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Research Paper

Preincisional and postoperative epidural morphine, ropivacaine, ketamine, and naloxone treatment for postoperative pain management in upper abdominal surgery

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ABSTRACT

Objective(s): Previous studies have shown that preincisional epidural morphine, bupivacaine, and ketamine combined with epidural anesthesia (EA) and general anesthesia (GA) provided pre-emptive analgesia for upper abdominal surgery. Recent studies reported that ultralow-dose naloxone enhanced the antinociceptive effect of morphine in rats. This study investigated the benefits of preincisional and postoperative epidural morphine + ropivacaine + ketamine + naloxone (M + R + K + N) treatment for achieving postoperative pain relief in upper abdominal surgery.

Methods: Eighty American Society of Anesthesiology I–II patients scheduled for major upper abdominal surgery were allocated to four groups in a randomized, single-blinded study. All patients received combined GA and EA with a continuous epidural infusion of 2% lidocaine (6–8 mL/h) 30 minutes after pain regimen. After GA induction, in Group I, an epidural pain control regimen (total 10 mL) was administered using 1% lidocaine (8 mL) + morphine (2 mg) + ropivacaine (20 mg; M + R); in Group II, 1% lidocaine 8 (mL) + morphine (2 mg) + ropivacaine (20 mg) + ketamine (20 mg; M + R + K); in Group III, 1% lidocaine (8 mL) + morphine (2 mg) + ropivacaine (20 mg) + naloxone (2 μg; M + R + N); and in Group IV, 1% lidocaine (8 mL) + morphine (2 mg) + ropivacaine (20 mg) + ketamine (20 mg) + naloxone (2 μg; M + R + K + N), respectively. All patients received patient-controlled epidural analgesia (PCEA) with different pain regimens to control subsequent postoperative pain for 3 days following surgery. During the 3-day period following surgery, PCEA consumption (mL), numerical rating scale (NRS) score while cough/moving, and analgesic-related adverse effects were recorded.

Results: Total PCEA consumption for the 3-day observation period was 161.5 ± 17.8 mL, 103.2 ± 21.7 mL, 152.4 ± 25.6 mL, and 74.1 ± 16.9 mL for Groups I, II, III, and IV, respectively. ($p < 0.05$). The cough/moving NRS scores were significantly lower in Group IV patients than Groups I and III patients at 4 hours, 12 hours, and on Days 1 and 2 following surgery except for Group II ($p < 0.05$).

Conclusion: Preincisional and postoperative epidural M + R + K + N treatment provides an ideal postoperative pain management than preincisional and postoperative epidural M + R, M + R + K, and M + R + N treatments in upper abdominal surgery.

1. Introduction

Tissue damage during surgery generates ongoing sensory signals and affects central nervous system function, while the response of nociceptive neurons in the spinal cord further complicates postoperative pain management. Inadequately treated pain may result in detrimental physiological, psychological, economic,

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and social adverse effects. Early studies proposed that adequate prevention of nociceptive neuron sensitization in the spinal cord could significantly enhance postoperative pain relief, thereby resulting in a lower analgesic requirement than administering analgesia after surgery.[1–3]

Upper abdominal surgeries lead to severe abdominal pain, which if treated inadequately, can cause shallow breathing, atelectasis, retention of secretions, and patients to refuse physiotherapy. This increases the incidence of postoperative morbidity and leads to delayed recovery.[4] Postoperative epidural analgesia for major upper abdominal surgery provides significant benefits, including superior analgesia and reduced pulmonary dysfunction.[5] The existence of opioid receptors in the spinal cord permits the use of epidural morphine (National Bureau of Controlled Drugs, Department of Health, R.O.C.) to control various pain conditions.[6,7] When ropivacaine (Nang Kuang Pharmaceutical CO., LTD, R.O.C.) is combined with morphine, the duration and efficacy of analgesia are greater.[8] The *N*-methyl-D-aspartate (NMDA) antagonist ketamine (United Biomedical, Inc., Asia) not only attenuates peripheral afferent noxious stimuli, but also prevents the central sensitization of spinal neurons.[9–11] Epidural administration of ketamine not only potentiated the analgesic effect of morphine,[12] but also provided a pre-emptive analgesic effect on patients who underwent total knee joint replacement.[2] Our previous study showed that preincisional epidural morphine, bupivacaine, and ketamine in combination with epidural anesthesia (EA) and general anesthesia (GA) provided pre-emptive analgesia for upper abdominal surgery.[13] Interestingly, recent studies have reported that ultralow-dose naloxone (Genovate Biotechnology CO., LTD, R.O.C.) enhanced the antinociceptive effect of morphine in rats.[14–16] In this study, the epidural analgesic effect of a four-drug pain regimen [morphine + ropivacaine + ketamine + naloxone (M + R + K + N)] was investigated on major upper abdominal surgery.

2. Methods

This study was approved by the Ethics Committee (TSGHIRB No: 517) of Tri-Service General Hospital, Taipei, Taiwan (Chairman, Professor Chih-Shung Wong) on December 23, 2005. All patients provided written informed consent before being enrolled.

From June 2006 to October 2007, 80 American Society of Anesthesiology I–II patients undergoing upper abdominal surgery with hepatic resection were selected for a randomized, single-blind experiment. Patients who had received opioids or nonsteroidal anti-inflammatory drugs within 1 week of surgery were excluded from participation. All the selected 80 patients were randomly divided into four groups using a random number table and they remained in the study for the entire observation period. One day before surgery, an epidural catheter (Smiths Medical Australasia Pty. Ltd., Australia) was inserted at T_8–T_{10} and advanced 5 cm into the epidural space. A test dose of 3 mL of 2% lidocaine (AstraZeneca, Sweden) containing epinephrine (5 μg/mL, China Chemical & Pharmaceutical Co., Ltd., R.O.C.) was also administered to rule out intrathecal or intravascular misplacement. Patients were also instructed in the use of the numerical rating scale (NRS; 0 = no pain, 10 = greatest pain) and the patient-controlled epidural analgesia (PCEA) device (Hospira Costa Rica Ltd., Costa Rica).

On the day of surgery, GA was induced with fentanyl (2 μg/kg, National Bureau of Controlled Drugs, Department of Health, R.O.C.), thiopental (3–5 mg/kg, Shinlin Sinseng Pharmaceutical Co., Ltd, R.O.C.), and succinylcholine (1.5 mg/kg, Shinlin Sinseng Pharmaceutical Co., Ltd, R.O.C.) and maintained with atracurium (Genovate Biotechnology CO., LTD, R.O.C.) and isoflurane (AESICA QUEENBOROUGH LIMITED, UK) in oxygen (0.5 L/min). Monitoring included pulse oximetry, electrocardiogram, end-tidal CO_2, anesthetic gases (5330 Agent Monitor, Ohmeda), noninvasive blood pressure, central venous pressure, and intra-arterial pressure. After GA induction, the epidural pain regimens (total 10 mL) were prescribed in each group as follows: Group I, an epidural pain control regimen was administered using 1% lidocaine (8 mL) + morphine (2 mg) + ropivacaine (20 mg; M + R); Group II, 1% lidocaine (8 mL) + morphine (2 mg) + ropivacaine (20 mg) + ketamine (20 mg; M + R + K); Group III, 1% lidocaine (8 mL) + morphine (2 mg) + ropivacaine (20 mg) + naloxone (2 μg; M + R + N); and Group IV, 1% lidocaine (8 mL) + morphine (2 mg) + ropivacaine (20 mg) + ketamine (20 mg) + naloxone (2 μg; M + R + K + N), respectively (Table 1). The EA with a continuous epidural infusion of 2% lidocaine (6–8 mL/h) 30 minutes after preincisional epidural pain regimen was prescribed. No additional intravenous opioids or ketamine was given during the operation. The level of anesthesia was considered adequate if the heart rate and arterial blood pressure remained within 20% of the preinduction values. Furthermore, isoflurane was adjusted to keep the auditory evoked potential index (AEP version 1.4, Danmeter, Odense, Denmark) between 15 and 25 during maintenance of anesthesia. All patients received different PCEA regimens according to different groups to control subsequent postoperative pain for 3 days following surgery. PCEA morphine in 0.1% ropivacaine (0.05 mg/mL, 15-minute lockout interval, and no 4-hour limit) was also available as needed for any breakthrough pain. The PCEA solution contents and the setting of bolus amount in each group are shown in Table 1.

Patient response was observed for 3 days following the surgery. Total PCEA consumption (mL) was recorded for each patient. Patients provided NRS while resting and coughing/moving. Analgesic-associated adverse effects (such as nausea, vomiting, pruritus, urinary retention, and respiratory depression) were recorded by both patients and the nurse in-charge every 24 hours. Respiratory depression was defined as a respiratory rate less than 10 breaths/min. Pruritus was treated with chlorpheniramine maleate (10 mg, intravenously, Sintong Taiwan Biotech CO., LTD, R.O.C.), and metoclopramide (10 mg, intravenously, SANOFI WINTHROP INDUSTRIE, France) was given for nausea or vomiting.

Patient characteristics were expressed as means ± standard deviation, number, or median with range (Table 2). Postoperative pain evaluation values were not normally distributed and median values are presented. The four groups were then compared using analysis of variance to determine whether the M + R + K + N procedure had a beneficial effect on postoperative pain relief. Data on PCEA consumptions and NRS among groups in the following periods were analyzed for each measure using analysis of variance with repeated measures. The Bonferroni procedure was conducted for multiple comparisons between groups in different time points. The level of statistical significance was determined as $p < 0.05$. Statistical analysis was performed using SigmaStat 3.5 for Windows.

3. Results

The demographic characteristics were comparable in the four groups (Table 2). Total PCEA consumption for the 3-day observation period were 161.5 ± 17.8 mL, 103.2 ± 21.7 mL, 152.4 ± 25.6 mL, and 74.1 ± 16.9 mL for Groups I, II, III, and IV, respectively ($p < 0.05$, Figure 1A). Furthermore, total PCEA consumption for the 3-day observation period was significantly lower in Group II than Groups I and III following surgery ($p < 0.05$, Figure 1A). Data on PCEA consumptions among groups in each following time point were shown as mean ± standard deviation (Figure 1B). Group IV patients had significantly lower PCEA consumption than Groups I, II, and III at 4 hours and on Day 1 following surgery ($p < 0.05$, Figure 1B). Group II and IV patients had significantly lower PCEA consumption than Groups I and III at 12 hours and on Days 2 and 3

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