Study Protocal

Official Title: Propofol EC50 for Inducing Loss of Consciousness in General Combined Epidural Anesthesia

NCT05124704

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Study population and randomization

This study was approved by the Ethics Committee of Zhejiang Cancer Hospital prior to patient enrolment (IRB-2021-214, date of approval: 1 July 2021) and registered at ClinicalTrials.gov (identifier: NCT05124704, registration date: 11 October 2021, principal investigator: JW). We followed the consolidated Standards of Reporting Trials (CONSORT) statement when conducting and reporting this trial. This study was conducted between 20 November 2021 and 25 May 2022 at the Department of Anesthesiology, Zhejiang Cancer Hospital.

After obtaining written informed consent, 60 ASA physical states II or III patients with gastric cancer aged 18–75 years scheduled for open gastrectomy were enrolled in this study. The exclusion criteria were as follows: contraindications to epidural puncture or catheter placement; chronic or acute (within 48 h) intake of psychotropic drugs, benzodiazepines, anticonvulsants, or opioids; alcoholism; hepatic, renal, neurological, or other organ dysfunction; allergy to any drugs used in this study; or refusal to receive epidural puncture.

The eligible patients were randomized to one of the two groups with different anesthesia protocols: the GA + EA group (combined epidural-general anesthesia) or the GA alone group (general anesthesia alone). Randomization was performed by a research assistant who did not take part in the study using computer-generated numbers (Microsoft Excel for MAC, Microsoft, Redmond, WA, United States). The randomization codes were concealed in numbered, sealed opaque envelopes, one of which was opened for each patient.

Before induction of anesthesia

No premedication was given. Upon arrival in the operating theater, standard monitoring including electrocardiogram (ECG), pulse oximetry (SpO2), invasive artery blood pressure (IBP) via the left radial artery, bispectral index (BIS), and end-tidal carbon dioxide (EtCO2) was applied. A central venous catheter was placed

in the right internal jugular vein and commenced an infusion of 37°C Ringer's lactate solution at a rate of 10 mL kg−1 h−1.

Induction of anesthesia

Prior to general anesthesia induction, all patients had an epidural catheter placed in the left lateral position. Epidural anesthesia was performed based on the usual procedure in our center and procedures described before. After skin infiltration with lidocaine, epidural puncture was performed with a 16-gauge Tuohy needle at the estimated T8–T9 vertebral interspace using a loss-of-resistance to saline technique and then inserted a nylon multiport catheter 4 cm into the epidural space with the needle orifice oriented cephalad.

An anesthesia nurse who was not involved in the study prepared the epidural medication (normal saline or 0.375% ropivacaine) in a 20 mL syringe. A test dose of 3 mL of the epidural medication (normal saline for the GA group and 0.375% ropivacaine for the GA + EA group) was given to exclude an intrathecal placement of the epidural catheter. After 4 min, in the absence of significant sensory or motor blockade, the patient received an extra 5 to 8 mL (depending on the height and weight) of the epidural medication (normal saline for the GA alone group and 0.375% ropivacaine for the GA + EA group) through the epidural catheter. The level of sensory blockade was assessed bilaterally in the anterior axillary line by pinprick 15 min after epidural injection. The upper and lower limits of the block level were recorded. If the upper block level reached T4 or above, but did not exceed T3, the epidural infusion was then maintained with 0.375% ropivacaine at an infusion rate of 4–6 mL h−1.

General anesthesia was induced with propofol oxycodone and rocuronium by the fixed attending anesthesiologists (JW, YS, and WG) who were blinded to the patient grouping and epidural administration. Propofol was administered via a target-controlled infusion (TCI) (Base Premea, Ochestraw, Fresenius Company, Bre'zins France) with the pharmacokinetic model of Schnider et al. .

To explore the EC50 of propofol-inducing LOC (defined as the loss of response to verbal commands) in patients with or without prior epidural anesthesia, the administration of propofol for each patient was applied according to that applied in our previous study using the up–down sequential allocation method. The initial TCI Ceprop for the first patient of each group was set at 3.5 μg mL−1. The initial TCI Ceprop for the next patient was determined by the response of the previous patient to the initial dose of propofol administered. A positive response was defined as LOC occurring within 4 min of TCI propofol, and a negative response was defined as no LOC within 4 min of TCI propofol. If a positive response happened, the initial TCI Ceprop was decreased by 0.5 ug mL−1 for the next patient in the same group. If a negative response happened, the initial TCI Ceprop was increased by 0.5 μg mL−1 for the next patients. The TCI Ceprop for the negative patient would increase by 0.5 μg mL−1 stepwise at 4 min intervals unti the patient showed LOC. After LOC, an intravenous bolus of 0.25 mg kg−1 oxycodone was administered, and then 0.6 mg kg−1 rocuronium was given to facilitate tracheal intubation.

Maintenance of anesthesia

Anesthesia was maintained with propofol and remifentanil. Ceprop was adjusted immediately after intubation by increasing or decreasing in steps of 0.5 μg mL−1 to keep the BIS value between 40 and 60 throughout the surgery. The lowest Ceprop was 2.0 μg mL−1 in order to prevent intraoperative awareness. In the meantime, intravenous infusion of remifentanil began at a rate of 0.1 μg kg−1 min−1 and was then adjusted by increasing or decreasing in steps by 0.05 μg kg−1 min−1 to keep adequate anesthesia. The criteria of inadequate anesthesia were as follows: (1) hypertension: a mean blood pressure (MAP) >120% of baseline or >100 mmHg; (2) tachycardia: heart rate >90 beats·min−1; (3) somatic arousal: signs of coughing, chewing, and grimacing; and (4) somatic response: purposeful movement. The maximum infusion rate was 0.25 μg kg−1 min−1. Hypotension, defined as a MAP <80% of baseline or <60 mmHg, was treated initially by speeding intravenous infusion and decreasing the remifentanil infusion rate by 0.05 μg kg−1 min−1 in a

stepwise manner until the minimum rate of 0.05 μg kg−1 min−1, and finally, ephedrine, phenylephrine, or metaraminol were given. Bradycardia was treated with intravenous atropine 0.5 mg.

Recovery period

Both propofol and remifentanil infusions were discontinued when the final surgical suture was completed. Emergence time from anesthesia was assessed by measuring the duration between the time of discontinuation of anesthetics and the time of spontaneous opening of eyes. Patient-controlled epidural analgesia (PCEA) with 0.175% ropivacaine mixed with 0.7 μg mL−1 sufentanil was applied for postoperative pain for all patients. In the postanesthesia care unit (PACU), the modified Aldrete-Score, postoperative nausea and vomiting, pain intensity (visual analog scale of 0–10, 0 = no pain, 10 = worst pain imaginable), and other side effects were recorded. All patients were visited on the 1st day postoperatively to check for adverse effects of anesthesia, and patient satisfaction with the anesthesia procedure was assessed using a scale of 0–10 rating (0 = completely dissatisfied and 10 = completely satisfied) and the quality of postoperative analgesia with PCEA using the variables such as pain VAS and the number of total PCE presses and effective presses.