Study Protocol and Statistical Analysis Plan

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Materials and methods

This prospective observational study was conducted in Tri-Service General Hospital, Taipei. Written informed consent was obtained from each participating patient the day before data collection and surgery. We included adult patients with American Society of Anesthesiology physical status I-II, who were scheduled for shoulder rotator cuff repair under combined ipsilateral interscalene block (ISB) and general anesthesia. Patients with conditions that could interfere with pupillary measurement, such as chronic opioid use (>3 months), the presence of ophthalmologic or neurological diseases, and long-term medication influencing the autonomic nervous system (e.g., β-blockers, anticholinergics) were excluded.

Conduct of anesthesia

On the day of the surgery, the patient was initially sent to the anesthesia preparation room where their vital signs, including pulse oximetry, electrocardiography, and noninvasive blood pressure, were monitored. A single injection ISB was performed using sterile technique on the ipsilateral side of the surgical site. We utilized nerve simulation concurrently with ultrasound guidance to ensure accurate needle tip placement. Following a negative aspiration, a bolus of a 15 mL mixture containing 7.5 mL of 2% lidocaine and 7.5 mL of 0.5% ropivacaine was slowly administered in 5 mL increments. Then after the patient was transported to the operating room, the success of ISB was assessed by conducting a cold and pinprick sensory test over the C5 and C6 dermatomal segments.

In addition to the standard basic monitoring, we also use Bispectral Index to monitor the depth of anesthesia. After preoxygenation, the patient was given Fentanyl (1-1.5 ug/kg), Lidocaine (0.5-1 mg/kg), Propofol (1.5-2 mg/kg), and Cisatracurium (0.15-0.2 mg/kg) as induction agents to complete endotracheal intubation. Inhaled sevoflurane was used to maintain general anesthesia, with a targeted Bispectral Index (BIS) range of 40 to 60. Fentanyl is the sole analgesic permitted for use throughout the surgery. Subsequent administration of fentanyl and/or cisatracurium, as well as ventilator settings and hemodynamic management, were left to the discretion of the attending anesthesiologist in charge of the patient. At the end of the surgery, sevoflurane was discontinued and neuromuscular block was reversed with neostigmine and glycopyrrolate. The patient was extubated once they were able to open their eyes on verbal command and resume spontaneous breathing, with a train-of-four ratio greater than 0.9 using a neuromuscular stimulator.

Within 15 minutes of the patient being transported to the post-anesthesia care unit (PACU), nursing staff would ask the patient to rate their pain at the surgical site using the NRS, which ranges from 0 to 10. The choice of postoperative analgesics, if

necessary, was decided by the responsible anesthesiologist. The rest of patient care in the PACU was conducted in accordance with established standards.

Pupillary measurement

We used a portable video pupillometer (AlgiScan; IDMED, Marseille, France) with its built-in pupillary pain index (PPI) mode to measure pupillary reflex dilation. The PPI mode applies a standardized, incremental transcutaneous electrical stimulation (100Hz, 10mA to 60mA, with 1-second intervals) that progressively increases in intensity until a pupil dilation of more than 13% is observed. The degree of reflex dilation is quantified on a scale of 1 (very deep analgesia) to 9 (very light analgesia) and referred to as the Pupillary Pain Index (PPI) (18-20).

PPI measurements were conducted at two distinct time intervals: after the induction of general anesthesia but before the surgical incision, and before the patient was extubated after the end of surgery. To perform the measurement, two sets of electrodes were placed on the patient's deltoid regions, one set on each side. We tested both sides of the C5 and C6 dermatomal segment, with one side anesthetized by ISB and the other side used as a control. Hence, each patient served as their own control. To decrease measurement bias, the PPI was recorded in the eye opposite the block by the same investigator, who did not influence the decision of the anesthesiologist staff. The PACU nurse who documented the patient's NRS was not informed of the PPI value obtained.

Statistical analysis

Continuous data were reported as either means with standard deviations or medians with interquartile ranges (IQR), while categorical data as numbers with percentages. The normality of the distribution of data was assessed using the Kolmogorov-Smirnov and Shapiro-Wilk tests. To compare the PPI between the ISB and control sides during two PPI measurement time intervals, we used the paired Student's t-test or the Wilcoxon signed-rank test as appropriate. To examine the correlation between postoperative NRS and PPI on the ISB side, we performed Pearson's (or Spearman's) correlation analysis accordingly. Statistical analyses were conducted using online statistics calculator (DATAtab: Online Statistics Calculator. DATAtab e.U. Graz, Austria. URL https://datatab.net). A two-tailed P value less than 0.05 was considered statistically significant.