Study title: Dexmedetomidine and Brain Perfusion Monitor for Sedation of Endobronchial Ultrasound-guided Transbronchial Needle Aspiration

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Study protocol

This prospective, open-labelled, randomized study was conducted in a medical center (Chang-Gung Memorial Hospital, Linkou, Taiwan). The study protocol was approved by the Chang Gung Medical Foundation Institutional Review Board (No.201601093A3). The trial was registered at clinicaltrials.gov (NCT03521505). Patients who required EBUS-TBNA and agreed to undergoing the procedure under sedation were screened for enrolment. The exclusion criteria included age <20 years, American Society of Anaesthesiologists (ASA) physical status classification 4 or 5, a Mallampati score of 4, severe sleep apnoea syndrome (apnoea-hypopnea index >40), second or third degree atrioventricular blockage, heart rate <50 beats per minute, systolic blood pressure <90mmHg, neurologic disorders or other conditions contributing to difficulty in assessing response, body mass index >42 in males or >35 in females, and pregnancy. Patients with a known history of allergy to the study drugs, or to eggs, soybeans, or sulfite products, were also excluded. All enrolled patients provided written informed consent. Enrolled patients were randomised using a predetermined random computer code into the study group or the control group at a ratio of 1:1.

Patient preparation

Blood pressure was monitored using an automated pressure cuff, and heart rate (HR) was monitored using a three-lead electrocardiograph (ECG). A peripheral pulse oximeter was used to monitor oxyhemoglobin saturation (SpO_2), while a nasal cannula

delivered oxygens at rate of 2 L/min. A disposable BIS Quatro Sensor (Aspect Medical System Inc, Newton, MA, USA) was applied to the forehead of patients. Smoothening time was set at 15 s. The BIS level was covered (i.e., blinded to the investigator in charge of sedation). A patient monitor (Philips MP60) was used to continuously record all parameters except for the blood pressure, which was recorded every 2.5 minutes. The monitoring software was developed in Microsoft Visual Basic 6.0 (Windows XP) based on the Philip Patient Monitor communication protocol. An intravenous catheter was placed in the forearm for drug administration. An oral bite block was placed prior to sedation. Pre-medication was achieved using nebulized 2% xylocaine inhalation.

The investigators in charge of sedation were specifically trained in the administration of sedatives and monitoring sedative depth. They were responsible for monitoring patients for cardiopulmonary depression and determining the need for interventions. The interventions are detailed in the supplemental materials. EBUS-TBNA operations were performed by experienced bronchoscopists (Kuo C-H and Chung F-T) using a convex probe endobronchial ultrasound (BF-UC260FW, Olympus, Tokyo, Japan). via the oral route, with assistance from a well-trained technician.

Sedation protocol

Study group: Alfentanil (5 μg/kg) was administered in a 1:10 dilution with normal saline under slow injection for 2 min prior to full induction using an infusion of

dexmedetomidine (1μg/kg) for 10 min [18, 22, 30]. Maintenance was conducted via dexmedetomidine infusion (0.5~1.4 μg/kg/hour) with the aim of maintaining stable vital signs and The Observer Assessment of Alertness and Sedation scale (OAA/S) of 3~2.

Control group: Patients were slowly administered alfentanil (5 μg/kg) in a 1:10 dilution with normal saline for 2 min prior to induction using a propofol infusion at an initial effect-site concentration (Ce) of 2.0μg/ml using a Injectomat^{R} TIVA Agilia, (Fresenius Kabi, France)[11, 13]. OAA/S was evaluated every 30 s after the patients closed their eyes. In cases where OAA/S did not reach 3 when Ce reached 2.0 μg/ml, Ce was increased by 0.2μg/ml every 90 seconds until OAA/S reached 3~2. Maintenance of control group: Ce of propofol was titrated at a rate of 0.2μg/ml every 90 seconds to achieve stable vital signs and The Observer Assessment of Alertness and Sedation scale (OAA/S) 3~2.

Following the procedure, the patients were monitored continuously in a recovery room until full recovery.

Assessment

SPO_2, blood pressure, HR, and BIS were recorded immediately before induction (as a baseline), during induction, during the maintenance of sedation, and throughout the recovery period. The parameter levels and the difference from the baseline values

were analysed. We recorded episodes of hypoxemia (SpO_2<90%) and hypotension (mean arterial blood pressure (MAP) <65 mmHg or systolic blood pressure (SBP) <90 mmHg) of any duration. Sedative drug doses were recorded at the infusion pump. Procedure time was recorded as the duration from the insertion of bronchoscope to its removal. Recovery time was recorded as the duration between the time at which bronchoscopy finished and the time when the patients spontaneously opened their eyes and were able to recall their date of birth and correctly perform the finger-to-nose test.

After recovery, patients were asked to answer questionnaire about wakefulness, tolerance, and willingness to repeat the bronchoscopic procedure if clinically indicated. Wakefulness during the procedure was evaluated by asking patients if they heard or saw anything during the operation. The questionnaire used to assess patient tolerance to procedure-related symptoms included reactions to nebulized xylocaine inhalation, stimulation caused by insertion of the scope through the mouth, cough, dyspnea, pain, and global discomfort to the entire procedure. The questionnaire used a 100-mm visual analogue scale (VAS, 0: no bother, 100: intolerable). Patients were also asked about their willingness to undergo the bronchoscopic procedure again if clinically indicated (definitely not, possibly not, not sure, possibly yes and definitely yes). The bronchoscopist was questioned concerning the ease of scope insertion and biopsy,

coughing by the patient, and global cooperation throughout the procedure using a 100-mm VAS (0: most cooperative, 100: entirely uncooperative).

The diagnostic yield of EBUS-TBNA was evaluated in terms of the pathology or cytology of mediastinal lymph nodes. Specimens without lymphocytes were defined as inadequate samples. There are two criteria by which to confirm a result as a true negative. The first is confirming a lack of malignancy in specimens obtained surgically. The second is a confirmation of stability or regression via computed tomography at 6 months after the procedure.

Statistical analysis plan

Sample size

Power calculations were based on the proportion of patients with at least one episode of hypoxemia during sedation of bronchoscopy. Among the patients who underwent bronchoscopy, 3% of those under dexmedetomidine sedation and 36.7% of those under propofol sedation experienced episodes of hypoxemia. Considering the complexity of EBUS-TBNA, a difference of 30% would be of clinical importance (α=0.05, power=0.8). Our analysis revealed that 25 subjects per group would be sufficient to detect a difference between the two groups.

Statistical analysis

Analysis was performed on the outcomes of all randomized subjects. The diagnostic

yield among subjects who completed EBUS-TBNA was expressed as a number with a percentage or a mean with standard deviation. Ccontinuous variables were evaluated using the Mann-Whitney test. Patient characteristics and complications were analysed using the Chi-square test or Fisher's exact test, in cases where the sample size was small. A $p<0.05$ was considered statistically significant. All the statistical analysis was performed using Prism 5 (GraphPad software Inc., San Diego, CA, USA).