Study Protocol

Title: Effects of moderate versus deep neuromuscular block on respiratory mechanics and biotrauma during protective lung ventilation for robotic gynecologic surgery

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This study was approved by Ajou University Hospital Institutional Review Board (AJIRB-MED-OBS-18-115) and is registered at http://clinicaltrials.gov (NCT03576118). Between May 2018 and November 2019, 74 patients aged 25-80 years undergoing robotic gynecologic surgery with Trendelenburg position were enrolled. Written informed consent was obtained from all participants before randomization. The exclusion criteria were operation time <1 h, uncontrolled cardiovascular morbidity, cerebrovascular and respiratory diseases, neuromuscular disorder, prior abdominal surgery and morbid obesity (body mass index >30 kg/m^2).

Interventions

Patients were randomly allocated to either moderate NMB group or deep NMB group using a computer-generated randomization (http://www.random.org). Moderate NMB group (n = 37) was maintained with train of four (TOF) count of 1-2 combined with IAP at 12 mmHg during surgery and then reversed using IV neostigmine of 50 μg/kg and glycopyrrolate of 10 μg/kg after surgery. Deep NMB group (n = 37) was maintained with post-tetanic count (PTC) of 1-2 combined with IAP at 8 mmHg and then reversed using IV sugammadex of 4 mg/kg. Study intervention was conducted by an independent investigator who did not involve in the outcome assessment. The anesthetic provider, patients, and outcome assessors were blinded to the group assignment throughout the study period.

Standard monitoring included pulse oximeter, electrocardiogram, noninvasive blood pressure, and bispectral index (BIS™ Quattro Sensor; Covidien, Mansfield, MA, USA). Acceleromyography (TOF-Watch-SX; MSD BV, Netherlands) was applied to monitor the response of the adductor pollicis muscle. Anesthesia was implemented with total intravenous anesthesia using target-controlled infusion (TCI) of propofol and remifentanil. Anesthesia was induced with propofol of 4.0~6.0 μg/mL and remifentanil of 3.0~4.0 ng/mL as target concentration. After consciousness loss, the TOF-Watch-SX was calibrated and stabilized (<5% variation in the TOF ratios). IV rocuronium of 0.6 mg/kg was administered, and then tracheal intubation was done after confirmation of relaxation. A 20-G radial arterial catheter was inserted for continuous monitoring of hemodynamics and blood sampling. Mechanical ventilation was

composed of volume-controlled mode at a constant flow with a tidal volume 8 ml/kg of ideal body weight, and at an I:E ratio of 1:2 (FiO_2=0.5). Respiratory rate is set to an end-tidal carbon dioxide tension ($ETCO_2$) between 30 and 40mm Hg with 5 cmH_2O PEEP and an inspiratory pause of 10%. Anesthesia was maintained using propofol and remifentanil TCI to achieve the BIS value of 40-60 and mean arterial pressure (MAP) within 20% of baseline. Rocuronium (0.3 to 0.4 mg/kg/hr) or saline are continuously infused and titrated according to the group assignment until the end of the fascia suturing. After dressing, the NMB was reversed, and extubation was done after confirming TOF ratio >0.9. Lactate Ringer's solution or normal saline was infused at a rate of 6 mL/kg/h.

Trendelenburg position was performed at 30°. PP was controlled through the limit of CO_2 insufflator. IV patient-controlled analgesia was administered with fentanyl at a rate of 0.4 μg/kg/hr for 48 hr as patient's need.

Data collection

The primary end point was the levels of inflammatory cytokines; pro-inflammatory cytokines including tumor necrosis factor (TNF)-α, TNF receptor (TNFR)-1, interleukin (IL)-1β, and IL-6, and anti-inflammatory cytokines including IL-4 and IL-10. Blood samples were collected at 3 time points; after induction (baseline), the end of PP, and 24 hr after surgery. The collected blood samples were transferred to EDTA tubes and sent to the laboratory in a container. They were centrifuged at 3600 rpm for 30 min. Then, the supernatant serum of 1.5 mL was gathered into an Eppendorf tube and frozen at −80°C for later analysis. Levels of the cytokines were measured by using commercially available ELISA kit (R&D systems, Minneapolis, Minnesota, USA). Each sample was analyzed in triple and excluded when at least one was not determined, and the average value was calculated.

Respiratory parameters including peak inspiratory pressure (Ppeak) and plateau pressure (Pplat) were measured at 5 time points; after induction (baseline), 15 min and 60 min after PP, the end of PP and the end of surgery. Hemodynamics such as heart rate (HR) and MAP and parameters relating with arterial blood gas analysis (pH, PaO_2 and $PaCO_2$) were measured at abovementioned 5 time points and in post-

anesthesia care unit. The abdominal and shoulder pains were measured using numeric rating scale (NRS, 0-10) including the numbers of patients requesting analgesics and antiemetics. White blood cell (WBC) count was measured at preoperative and 24 hr after surgery. C-reactive protein (CRP, normal range ≤0.5 mg/dL) and chest x-ray were evaluated at 24 hr after surgery.

Statistical Analysis

Sample size are determined based on the findings of a previous study, where the mean ± SD of IL-6 was 45 ± 8.6 pg/L in mechanical ventilation after conventional pneumoperitoneum. We considered a 15% reduction of IL-6 to be clinically relevant. With a significant level of 5 % and a power of 90%, 36 subjects were required in each group. We included 37 patients per group to allow for possible dropouts. Values are expressed as mean ± SD (or standard error) or medians (range) or numbers (proportion). Normality of distribution was assessed with the Kolmogorov-Smirnov test. Parametric data and nonparametric data were analyzed by using the independent *t* test and the Mann–Whitney *U* test, respectively. Categorical variables were evaluated by using the chi-square test or Fisher's exact test. Repeated-measured variables were analyzed by using a linear mixed model with a Bonferroni-correction. A *P* value <0.05 was considered statistically significant. Statistical analysis was conducted using SAS (version 9.3, SAS Inc., Cary, NC, USA) and R package (version 3. 6.1).