Low Concentration of Dezocine in Combination With Morphine Enhance the Postoperative Analgesia for Thoracotomy

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Objective: When morphine and dezocine are mixed together, the clinical interactions with analgesic effects and adverse events remain unknown. The authors aimed to investigate the efficacy of low concentrations of dezocine in combination with morphine for postoperative pain.

Design: A prospective, randomized, double-blinded clinical trial.

Setting: Cancer Institute and Hospital, National Cancer Center, China.

Participants: Sixty patients undergoing thoracotomy were randomized into 3 groups to investigate the analgesic efficacy of different ratios of morphine and dezocine.

Interventions: The morphine group (Group M) received morphine (1 mg/mL) alone for patient-controlled analgesia (PCA); the morphine + dezocine 1 group (Group MD1) received morphine (1 mg/mL) combined with dezocine (0.05 mg/mL) at a ratio of 20:1 for PCA; the morphine + dezocine 2 group (Group MD2) received morphine (1 mg/mL) combined with dezocine (0.1 mg/mL) at a ratio

of 10:1 for PCA. Cumulative morphine consumption, verbal rating scores (VRS), and adverse events were evaluated throughout a 48-hour postoperative period.

Measurements and Main Results: Cumulative morphine requirements were (1) statistically higher in Group M than in Group MD2 at 24 and 48 hours after surgery and (2) statistically higher in Group M than Group MD1 at 48 hours after surgery. Postoperative VRS for evaluating pain were similar among the 3 groups. The incidence of postoperative nausea and pruritus was statistically higher in Group M than in Groups MD1 and MD2. The incidence of dizziness was not significantly different among groups.

Conclusions: The combination of morphine and dezocine at the concentrations [morphine (mg/mL)]/[dezocine (mg/mL]] of 1/0.05 (ratio 20:1) and 1/0.1 (ratio 10:1) may enhance postoperative analgesia after thoracotomy.

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IN CLINICAL SETTINGS, COMBINED or alternating use of different analgesic drugs for the treatment of pain increasingly has attracted the attention of clinicians and researchers.[1,2] In recent years, studies have shown that morphine combined with small doses of opioid-receptor agonists or antagonists exhibit good analgesic effects and few adverse reactions.[3,4] Opioid-receptor agonist/antagonists, including dezocine, pentazocine, and buprenorphine, are a class of opioid drugs widely used for clinical anesthesia and pain therapy. However, there long has been controversy over the clinical effect of the combination of opioid-receptor agonists/antagonists with other opioid-receptor agonists.[5,6] Generally, opioid-receptor agonists/antagonists may weaken the analgesic effect of morphine.[6] However, studies have found that opioid-receptor agonists/antagonists combined with morphine can have synergistic analgesic effects.[7,8] In addition, opioid-receptor agonists/antagonists in combination with pure opioid agonists may reduce the incidence of opioid-related side effects.[9,10]

Dezocine, as a representative opioid-receptor agonist/antagonist, has been used widely in clinical practice. Some studies found that dezocine was a promising and safe analgesic that was slightly more potent than morphine for the relief of

perioperative pain.[11–13] Dezocine (10 mg) reportedly appeared equipotent with morphine (10 mg).[14] The authors invariably treated dezocine as a κ-opioid-receptor (KOR) agonist and an MOR agonist/antagonist. However, recent studies have demonstrated that dezocine was a KOR antagonist as well as a partial MOR antagonist.[15,16] Therefore, it is undetermined whether there are some similarities between dezocine and pure opioid-receptor antagonists. One study suggested that dezocine acted as an opioid antagonist, precipitating a withdrawal syndrome only slightly different from that produced by naloxone. At the same time, the antagonistic effects of dezocine were not directly dose-related but peaked at intermediate doses and declined at higher doses, which resulted in a bell-shaped dose-response curve for its antagonist effects.[17] Numerous studies have confirmed that low doses of naloxone can enhance the analgesic potency of opioid analgesics and reduce opioid tolerance.[18–20] Consequently, the authors hypothesized that dezocine might have an antinociceptive strengthening effect when combined with morphine at certain low doses or concentrations, similar to naloxone. This study aimed to investigate the combination efficacy of low-dose dezocine and morphine for postoperative thoracotomy analgesia; the consumption of morphine was the primary endpoint, and adverse effects were the secondary endpoint, with the hope of providing a reference for rational clinical use of opioids.

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METHODS

This study was approved by the Human Ethics Committee of the National Cancer Center and registered with http://www.chictr.org/cn/ (Ref.: ChiCTR-TRC-14004661). The work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). Written informed consent was obtained from patients before randomization.

Sixty ASA I–II patients who selected patient-controlled intravenous analgesia (PCIA) for postoperative pain management and understood the use of the patient-controlled analgesia (PCA) technique, aged between 20 and 65 years and scheduled for elective lobectomy under thoracotomy, were enrolled in the study. The following exclusion criteria were applied: (1) history of chronic pain, drug or alcohol abuse or psychiatric disease; (2) current regular use of analgesics; (3) renal, hepatic, or cardiovascular dysfunction; (4) allergy to any study drug; and (5) body mass index ≥ 30 kg/m^2 or ≤ 19 kg/m^2.

Included patients were assigned randomly to 1 of 3 treatment groups based on the following different postoperative PICA strategies: (1) Group M: morphine (1 mg/mL); (2) Group MD1: morphine (1 mg/mL) + dezocine (0.05 mg/mL); and (3) Group MD2: morphine (1 mg/mL) + dezocine (0.1 mg/mL). Randomization was based on computer-generated random numbers maintained in sequentially numbered envelopes. Before surgery, patients were instructed on the 0-10 verbal rating scores (VRS) of pain and the use of PCA. On the VRS scale, a value of 0 represented no pain and 10 represented the worst pain imaginable. Pharmacy-prepared 100-mL PICA infusions were given to the responsible anesthesiologists. Neither the anesthesiologists nor the patients were cognizant of the patient's group assignment (double-blind design). The observer who performed postoperative evaluations was unaware of the treatment groups.

Just before induction of anesthesia, all patients were given intravenous (IV) midazolam, 0.04 mg/kg. Electrocardiogram, pulse oxygen saturation (SpO2), noninvasive arterial pressure, end-tidal CO_2 (EtCO$_2$), and end-tidal concentration of sevoflurane were applied and measured every 5 minutes throughout the surgery. General anesthesia was induced by combined use of 0.3 µg/kg of sulfentanil and 1.5-2 mg/kg of propofol. Rocuronium, 0.6 mg/kg, was given to facilitate endotracheal intubation and maintained with 0.2 mg/kg every 45 minutes. Mechanical ventilation was maintained with an 8-mL/kg tidal volume during double-lung ventilation and 6-mL/kg tidal volume during one-lung ventilation. Ventilation frequency was adjusted to maintain EtCO$_2$ between 4.6-5.3 kPa. Maintenance of anesthesia was performed using sevoflurane, which was regulated at 0.6 to 1.4 age-adjusted minimal alveolar concentration to maintain a Bispectral Index between 35 and 45. When adequate and proper anesthesia was maintained, an increase or decrease in mean arterial pressure of more than 20% of the preanesthetic baseline level was corrected using IV nicardipine (0.2-0.4 mg) or ephedrine (4-8 mg). Bradycardia [heart rate <50 beats/min] was treated with IV atropine at 0.5 mg. Tachycardia (heart rate 110 beats/min) was treated with IV esmolol at 10 mg.

When the surgery was completed, sevoflurane was turned off and the oxygen flow rate was converted to 8 L/min. When the patients opened their eyes, neuromuscular blockade was reversed with IV administration of neostigmine (0.04 mg/kg) and atropine (0.02 mg/kg). Tracheal extubation was performed with a Bispectral Index value of >80 when the patients achieved a regular breathing pattern and were able to follow the verbal command to squeeze the anesthesiologist's hand.

Patients were transferred to the post-anesthesia care unit after extubation and stayed for 1 hour. If the VRS > 3, 3 mg of morphine was titrated IV every 5 minutes until VRS ≤ 3. Titration was stopped when achieving sedation scores >3 or

breathing frequency <12 times/min. After being transferred back to the general ward, all patients were observed for 48 hours after surgery. They were allowed to use the PCA machine by themselves. The setting for PCIA was the same in all patients (total volume: 100 mL; bolus: 1 mL; lock time: 5 minutes, with no background infusion). VRS at rest, analgesic requirement and side effects such as nausea, vomiting, pruritus, and dizziness were assessed based on the complaints of patients and recorded during the first 48 hours after surgery. A rescue antiemetic (metoclopramide, 10 mg oral) was given upon patient request. All data were collected by the investigators at 1, 6, 24, and 48 hours after surgery.

Treatment failures were considered to be insufficient analgesia, intolerable nausea and vomiting, and pruritus. Insufficient analgesia was defined as VRS > 6 at rest. As an adjunctive analgesic, IV meperidine, 50 mg, would be administered for insufficient analgesia. Intolerable nausea and vomiting were defined as persistent nausea or vomiting episodes that required more than 3 administrations of antiemetics (metoclopramide). Intolerable pruritus was defined as persistent pruritus requiring more than 3 administrations of antipruritics (diphenhydramine). In any of these situations, the patient could decide to continue with the PCIA or receive nonsteroidal anti-inflammatory drugs (flurbiprofen) for postoperative pain management.

Statistical Analysis

The sample size of 20 in each group was chosen to give power to detect a 20% difference in a 48-hour PCIA requirement among the groups, with an alpha level of 0.05 (two-tailed) and beta level of 0.1 (90% power). Based on the results of a preliminary trial, the authors assumed a 48-hour PCIA requirement of 54.7 (18.4) mL. Parametric data are presented as the mean (SD). One-way analysis of variance was conducted to examine differences among the 3 groups with respect to parametric variables. The Bonferroni test was used for post hoc comparisons. A p value of 0.05 was considered significant. The Kruskal-Wallis test was used to determine differences among the three groups with respect to nonparametric variables. If a significant difference was detected using the Kruskal-Wallis test, the Mann-Whitney U-test was used for intergroup comparison. The incidences of nausea, vomiting, pruritus, and use of antiemetics were analyzed using X^2 tests or Fisher's exact test. A p value of 0.05 was considered significant.

Table 1. Patients' Characteristics

	Group M (n = 19)	Group MD1 (n = 19)	Group MD2 (n = 19)	p Value
Age (yr)	54 (8)	53 (8)	52 (9)	0.808
Gender (M/F)	10/9	10/9	6/13	0.323
Weight (kg)	61 (9)	60 (10)	59 (9)	0.685
Height (cm)	165 (6)	162 (8)	161 (6)	0.163
ASA I/II	8/11	7/12	9/10	0.806
Duration of surgery (min)	162 (39)	155 (44)	158 (39)	0.849
Duration of anesthesia (min)	181 (38)	177 (42)	180 (36)	0.941
Sufentanil (µg)	39 (13)	35 (10)	36 (11)	0.452

NOTE: Data are mean (SD), or number of patients.

Abbreviations: ASA, American Society of Anesthesiologists; F, female; M, male; SD, standard deviation.