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Which has the least immunity depression during postoperative analgesia—morphine, tramadol, or tramadol with lornoxicam?

Z.Y. Wang [a], C.Q. Wang [a], J.J. Yang [b], J. Sun [a], Y.H. Huang [a], Q.F. Tang [c], Y.N. Qian [a,*]

[a] Department of Anesthesiology, First Affiliated Hospital of Nanjing Medical University, Nanjing, 210029, PR China
[b] Department of Anesthesiology, Jinling Hospital, School of Medicine, Nanjing University, Nanjing, PR China
[c] Department of Anesthesiology, Affiliated Suzhou Hospital of Nanjing Medical University, Suzhou, PR China

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Abstract

Background: Analgesics are commonly used to provide pain relief after surgery. These drugs produce some extended depression of immunity. A prospective randomized controlled trial was designed to observe expressions of T-lymphocyte subsets ($CD3^+$, $CD3^+CD4^+$ and $CD3^+CD8^+$), natural-killer cells ($CD3^-CD16^+CD56^+$), and activated T-lymphocytes ($CD3^+CD25^+$) of patients undergoing gastric cancer surgeries and receiving patient-controlled intravenous analgesia (PCIA).

Methods: Forty-five patients undergoing elective gastric cancer surgeries under general anesthesia were randomly allocated into 3 groups. Group I received PCIA using morphine after surgery, group II using tramadol, and group III using tramadol with lornoxicam. The analgesic efficacy was evaluated by visual analog scale (VAS) and Bruggrmann comfort scale (BCS). Expressions of $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD3^-CD16^+CD56^+$, and $CD3^+CD25^+$ were measured as percentages of total lymphocytes by flow cytometer at 5 time points.

Results: There was no significant difference in analgesic efficacy and the baselines of $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD3^-CD16^+CD56^+$, and $CD3^+CD25^+$ in all groups. Compared with the baseline, $CD3^+CD8^+$ had no changes in all groups at any time point. Ninety minutes after incision, $CD3^+$, $CD3^+CD4^+$, $CD3^-CD16^+CD56^+$, and $CD3^+CD25^+$ were lower in all groups ($P<0.05$). 24 h after surgery, $CD3^+$, $CD3^+CD4^+$, $CD3^-CD16^+CD56^+$, and $CD3^+CD25^+$ were lower in group I and group II ($P<0.05$); meanwhile $CD3^+$, $CD3^+CD4^+$, and $CD3^+CD25^+$ returned to the baseline but $CD3^-CD16^+CD56^+$ was still low ($P<0.05$) in group III. 48 h after surgery, $CD3^+$, $CD3^+CD4^+$, $CD3^-CD16^+CD56^+$, and $CD3^+CD25^+$ returned to the baseline in group II and group III, but not in group I ($P<0.05$). 72 h after surgery, $CD3^+$, $CD3^+CD4^+$, $CD3^+CD4^+/CD3^+CD8^+$ returned to the baseline, but $CD3^+CD25^+$ and $CD3^-CD16^+CD56^+$ were still low in group I ($P<0.05$).

Conclusion: PCIA using lornoxicam with tramadol has the same good analgesic efficacy and less immunity depression than PCIA using morphine or tramadol.

Keywords: Patient-controlled intravenous analgesia; Lornoxicam; Tramadol; Morphine; $CD3^+$; $CD3^+CD4^+$; $CD3^+CD8^+$; $CD3^-CD16^+CD56^+$; $CD3^+CD25^+$

1. Introduction

With the rapid progress in immunology, the relationship between immunity and homeostasis has been of great interest to researchers. Many studies have revealed that patients would suffer from immunity depression, especially cellular immunity depression, after sever traumas and/or major surgeries [1–3]. Injuries and stresses caused by surgeries are the primary reasons of immunity depression; however, the immune effect of anesthesia and pain relief treatment should also be considered [4–6].

Many analgesics, e.g. morphine and tramadol, could provide a good analgesic efficacy, but they also have some side effects including immune depression [7–9]. Therefore, many authors advocate a multi-analgesia mode that could increase the analgesic effects and decrease side effects.

* Corresponding author. Fax: +86 25 84806839.
E-mail address: yanning_qian@yahoo.com.cn (Y.N. Qian).

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Lornoxicam, a balanced type non-steroidal anti-inflammatory drug, but mainly inhibiting cyclooxygenase 2, is widely used in postoperative analgesia for their analgesic and anti-inflammatory action with fewer side effects [10,11]. But in large doses, its effects on coagulation system, gastrointestinal mucosa, renal function and even cardiovascular system should be considered [12]; furthermore it is not clear about the immune effect of lornoxicam during postoperative analgesia.

T-lymphocytes and natural-killer cells are the important immune active cells in the peripheral blood circulation, whose expressions of surface antigen and some receptors is vital for the immune system. A trial was designed to compare the expressions of peripheral blood T lymphocyte subsets ($CD3^+$, $CD3^+CD4^+$and $CD3^+CD8^+$), NK cells ($CD3^-CD16^+CD56^+$), and activated T-lymphocytes ($CD3^+CD25^+$) in patients scheduled for gastric cancer surgeries under general anesthesia and receiving postoperative patient-controlled intravenous analgesia (PCIA) with different analgesics.

2. Materials and methods

Forty-five patients (ages 26–60 y) with American Society of Anesthesiologists (ASA) physical status I or II scheduled for gastric cancer surgeries under general anesthesia were enrolled in this trial. The Ethics Committee of Nanjing Medical University approved the study. Informed written consent was obtained from each patient.

All the patients did not receive radiotherapy, chemotherapy, immunodepressants, or blood transfusion before the surgery. They did not receive any long-acting medication that may influence the effect of lornoxicam including digoxin, furosemide, warfarin sodium, monoamine oxidase inhibitor, benzodiazepines and barbital. They also did not have a history of blood coagulation disorder, more than midrange anemia, peptic ulcer in within the prior 6 months or allergy to NASIDS. Patients who received intra-operative and postoperative therapies of corticosteroids or blood transfusion (blood loss > 800 ml) were also excluded.

2.1. Total intravenous anesthesia (TIVA)

Phenobarbital sodium 0.1 g and atropine 0.5 mg were intramuscular injected 30 min before anesthesia. Midazolam 0.1 mg/kg, fentanyl 3 μg/kg, and target controlled infusion (TCI) of propofol 3 μg/ml induced anesthesia, and vecuronium 0.15 mg/kg facilitated orotracheal intubation. Anesthesia was maintained with continuous infusion of vecuronium 0.055–0.065 mg/kg/h, TCI of propofol 3–3.5 μg/ml, and intermittent infusion of 2–3 μg/kg (total dose 6–8 μg/kg) according to the hemodynamic changes. All patients were mechanically ventilated to control the end tidal carbon-dioxide tension at 30–35 mm Hg.

2.2. PCIA

At the end of surgery, patients received intravenous ondansetron 8 mg and then PCIA performed by the electronic pump (Gasbi9300, Britain). Group I received PCIA using morphine (First Pharmacological Company of Shenyang, China) 1 mg/kg with ondansetron 16 mg diluted to 100 ml, group II using tramadol (Grunenthal, Germany) 13 mg/kg with ondansetron 16 mg diluted to 100 ml, and group III using the same prescription of group II with additional intravenous injection of lornoxicam (Nycomed Australia) 8 mg before the anesthesia and 8 mg after the surgery. Group I received loading dosage morphine 0.1 mg/kg, and group II and group III received loading dosage tramadol 1.3 mg/kg. Then they all received PCIA: background infusion 0.5 ml/h, bolus 0.7 ml/h, and lockout time 6 min.

2.3. Evaluation of analgesic efficacy

Visual analog scale (VAS) includes: 0 (no pain and highly satisfactory), 1–2 (satisfactory), 3–5 (primary satisfactory), 6–7 (primary unsatisfactory), 8–9 (unsatisfactory), and 10 (the utmost pain and highly unsatisfactory). Bruggrmann comfort scale (BCS) includes: 0 (continuous pain), 1 (no pain without movement but serious pain when deep breathe or cough), 2 (no pain without movement but mild pain when deep breathe or cough), 3 (no pain even in deep breath) and 4 (no pain in cough). All patients evaluated analgesic efficacy through VAS and BCS 4, 24, 48, and 72 h after the surgeries in the trial.

2.4. Evaluation of side effects

Side effects including urinary retention, drowsiness, and nausea or vomiting were evaluated at the end of PCIA. If the patients experienced urinary retention, it was treated with urethral catheterization. If they experienced drowsiness the PCA background was decreased by infusion of 20% to 0.4 ml. If they experienced nausea or vomiting, we injected ondansetron 8 mg intravenously.

2.5. Evaluation of immunity

Expressions of $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD3^-CD16^+CD56^+$, and $CD3^+CD25^+$ in blood samples were measured as percentages of total lymphocytes by flow cytometer (FACS, BD, United States) as follow steps at five time points: (1) obtaining 3 ml blood samples of each patient from non-infused median cubital vein at 5 time points: before anesthesia, 90 min after incision, 24, 48 and 72 h after surgery and keeping it in an EDTA-anticoagulation tube (Becton-Dickinson, Heidelberg, Germany); (2) incubating 50 μl of the blood with 10 μl $CD3^+$, $CD3^+CD4^+$, $CD3^+CD8^+$, $CD3^+CD16^+CD56^+$ or $CD3^+CD25^+$ monoclonal antibodies (BD, United States) at 25 °C for 30 min; (3) lysing erythrocytes