Study of dexmedetomidine combined with nalbuphine over-the-top analgesia on the quality of awakening after general anesthesia and on perioperative lung protection in elderly patients - a prospective, double-blind, completely randomized clinical trial

Programme Summary

Study Title	Dexmedetomidine combined with nalbuphine over-the-top analgesia on the quality of awakening after general anaesthetic surgery in elderly patients and perioperative lung protection
Programme number	20221201
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Principal Investigator	Tianjin First Central Hospital
Purpose of the study	The awakening period of general anaesthesia refers to the time period between the end of surgery and the patient's awakening when the infusion of anaesthetic drugs is stopped. During the initial period of general anaesthesia, the depth of anaesthesia is reduced, the cerebral cortex is still in a state of inhibition and the subcortical centres are often hypersensitive to external stimuli. At this time, factors such as drug effects, pain, hypoxaemia, unrecognised aspiration, pneumothorax, urinary retention, tracheal tube irritation and urinary catheter irritation may induce agitation and cause dramatic haemodynamic changes. Especially in elderly people with reduced organ function, this may increase postoperative complications, prolong the hospital stay and increase hospital costs. In recent years, several studies have demonstrated that dexmedetomidine and nalbuphine reduce postoperative agitation and choking during extubation, respectively, without increasing the time to extubation. Nalbuphine is a mixed agonist-antagonist analgesic for opioid receptors, binding to μ, κ and δ receptors, with a complete agonist effect on κ receptors and a partial antagonist effect on μ receptors, thus providing analgesia and sedation. Its analgesic strength is comparable to that of morphine and can be used to relieve moderate to severe pain, as well as to reduce visceral pain. Nalbuphine has few cardiovascular side effects, minimal respiratory depression and a capping effect. As with other agonist antagonists, nalbuphine interferes with the adverse

	effects associated with pure mu agonists such as nausea, vomiting and pruritus. Dexmedetomidine is an agonist of the alpha2 adrenergic receptor, which has analgesic, sedative, anxiolytic, kinetic stabilizing and stress-reducing effects. It can activate the α2 receptors in the patient's body, thus inhibiting the release of norepinephrine in the patient's body, which in turn has analgesic, sedative and anti-anxiety effects on the patient. According to relevant reports at home and abroad, dexmedetomidine can reduce the synthesis and release of pro-inflammatory factors [such as tumour necrosis factor α and interleukin 6], inhibit the inflammatory response, improve lung function and protect the lung. The aim of this study is to explore whether the combination of the two can provide better analgesic effect, alleviate patients' discomfort during the awakening period, and reduce patients' perioperative inflammation level, improve lung function and protect the lung. Main research objectives 1. A study to evaluate the combination of dextromethorphan and nalbuphine on the quality of postoperative awakening in elderly people undergoing general anaesthesia. 2. A study of the combination of dextromethorphan and nalbuphine on perioperative levels of inflammation and the occurrence of pulmonary complications in elderly people undergoing general anaesthesia.
Study endpoints	The occurrence of agitation within 1h after extubation and the occurrence of pulmonary complications within 7d after surgery.
Study population	Elderly patients aged ≥60 years admitted to the PACU with a tube after major surgery under general anaesthesia.
	For patients aged ≥60 years admitted to the operating room for general anaesthetic surgery, oxygen was administered by face mask, intravenous access was opened, blood pressure, oxygen saturation, ECG and BIS values were monitored; radial

Study design	artery puncture was performed under local anaesthesia and invasive blood pressure was monitored. After triple checking, general anaesthesia was induced and intravenous methylprednisolone 40mg, gronobromine 1mg, midazolam 0.05 mg/kg, etomidate 0.3mg/kg, sufentanil 0.5μg/kg, rocuronium 0.6mg/kg was administered. Intraoperative volume control ventilation was adopted with tidal volume 6-8 mL/kg, frequency 12 times/min and oxygen flow rate 12 times. Intraoperative ventilation was volume-controlled, with a tidal volume of 6-8 mL/kg, a frequency of 12 breaths/min, an oxygen flow rate of 2 L/min, an inspiratory-to-expiratory ratio of 1:2, and a partial pressure of carbon dioxide at 30-40 mmHg. Intra-operative maintenance: use static inhalation compound anaesthesia, remifentanil 0.05-2.00 μg/(kg-min), propofol 4.0-6.0 mg/(kg-h), 1%-2% sevoflurane inhalation, intra-operative control of mean arterial pressure fluctuations not exceeding 20% of the basal value, BIS maintained between 40-60, 30 min before the end of the operation, stop sevoflurane, according to the drug The subjects were divided into group A with continuous intraoperative pumping of saline and an intravenous push of 5 mL of saline 30 min before the end of surgery; group B with continuous intravenous pumping of DEX 0.5 μg/kg for 10 min and an intravenous push of nalbuphine 0.20 mg/kg (5 mL) 30 min before the end of surgery. At the end of the operation, all anesthetic drugs were stopped and the patient was transferred to the PACU with intubation.

	The primary outcome of this study was the occurrence of agitation from the awakening period to 30 min after extubation, with a Riker sedation-agitation score of 5 to 7 determining the occurrence of agitation. Secondary research indicators. (1) EA occurred 0, 10, 20 and 30 min after PACU extubation. (2) Chills occurred 0, 10, 20 and 30 min after PACU tubation. (3) Postoperative pain was assessed by visual analogue scale AS) at 0, 10, 20 and 30 min after PACU extubation. (4) Grading of choking and coughing from awakening to 30 min ter extubation (5) Observe the changes in vital signs (heart rate, blood pressure, oxygen saturation) at 0min, 10min, 20min and 30min after extubation. (6) Time of extubation: from discontinuation of anaesthetic medication to time of extubation. (7) PACU length of stay: the time from the end of the procedure to discharge from the PACU. (8) Oxygenation index: Blood gas analysis was taken from the radial artery for oxygenation index (PaO2/FiO2) before skin incision, at the end of surgery and 5 min after extubation.

Entry criteria	(1) Age ≥ 60 years, regardless of gender. (2) Post-tracheal intubation, ventilator-assisted ventilation. (3) Performing general anaesthetic surgery.
Exclusion criteria	(1) Hypersensitivity to the drugs used in this study. (2) Any sedative, analgesic, antiemetic or antipruritic medication taken 24 hours prior to surgery. (3) History of severe bradycardia (heart rate <50 beats/min). (4) Moderate to severe liver and kidney dysfunction. (5) Persons with combined neurological disorders.
Exit criteria	Termination of the trial is required if the subject meets one or more of the following criteria. (1) The emergence of life-threatening complications that urgently require resuscitation of the patient. (2) The subject or guardian requests to withdraw from the trial. (3) Other circumstances which, in the judgment of the investigator, warrant withdrawal from the trial.
Determination of sample size	The primary endpoint of this study was the incidence of post-operative agitation. The incidence of postoperative agitation in adults has been reported to be 3.7%-41%. We based the incidence of postoperative agitation in patients in the placebo group on a 40% incidence of postoperative agitation at a design test efficiency (1-β) = 0.8 and a test level of α = 0.05 (bilateral), which would require 108 patients per group if we expected a 30% reduction in the incidence of EA with dextromethorphan + nalbuphine prophylaxis. An estimated 10% of patients dropped out of the study during the trial; therefore, we planned to recruit 120 patients per group, for a total of 240 patients.
Statistical analysis	Statistical analysis was performed using SPSS statistical software. the total incidence of EA was expressed as a percentage and analysed using the chi-square test. Logistic regression analysis was used to compare the incidence of EA in the two groups at different times after extubation, and the WALD χ2 test was used to estimate the parameters associated with the two groups at different times after extubation. flacc scores were expressed as mean ± standard deviation, and within-group repeated measures ANOVA was performed. Comparisons between groups at different time points were made using independent samples t-tests. Where appropriate, demographic data and anaesthetic characteristics were analysed using chi-square tests and t-tests. The incidence of adverse events was expressed as frequencies and percentages (n, %). The difference was statistically

	significant at P<0.05 bilaterally.