***Data regarding the heart rate, systolic, diastolic, and mean blood pressure AUC lower than baseline were missing for 20 patients in the muscular tissue oxygen saturation-guided care group and 29 patients in the usual care group.

AUC, area under the curve.

Primary Outcome

In total, 127 patients (32%, 127 of 400) in the muscular tissue oxygen saturation–guided care group and 142 patients (36%, 142 of 399) in the usual care group had 24-h postoperative nausea and vomiting, which was not statistically significantly different (risk ratio, 0.89; 95% CI, 0.73 to 1.08; $P = 0.251$; table 3).

Secondary Outcomes

Patients in the muscular tissue oxygen saturation–guided care group had less moderate-to-severe nausea during the first postoperative 2 h (5% *vs.* 9%; risk ratio, 0.54; 95% CI, 0.32 to 0.91; $P = 0.019$) and 24 h (16% *vs.* 21%; risk ratio, 0.74; 95% CI, 0.55 to 0.99; $P = 0.042$); they reported a better quality of recovery in the following aspects: being able to enjoy food, feeling rested, feeling comfortable and in control, having a feeling of general well-being, and feeling well overall; they also reported a better quality of the first night's sleep; however, these between-group differences were not significant after adjustment for multiple testing (table 3). The incidences of postoperative nausea and vomiting at very early (0 to 2 h), early (2 to 6 h), and late (6 to 24 h) postoperative stages were similar between groups (table 3). The severity of pain, the time to first ambulation, and the recovery of oral feeding tolerance were similar between groups (table 3). No patient in either group died or had any major organ system complications within 30 days after surgery.

Sensitivity Analyses

Based on the per-protocol population, the incidence rates of 24-h postoperative nausea and vomiting were 30% (112 of 370) in the muscular tissue oxygen saturation–guided care group and 36% (139 of 383) in the usual care group, which was not statistically significantly different (risk ratio, 0.83; 95% CI, 0.68 to 1.02; $P = 0.080$; table S1 to S3 in Supplemental Digital Content, http://links.lww.com/ALN/C353). The effects of muscular tissue oxygen saturation–guided care on the incidence of 24-h postoperative nausea and vomiting in the modified intention-to-treat population (risk ratio, 0.94; 95% CI, 0.74 to 1.16; $P = 0.553$; table S4 in Supplemental Digital Content, http://links.lww.com/ALN/C353) and the per-protocol population (risk ratio, 0.85; 95% CI, 0.66 to

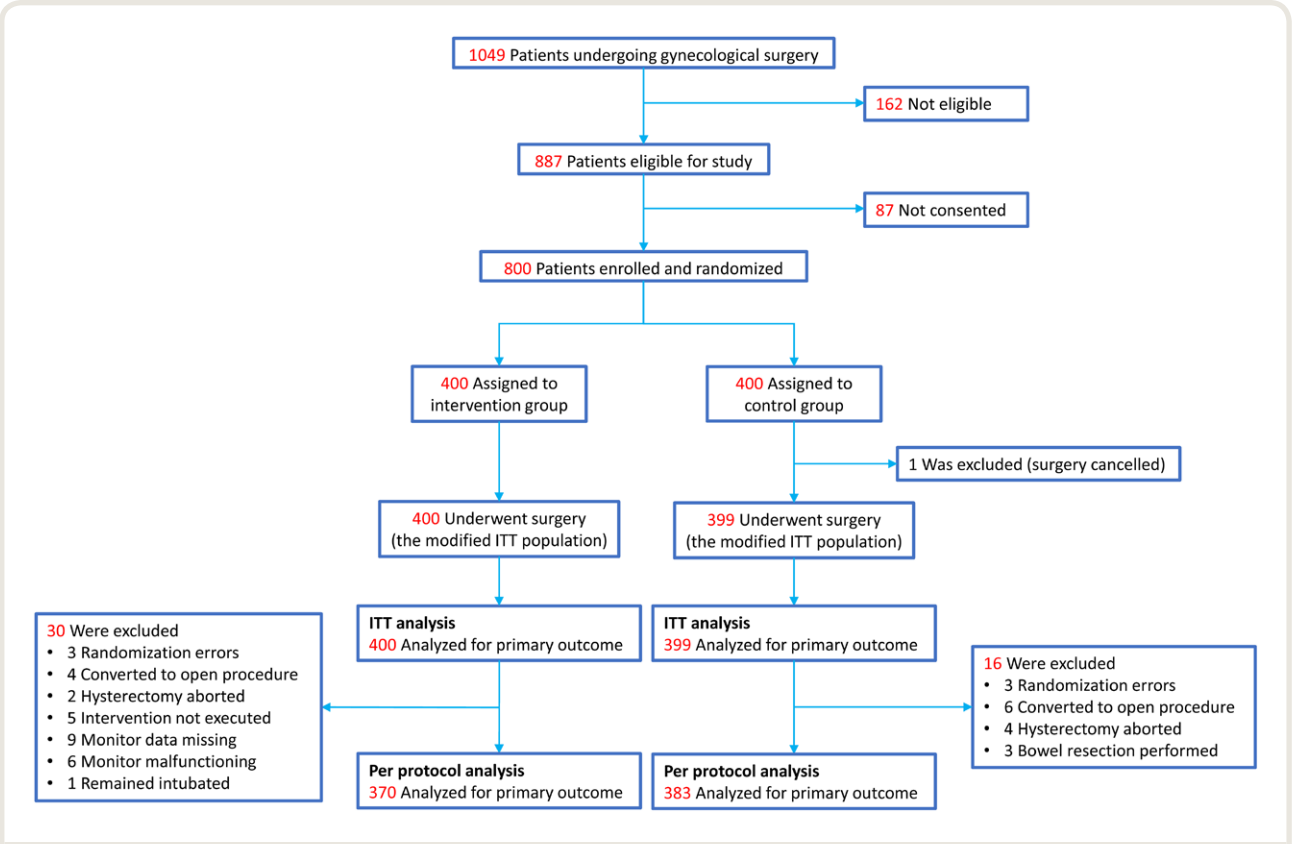

Fig. 2. Flow diagram according to Consolidated Standards of Reporting Trials.

1.08; $P = 0.189$; table S5 in Supplemental Digital Content, http://links.lww.com/ALN/C353) remained insignificant after multivariable adjustments.

Subgroup Analyses

In patients with a body mass index of 25 or higher, the incidence of 24-h postoperative nausea and vomiting was significantly reduced from 41% (66 of 160) in the usual care group to 24% (44 of 183) in the muscular tissue oxygen saturation–guided care group (risk ratio, 0.58; 95% CI, 0.42 to 0.80; $P < 0.001$); this between-group difference remained significant after adjustment for multiple testing (fig. 3 and table S6-S8 in Supplemental Digital Content, http://links.lww.com/ALN/C353). The effect of muscular tissue oxygen saturation–guided care on the incidence of 24-h postoperative nausea and vomiting in patients with a body mass index of 25 or higher remained significant after multivariable adjustments (risk ratio, 0.58; 95% CI, 0.37 to 0.86; $P = 0.006$; table S9 in Supplemental Digital Content, http://links.lww.com/ALN/C353).

In patients with a body mass index of 25 or higher, muscular tissue oxygen saturation–guided care significantly reduced the incidence rates of 24-h postoperative nausea and vomiting from 33% (13 of 40) in the usual care group to 13% (7 of 56) in the muscular tissue oxygen saturation–guided care group in Peking University Third Hospital (risk ratio, 0.38; 95% CI, 0.17 to 0.88; $P = 0.018$) and from 68% (26 of 38) in the usual care group to 44% (16 of 36) in the muscular tissue oxygen saturation–guided care group in Shandong Provincial Hospital (risk ratio, 0.65; 95% CI, 0.42 to 0.99; $P = 0.039$), whereas in the other four hospitals, muscular tissue oxygen saturation–guided care did not lead to a significant between-group difference in the incidence of 24-h postoperative nausea and vomiting (fig. S2 in Supplemental Digital Content, http://links.lww.com/ALN/C353).

Discussion

In this multicenter trial conducted in relatively young and healthy female patients having laparoscopic hysterectomy, we compared the effects of muscular tissue oxygen saturation–guided care *versus* usual care on postoperative nausea and vomiting. The goal of intervention was to maintain flank and forearm muscular tissue oxygen saturation greater than or equal to the baseline level or 70%, whichever was higher. Muscular tissue oxygen saturation–guided care did not significantly reduce the incidence of 24-h postoperative nausea and vomiting compared with usual care; however, it significantly reduced the incidence of

Table 3. Primary and Secondary Outcomes

Outcome	Muscular Tissue Oxygen Saturation-guided Care (N = 400)	Usual Care (N = 399)	Risk Ratio or Median Difference (95% CI)*	*P* Value	*P* Value (Adjusted)†
Primary outcome					
Incidence of postoperative nausea and vomiting within postoperative 24 h, no. (%)	127 (31.8)	142 (35.6)	0.89 (0.73–1.08)	0.251	
Secondary outcomes					
Incidence of postoperative nausea and vomiting at different stages					
Postoperative 0–2 h (very early), no. (%)	56 (14.0)	68 (17.0)	0.82 (0.59–1.14)	0.235	> 0.999
Postoperative 2–6 h (early), no. (%)	67 (16.8)	76/398 (19.1)	0.88 (0.65–1.18)	0.388	> 0.999
Postoperative 6–24 h (late), no. (%)	85 (21.2)	99/398 (24.9)	0.85 (0.66–1.10)	0.224	> 0.999
Incidence of moderate-to-severe nausea at different stages‡					
Postoperative 0–2 h (very early), no. (%)	20 (5.0)	37 (9.3)	0.54 (0.32–0.91)	**0.019**	0.703
Postoperative 2–6 h (early), no. (%)	28 (7.0)	35 (8.8)	0.80 (0.50–1.29)	0.353	> 0.999
Postoperative 6–24 h (late), no. (%)	38 (9.5)	47 (11.8)	0.81 (0.54–1.21)	0.296	> 0.999
Postoperative 0–24 h (overall), no. (%)	62 (15.5)	84 (21.1)	0.74 (0.55–0.99)	**0.042**	> 0.999
Incidence of moderate-to-severe pain at different stages‡					
Postoperative 0–2 h (very early), no. (%)	73 (18.3)	65 (16.3)	1.12 (0.83–1.52)	0.464	> 0.999
Postoperative 2–6 h (early), no. (%)	56 (14.0)	64 (16.0)	0.87 (0.63–1.21)	0.411	> 0.999
Postoperative 6–24 h (late), no. (%)	36 (9.0)	53 (13.3)	0.68 (0.45–1.01)	0.054	> 0.999
Postoperative 0–24 h (overall), no. (%)	105 (26.3)	112 (28.1)	0.94 (0.75–1.17)	0.563	> 0.999
Median quality of recovery (QoR-15;interquartile range)§					
Part A: How have you been feeling in the last 24 h? (0 to 10, where 0 = none of the time [poor] and 10 = all of the time [excellent])					
Able to breathe easily	10 (9–10)	10 (9–10)	0.0 (0.0–0.0)	0.939	> 0.999
Been able to enjoy food	8 (7–10)	8 (6–10)	0.0 (0.0–0.0)	**0.046**	> 0.999
Feeling rested	8 (7–9)	7 (6–8)	0.0 (0.0–1.0)	**0.003**	0.120
Have had a good sleep	7 (5–8)	7 (4–8)	0.0 (0.0–1.0)	0.068	> 0.999
Able to look after personal toilet and hygiene unaided	7 (1–10)	6 (1–9)	0.0 (0.0–0.0)	0.153	> 0.999
Able to communicate with family or friends	10 (10–10)	10 (10–10)	0.0 (0.0–0.0)	0.436	> 0.999
Getting support from hospital doctors and nurses	10 (10–10)	10 (10–10)	0.0 (0.0–0.0)	0.699	> 0.999
Able to return to work or usual home activities	8 (5–9)	7 (4–9)	0.0 (0.0–1.0)	0.115	> 0.999
Feeling comfortable and in control	8 (6–10)	8 (5–9)	0.0 (0.0–1.0)	**0.023**	0.828
Having a feeling of general well-being	8 (6–9)	7 (6–9)	0.0 (0.0–1.0)	**0.012**	0.456
Part A score	80 (69–92)	76 (65–88)	3.0 (1.0–5.0)	**0.008**	0.312
Part B: Have you had any of the following in the last 24 h? (10 to 0, where 10 = none of the time [excellent] and 0 = all of the time [poor])					
Moderate pain	9 (8–10)	9 (8–10)	0.0 (0.0–0.0)	0.424	> 0.999
Severe pain	10 (10–10)	10 (10–10)	0.0 (0.0–0.0)	0.168	> 0.999
Nausea or vomiting	10 (9–10)	10 (8–10)	0.0 (0.0–0.0)	0.623	> 0.999
Feeling worried or anxious	10 (8–10)	10 (8–10)	0.0 (0.0–0.0)	0.559	> 0.999
Feeling sad or depressed	10 (8–10)	10 (8–10)	0.0 (0.0–0.0)	0.447	> 0.999
Part B score	47 (42–49)	46 (42–50)	0.0 (0.0–1.0)	0.183	> 0.999
Sleep, ambulance, and *per os* tolerance					
Median quality of the first night's sleep (interquartile range)‖	7 (4–8)	6 (4–8)	0.0 (0.0–1.0)	**0.042**	> 0.999
Able to get out of bed at postoperative 48 h, no. (%)	379 (94.8)	385 (96.5)	0.98 (0.95–1.01)	0.229	> 0.999
Median time to get out of bed for the first time (interquartile range), h#	22 (18–30)	21 (17–30)	0.0 (–1.0–2.0)	0.489	> 0.999
Able to tolerate *per os* at postoperative 48 h, no. (%)	382 (95.5)	384 (96.2)	0.99 (0.96–1.02)	0.599	> 0.999
Median time to tolerate the first *per os* (interquartile range), h**	19 (12–26)	19 (11–26)	0.0 (–1.0–1.5)	0.683	> 0.999
30-Day complications					
Mortality, no. (%)	0 (0.0)	0 (0.0)	Not applicable	Not applicable	Not applicable
Neurologic, no. (%)	0 (0.0)	0 (0.0)	Not applicable	Not applicable	Not applicable
Cardiovascular, no. (%)	0 (0.0)	0 (0.0)	Not applicable	Not applicable	Not applicable
Pulmonary, no. (%)	0 (0.0)	0 (0.0)	Not applicable	Not applicable	Not applicable
Renal, no. (%)	0 (0.0)	0 (0.0)	Not applicable	Not applicable	Not applicable
Gastrointestinal, no. (%)††	0 (0.0)	1 (0.3)	Not applicable	0.316	> 0.999
Hematologic, no. (%)‡‡	1 (0.2)	2 (0.5)	0.50 (0.05–5.48)	0.562	> 0.999
Surgery-related, no. (%)§§	1 (0.2)	0 (0.0)	Not applicable	0.318	> 0.999
Infectious, no. (%)‖‖	2 (0.5)	3 (0.8)	0.67 (0.11–3.96)	0.652	> 0.999

(*Continued*)

Table 3. (Continued)

Outcome	Muscular Tissue Oxygen Saturation-guided Care (N = 400)	Usual Care (N = 399)	Risk Ratio or Median Difference (95% CI)*	*P* Value	*P* Value (Adjusted)†
Other outcomes					
Median length of hospital stay (interquartile range), h	118 (72–161)	117 (91–144)	0.0 (–5.0–3.0)	0.635	> 0.999
ICU admission, no. (%)	5 (1.2)	1 (0.3)	4.99 (0.59–42.50)	0.102	> 0.999
Readmission within 30 days after surgery, no. (%)	28 (7.0)	31 (7.8)	0.90 (0.55–1.47)	0.678	> 0.999

Bold text indicates $P < 0.05$.

*The risk ratio and 95% CI were used to characterize the effectiveness of muscular tissue oxygen saturation-guided care for categorical variables. The between-median difference and 95% CI based on the Hodges–Lehmann estimator were used to characterize the effectiveness of muscular tissue oxygen saturation-guided care for continuous variables. †The *P* value was adjusted for multiple comparisons based on the Holm–Bonferroni method. All 45 hypotheses for secondary outcomes in this table were regarded as a family during calculation. ‡The severity of nausea and pain was assessed using a numeric rating scale, an 11-point scale where 0 indicates no nausea or pain and 10 indicates the worst nausea or pain. A score of 5 or higher indicates moderate-to-severe nausea or pain. §Data regarding QoR-15 were missing for one patient in the muscular tissue oxygen saturation-guided care group and one patient in the usual care group. ‖The quality of the first night's sleep was assessed based on a 0 to 10 scale, where 0 = none of the time [poor] and 10 = all of the time [excellent]. Data regarding the quality of the first night's sleep were missing for one patient in the muscular tissue oxygen saturation-guided care group. #Data regarding the time to get out of bed for the first time were missing for three patients in the muscular tissue oxygen saturation-guided care group and two patients in the usual care group. **Data regarding the time to tolerate the first *per os* were missing for four patients in the control group. ††Ileus occurred in one patient in the usual care group. ‡‡Deep vein thrombosis occurred in one patient in the muscular tissue oxygen saturation-guided care group and two patients in the usual care group. §§Wound dehiscence occurred in one patient in the muscular tissue oxygen saturation-guided care group. ‖‖Urinary tract infection occurred in q patient in the muscular tissue oxygen saturation-guided care group; surgical site infection occurred in one patient in the muscular tissue oxygen saturation-guided care group and three patients in the usual care group.

ICU, intensive care unit; QoR, quality of recovery.

24-h postoperative nausea and vomiting in patients with a body mass index of 25 or higher based on preplanned subgroup analyses.

Compared with previous studies on goal-directed therapy, our study introduced the use of below-goal area under the curve to assess the degree of how well the predetermined goal is accomplished. This measure is important because if there is no between-group difference in area under the curve (*i.e.*, the goal is not accomplished), it is difficult to understand the relationship between the goal-directed therapy and the outcome. Our findings suggested that the intervention protocol we used in this trial is effective in treating muscular tissue oxygen saturation decrements, because both the flank and forearm muscular tissue oxygen saturation areas under the curve in the muscular tissue oxygen saturation–guided care group were significantly smaller than those in the usual care group. The muscular tissue oxygen saturation–guided intervention protocol we used in this trial has prominent differences from the previously published ones.[27,28] One important difference is the use of a hemodynamic monitor in our protocol to facilitate the differential diagnosis and treatment of muscular tissue oxygen saturation decrements. This approach is related to the complicated physiology underlying tissue oxygen saturation measured by near-infrared spectroscopy. The factors that are frequently responsible for an adverse muscular tissue oxygen saturation decrease in anesthetized and paralyzed surgical patients are reduced cardiac output and reduced tissue perfusion.[14,29] Therefore, it is important to incorporate a hemodynamic monitor that offers dynamic information on intravascular volume, cardiac output, stroke volume, and systemic vascular resistance.

Our study presents a potential innovative measure for further quality improvement in perioperative care. Our patients were relatively young and healthy and underwent a relatively low-risk surgical procedure. We do not normally expect major perioperative complications in this patient population; rather, the priority is to promote enhanced recovery after surgery. Postoperative nausea and vomiting are roadblocks to enhanced recovery and have a relatively high incidence in this patient population.[1] In our study, despite the use of different prophylactic measures against postoperative nausea and vomiting, including propofol-based intravenous anesthesia, dexamethasone, and 5-HT3 antagonists, postoperative nausea and vomiting still occurred in 36% of patients in the usual care group. Although muscular tissue oxygen saturation–guided care did not significantly reduce the 24-h postoperative nausea and vomiting among all patients, it significantly reduced the postoperative nausea and vomiting risk in patients with a body mass index of 25 or higher. In patients with a body mass index of 25 or higher, muscular tissue oxygen saturation–guided care significantly reduced the occurrence of postoperative nausea and vomiting in two hospitals, but not the other four hospitals, suggesting the favorable outcome is primarily driven by the data from these two hospitals (fig. S2 in Supplemental Digital Content, http://links.lww.com/ALN/C353). The validity and mechanisms of this finding merit further investigation.

Muscular tissue oxygen saturation–guided care targets essential physiology (*i.e.*, the balance between tissue oxygen consumption and supply) and offers personalized care when patient baseline measurements are referenced in decision-making. However, whether muscular tissue oxygen saturation–guided

Subgroup	Muscular Tissue Oxygen Saturation Guided Care (no. of patients/total no.)	Usual Care (no. of patients/total no.)	Risk Ratio [95% CI]	*P* Value	*P* Value for Interaction
All patients	127/400	142/399	0.89 [0.73, 1.08]	0.251	
Hospital					0.906
Peking University First Hospital	5/30	7/30	0.71 [0.25, 2.00]	0.519	
Peking University Third Hospital	27/122	37/122	0.73 [0.48, 1.12]	0.146	
Shandong Provincial Hospital	43/68	43/68	1.00 [0.77, 1.29]	1.000	
Zhengzhou University First Hospital	16/76	17/76	0.94 [0.51, 1.72]	0.844	
Hebei Medical University Second Hospital	22/64	25/63	0.87 [0.55, 1.37]	0.536	
Beijing Obstetrics Gynecology Hospital	14/40	13/40	1.08 [0.58, 1.99]	0.813	
Age (year)					0.072
18–39	19/40	7/27	1.83 [0.90, 3.75]	0.075	
40–49	43/148	65/175	0.78 [0.57, 1.07]	0.125	
50–65	65/212	70/197	0.86 [0.65, 1.14]	0.295	
Body mass index					< 0.001*
< 25	83/217	76/239	1.20 [0.94, 1.55]	0.149	
≥ 25	44/183	66/160	0.58 [0.42, 0.80]	< 0.001†	
Education level					0.598
College or higher	33/105	38/99	0.82 [0.56, 1.19]	0.297	
Below college	94/295	104/300	0.92 [0.73, 1.15]	0.468	
Diagnosis					0.812
Benign	68/206	73/202	0.91 [0.70, 1.19]	0.506	
Malignant	59/194	69/197	0.87 [0.65, 1.16]	0.331	
ASA physical status classification					0.709
I	25/114	35/128	0.80 [0.51, 1.25]	0.330	
II–III	102/286	107/271	0.90 [0.73, 1.12]	0.352	
Baseline hemoglobin (g/l)					0.016‡
< 126	67/170	66/193	1.15 [0.88, 1.51]	0.303	
≥ 126	60/230	76/206	0.71 [0.53, 0.94]	0.015§	
Baseline creatinine (μmol/l)					0.701
< 57	74/196	78/192	0.93 [0.73, 1.19]	0.563	
≥ 57	53/203	64/207	0.84 [0.62, 1.15]	0.281	
Baseline systemic vascular resistance (mmHg·min/ml)					0.822
< 1380	69/229	67/196	0.88 [0.67, 1.16]	0.372	
≥ 1380	58/170	74/201	0.93 [0.70, 1.22]	0.589	
Baseline systolic blood pressure (mmHg)					0.988
< 130	97/307	113/319	0.89 [0.71, 1.11]	0.311	
≥ 130	30/93	29/80	0.89 [0.59, 1.35]	0.581	
History of postoperative nausea and vomiting					0.926
Never had surgery	48/153	53/150	0.89 [0.65, 1.22]	0.465	
Surgery without nausea and vomiting	66/223	71/215	0.90 [0.68, 1.18]	0.439	
Surgery with nausea and vomiting	13/24	18/34	1.02 [0.63, 1.66]	0.927	
History of motion sickness					0.570
Yes	36/95	37/80	0.82 [0.58, 1.16]	0.264	
No	91/305	105/319	0.91 [0.72, 1.14]	0.407	
Intraoperative propofol (mg)					0.908
< 830	56/178	70/196	0.88 [0.66, 1.17]	0.385	
≥ 830	71/222	72/203	0.90 [0.69, 1.18]	0.447	
Intraoperative remifentanil (mg)					0.450
< 1.0	46/164	63/181	0.81 [0.59, 1.11]	0.178	
≥ 1.0	81/236	79/218	0.95 [0.74, 1.22]	0.669	
Intraoperative sufentanil (μg)					0.360
< 30	45/184	61/195	0.78 [0.56, 1.09]	0.139	
≥ 30	82/216	80/203	0.96 [0.76, 1.23]	0.761	
Intraoperative muscle relaxant					0.867
Cisatracurium given	78/201	88/206	0.91 [0.72, 1.15]	0.422	
Rocuronium given	47/190	50/182	0.90 [0.64, 1.27]	0.548	
Both given	2/9	4/11	0.61 [0.14, 2.61]	0.642	
Duration of anesthesia (min)					0.077
< 120	41/109	34/107	1.18 [0.82, 1.71]	0.367	
≥ 120	86/291	108/292	0.80 [0.63, 1.01]	0.057	
Crystalloid (ml)					0.674
< 1500	48/140	84/233	0.95 [0.71, 1.27]	0.730	
≥ 1500	79/260	58/166	0.87 [0.66, 1.15]	0.326	
Colloid					0.899
Given	30/113	28/92	0.87 [0.56, 1.35]	0.539	
Not given	97/287	114/307	0.91 [0.73, 1.13]	0.396	
Estimated blood loss (ml)					0.313
< 100	80/266	99/273	0.83 [0.65, 1.06]	0.127	
≥ 100	47/134	43/126	1.03 [0.74, 1.44]	0.872	
Urine output (ml)					0.145
< 500	86/261	105/310	0.97 [0.77, 1.23]	0.816	
≥ 500	41/139	37/89	0.71 [0.50, 1.01]	0.061	

Fig. 3. Risk ratios for postoperative nausea and vomiting in prespecified subgroups Body mass index is defined as body mass in kilograms divided by the square of height in meters. The ASA criteria for physical status include classifications for normal health (I), mild systemic disease (II), and severe systemic disease (III). *$P = 0.030$ after adjustment of multiple testing (number of hypothesis tests = 71). †$P = 0.048$ after adjustment of multiple testing (number of hypothesis tests = 71). ‡$P > 0.999$ after adjustment of multiple testing (number of hypothesis tests = 71). §$P > 0.999$ after adjustment of multiple testing (number of hypothesis tests = 71). ASA, American Society of Anesthesiologists.

care reduces complications related to suboptimal tissue perfusion and oxygenation and promotes enhanced recovery after surgery remains to be further studied. Its values in different surgical patient populations having different surgical procedures remain to be elucidated. Muscular tissue oxygen saturation–guided care incurs certain costs and demands extra effort at the beginning of its implementation. Whether this personalized goal-directed muscular tissue oxygen saturation–guided intraoperative care is cost-effective remains unknown.

Our trial has certain limitations. Obviously, anesthesiologists could not execute muscular tissue oxygen saturation–guided care in a blinded manner. The lack of blinding may have introduced bias in the documentation of intraoperative information; however, the outcome data would be insulated from this source of bias because of the separation of these two processes. We did not directly measure gastrointestinal tissue oxygenation in this trial; therefore, whether the optimization of muscular tissue oxygenation also improves gastrointestinal tissue oxygenation remains a matter of speculation.[7] We performed baseline measurements in awake patients in the operating room. Situation anxiety, preoperative fasting, and bowel preparation may enhance or reduce cardiac performance and tissue perfusion and oxygenation. Although we made efforts to obtain "real" baseline values, including administering anxiolytics to seemingly anxious patients and checking the vital signs measured outside of the operating room, the measurements obtained in the operating room may not always represent a patient's resting and optimized condition. Finally, we may have underpowered this study by overestimating the effect size (20%) when planning the trial.

In conclusion, in relatively young and healthy female patients having laparoscopic hysterectomy, muscular tissue oxygen saturation–guided care during surgery is effective in treating muscular tissue oxygen saturation decrements but does not significantly reduce the incidence of 24-h postoperative nausea and vomiting compared with usual care. This innovative, personalized, goal-directed and muscular tissue oxygen saturation–guided pathway of care warrants further studies.

Acknowledgments

The authors thank CAS Medical Systems, Inc., (Branford, Connecticut; acquired by Edwards Lifesciences, Irvine, California) for providing the FORE-SIGHT ELITE tissue oximeters and disposable probes, and LiDCO (London, United Kingdom), for providing the hemodynamic monitors at no cost.

Research Support

Supported by CAS Medical Systems, Inc., which funded two iMODIPONV research meetings that were conducted in Beijing, China, in August 2018 and January 2019. Also supported by institutional and/or departmental sources at Yale University (New Haven, Connecticut), Peking University (Beijing, China), Shandong Provincial Hospital (Jinan, China), Zhengzhou University (Zhengzhou, China), Hebei Medical University (Shijiazhuang, China), and Capital Medical University (Beijing, China).

Competing Interests

Dr. Meng was a consultant to CAS Medical Systems, Inc. (Branford, Connecticut; now acquired by Edwards Lifesciences, Irvine, California). Dr. Dai was supported in part by CTSA grant No. UL1TR001863 from the National Center for Advancing Translational Sciences (Bethesda, Maryland); however, the contents of this work are solely the responsibility of the authors and do not necessarily represent the official view of National Institutes of Health. The other authors declare no competing interests.

Reproducible Science

Full protocol available at: lingzhong.meng@yale.edu. Raw data available at: lingzhong.meng@yale.edu.

Correspondence

Address correspondence to Dr. Meng: Yale University School of Medicine, 333 Cedar Street, TMP 3, P.O. Box 208051, New Haven, Connecticut 06520. lingzhong.meng@yale.edu.

References

1. Kovac AL: Prevention and treatment of postoperative nausea and vomiting. Drugs 2000; 59:213–43
2. Kranke P, Bergese SD, Minkowitz HS, Melson TI, Leiman DG, Candiotti KA, Liu N, Eberhart L, Habib AS, Wallenborn J, Kovac AL, Diemunsch P, Fox G, Gan TJ: Amisulpride prevents postoperative nausea and vomiting in patients at high risk: A randomized, double-blind, placebo-controlled trial. ANESTHESIOLOGY 2018; 128:1099–106
3. Gan TJ, Diemunsch P, Habib AS, Kovac A, Kranke P, Meyer TA, Watcha M, Chung F, Angus S, Apfel CC, Bergese SD, Candiotti KA, Chan MT, Davis PJ, Hooper VD, Lagoo-Deenadayalan S, Myles P, Nezat G, Philip BK, Tramèr MR; Society for Ambulatory Anesthesia: Consensus guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2014; 118:85–113
4. Gan TJ, Mythen MG: Does peroperative gut-mucosa hypoperfusion cause postoperative nausea and vomiting? Lancet 1995; 345:1123–4
5. Gan TJ, Mythen MG, Glass PS: Intraoperative gut hypoperfusion may be a risk factor for postoperative nausea and vomiting. Br J Anaesth 1997; 78:476
6. Jewer JK, Wong MJ, Bird SJ, Habib AS, Parker R, George RB: Supplemental perioperative intravenous

crystalloids for postoperative nausea and vomiting. Cochrane Database Syst Rev 2019; 3:CD012212
7. Meng L, Wang Y, Zhang L, McDonagh DL: Heterogeneity and variability in pressure autoregulation of organ blood flow: Lessons learned over 100+ years. Crit Care Med 2019; 47:436–48
8. Meng L, Xiao J, Gudelunas K, Yu Z, Zhong Z, Hu X: Association of intraoperative cerebral and muscular tissue oxygen saturation with postoperative complications and length of hospital stay after major spine surgery: An observational study. Br J Anaesth 2017; 118:551–62
9. Li G, Lin L, Dai F, Guo X, Meng L: Muscular tissue oxygen saturation during robotic hysterectomy and postoperative nausea and vomiting: Exploring the potential therapeutic thresholds. J Clin Monit Comput 2019; 33:597–604
10. Fan X, Lin L, Li G, He T, Xiao J, Deng X, Dai F, Meng L: Do cerebral and somatic tissue oxygen saturation measurements correlate with each other during surgery? J Clin Monit Comput 2019. DOI: 10.1007/s10877-019-00339-3. [Epub ahead of print]
11. Bickler P, Feiner J, Rollins M, Meng L: Tissue oximetry and clinical outcomes. Anesth Analg 2017; 124:72–82
12. Apfel CC, Läärä E, Koivuranta M, Greim CA, Roewer N: A simplified risk score for predicting postoperative nausea and vomiting: Conclusions from cross-validations between two centers. Anesthesiology 1999; 91:693–700
13. Kranke P, Eberhart L, Motsch J, Chassard D, Wallenborn J, Diemunsch P, Liu N, Keh D, Bouaziz H, Bergis M, Fox G, Gan TJ: I.V. APD421 (amisulpride) prevents postoperative nausea and vomiting: A randomized, double-blind, placebo-controlled, multicentre trial. Br J Anaesth 2013; 111:938–45
14. Meng L, Yu W, Wang T, Zhang L, Heerdt PM, Gelb AW: Blood pressure targets in perioperative care. Hypertension 2018; 72:806–17
15. Gan TJ, Meyer T, Apfel CC, Chung F, Davis PJ, Eubanks S, Kovac A, Philip BK, Sessler DI, Temo J, Tramèr MR, Watcha M; Department of Anesthesiology, Duke University Medical Center: Consensus guidelines for managing postoperative nausea and vomiting. Anesth Analg 2003; 97:62–71
16. Stark PA, Myles PS, Burke JA: Development and psychometric evaluation of a postoperative quality of recovery score: The QoR-15. Anesthesiology 2013; 118:1332–40
17. Geng ZY, Liu YF, Wang SS, Wang DX: Intra-operative dexmedetomidine reduces early postoperative nausea but not vomiting in adult patients after gynaecological laparoscopic surgery: A randomised controlled trial. Eur J Anaesthesiol 2016; 33:761–6
18. Yang D, Dalton JE: A unified approach to measuring the effect size between two groups using SAS®, SAS global forum, 2012, pp 1–6
19. Newcombe RG: Interval estimation for the difference between independent proportions: Comparison of eleven methods. Stat Med 1998; 17:873–90
20. Hodges JL Jr, Lehmann EL: Estimates of location based on rank tests. Ann Math Statistics 1963; 34: 598–611
21. Zhang J, Yu KF: What's the relative risk?: A method of correcting the odds ratio in cohort studies of common outcomes. JAMA 1998; 280:1690–1
22. Heinzen E, Sinnwell J, Atkinson E, Gunderson T, Dougherty G: arsenal: An arsenal of "R" functions for large-scale statistical summaries, 2019, R package version 3.3.0. Available at: https://CRAN.R-project.org/package=arsenal. Accessed March 1, 2020.
23. Du Z, Hao Y: stddiff: Calculate the standardized difference for numeric, binary and category variables, 2019, R package version 3.0. Available at: https://CRAN.R-project.org/package=stddiff. Accessed March 1, 2020.
24. Nakazawa M: fmsb: Functions for medical statistics book with some demographic data, 2018, R package version 0.6.3. Available at: https://CRAN.R-project.org/package=fmsb. Accessed March 1, 2020.
25. Lüdecke D: sjstats: Statistical functions for regression models, 2019, R package version 0.17.6. Available at: https://CRAN.R-project.org/package=sjstats. Accessed March 1, 2020.
26. Holm S: A simple sequentially rejective multiple test procedure. Scand J Stat 1979; 6: 65–70
27. Lei L, Katznelson R, Fedorko L, Carroll J, Poonawala H, Machina M, Styra R, Rao V, Djaiani G: Cerebral oximetry and postoperative delirium after cardiac surgery: A randomised, controlled trial. Anaesthesia 2017; 72:1456–66
28. Subramanian B, Nyman C, Fritock M, Klinger RY, Sniecinski R, Roman P, Huffmyer J, Parish M, Yenokyan G, Hogue CW: A multicenter pilot study assessing regional cerebral oxygen desaturation frequency during cardiopulmonary bypass and responsiveness to an intervention algorithm. Anesth Analg 2016; 122:1786–93
29. Meng L, Gruenbaum SE, Dai F, Wang T: Physiology, intervention, and outcome: Three critical questions about cerebral tissue oxygen saturation monitoring. Minerva Anestesiol 2018; 84:599–614