Effect of dexmedetomidine combined with low-dose nalmefene on preventing remifentanil-induced postoperative hyperalgesia

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This randomized double-blind controlled study was approved by the Tianjin Medical University General Hospital Ethic Committee (Tianjin, China; approval number IRB2017-009-01) and written informed consent was obtained from all patients.

Patients undergoing elective laparoscopic gynecological surgery were screened and enrolled between March 2017 and October 2017. Inclusion criteria were patients aged 20–64 yr; American Society of Anesthesiologists physical status I or II; cognitive capacity to use the patient-controlled analgesia (PCA).The exclusion criteria were as follows: bronchial asthma; coronary heart disease; severe hypertension; diabetes mellitus; obesity (BMI >30 kg/m^2); cardiac, hepatic, and renal dysfunction; psychiatric disease; history of chronic pain; history of alcohol or opioid abuse; chronic use of opioids; intake of any analgesic within 48 h before surgery; pregnancy; allergy and contraindication to dexmedetomidine or nalmefene; contraindication for the use of patient-controlled analgesia (PCA); or incapacity to comprehend pain

assessment. After randomization and allocation, patients were withdrawn if laparoscopy was converted to open surgery or if they required reinvestigation for postoperative bleeding.

All surgical procedures were performed by senior surgeons. Patients fasted preoperatively. Upon arrival at the operating room, the patients were generally monitored by non-invasive blood pressure, ECG, heart rate(HR), pulse oximetry, and bispectral index. A peripheral i.v. line in the left arm and urinary catheter were attached before induction of anesthesia.

Induction was performed with midazolam 0.05 mg/kg, sufentanil 0.2 μg /kg, and etomidate 0.3mg/kg, and tracheal intubation was facilitated with rocuronium 0.7mg/kg. After intubation, all the patients were mechanically ventilated [end-tidal carbon dioxide values of 35–45 mm Hg]. Anesthesia was maintained with continuous remifentanil (RenFu Co., Hubei, China) infusion (at 0.30 μg /kg /min) as an intraoperative analgesic, and desflurane (Baxter Co., Shanghai, China) as an initial 1.0 minimal alveolar concentration (MAC) and oxygen–air mixture (fraction of oxygen, 50%). The depth of anesthesia was adjusted during surgery by 1% stepwise titration of desflurane, based on targeting bispectral index (45–60) and hemodynamic changes: HR exceeding pre-induction values by 15% and mean arterial blood pressure (MAP) exceeding baseline values by 20% or <60 mm Hg for at least 1 min. Rocuronium (0.3 mg/kg)

was administered intermittently i.v. during anesthesia. If bradycardia (HR <45 beats/min) and continuous hypotension (MAP <60 mmHg) persisted, additional fluid infusion, atropine (0.5 mg), and phenylephrine (0.1 mg) were also administered. During skin suturing, desflurane and remifentanil were stopped, and tropisetron (2mg) was injected i.v. Residual neuromuscular block was antagonized by neostigmine 0.04 mg /kg and atropine 0.01 mg/kg when the tidal volume of spontaneous breathing exceeded 200 ml. When the bispectral index value reached 80, response to oral command was observed, followed by eye opening and spontaneous breathing rate exceeding 10 bpm, the patient was extubated and moved to the postanesthetic care unit (PACU) for recovery at least 1 h.

Patients were randomly divided into one of five groups, each of which received dexmedetomidine or nalmefene or placebo saline 10 min before the induction of anesthesia **as follow:** (i) Group R received 3ml normal saline; (ii) Group N received nalmefene (Tiantaishan Medicine Co., Chendu, China) 0.2μg /kg in bolus; (iii) Group D received continuous infusion of dexmedetomidine (Enhua Medicine Co., Jiasu, China) at 0.5 μg /kg/h for10min; (iv) Group DN received both nalmefene 0.1μg /kg and dexmedetomidine 0.25μg /kg/h; (v) Group S received 3ml normal saline. All patient assignments were guided by a computer-generated random number system and individually sealed envelope. Study medication were

provided by the hospital pharmacy and administrated by an anesthesiologist not involved in the intraoperative management and data collection. Patients were blinded to the group assignment. Primary and secondary outcomes were analyzed and documented by another anesthesiologist responsible for the data collection, but not directly involved in the treatment of the patients and was blinded to randomization.

Sedation scores were documented using the Ramsay scale (1=anxious and agitated or restless, or both; 2=cooperative, oriented, and tranquil; 3=responds to command only; 4=asleep, but has a brisk response to light tactile stimulus or a simple verbal command; 5=asleep, but arousable only by strong physical stimulus; and 6=asleep, unarousable) at 5, 10, 15, 30, and 60 min after arrival at the PACU.

Pain levels were evaluated on an 11-point numerical rating scale (NRS): 0=no pain; and 10=worst pain imaginable. The NRS score for pain at rest and after movement was assessed at 1, 3, 6, 12, and 24 h after surgery. Movement was specified as active mobilization and weight bearing while escaping any harm.

The baseline mechanical nociceptive threshold was assessed using 20 hand-held Von Frey filaments (North Coast Medical Inc., Gilroy, CA, USA) in an area 2–5 cm around the incision at 12 predefined positions in all four directions and on the dominant inner forearm according to the

published method[1,17,18]. Every position was measured three times at intervals of 15 s, then a mean value was calculated for statistical analysis. The mechanical hyperalgesia threshold was defined as the smallest force (in grams) necessary to bend a Von Frey filament that was detected as painful by the patient. The test was performed at 24 h preoperation and postoperation. The normalized area of hyperalgesia around the incision was measured at 24 h after surgery according to the previous published method. [17]

First postoperative pain (NRS>4) was primarily managed by sufentanil titration, which was administered in 3 μg doses at intervals of 3 min until NRS <4. However, sufentanil titration was discontinued if the Ramsay score was >3, peripheral oxygen saturation decreased <92%, or breathing rate was <10 bpm. The time and total dose of first postoperative sufentanil were documented in the PACU. Furthermore, each patient was administered analgesics using a PCA pump containing sufentanil (100 μg) diluted by normal saline to a total volume of 100 ml after discharge from the PACU. The device was set to deliver a basal infusion of 2 ml/h and bolus doses of 0.5 ml with a 15min lockout period. Sufentanil comsumption was recorded at 1, 3, 6, 12 and 24 h after sugery. The incidence of postoperative side-effects was monitored during the 24 h after surgery.