学 位 論 文 の 要 旨

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学　位　論　文　名　Prophylactic Pentazocine Reduces the Incidence of Pruritus After Cesarean Delivery Under Spinal Anesthesia With Opioids: A Prospective Randomized Clinical Trial

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論 文 内 容 の 要 旨

INTRODUCTION

Intrathecal morphine provides reliable and long-lasting postoperative analgesia for cesarean delivery. However, the use of intrathecal opioids is often associated with side effects such as pruritus and postoperative nausea and vomiting. The incidence of pruritus after cesarean delivery under spinal anesthesia with opioids is high, ranging from 50% to 100%. Pruritus is difficult to prevent; however, pentazocine has been shown to be an effective treatment. Pentazocine are used as κ-opioid receptor (KOR) agonists in clinical settings. There is experimental evidence suggesting that activation of selective KOR agonists attenuates opioid-induced pruritus in animals. Despite this, the prophylactic effect of pentazocine on pruritus has not been defined. This randomized double-blind trial aimed to evaluate the effect of intraoperative intravenous (IV) pentazocine on the incidence of opioid-induced pruritus within the first 24 hours after administration of neuraxial opioids.

MATERIALS AND METHODS

The study protocol was approved by the Research Ethics Committee of National Health Organization Hamada Medical Center. We obtained institutional review board approval and written informed consent from the 122 patients (American Society of Anesthesiologists [ASA] physical status II; aged 20–40 years) scheduled for elective cesarean delivery who were included in this study. Exclusion criteria were as follows: allergy to pentazocine, morphine, fentanyl, bupivacaine, or levobupivacaine; preexisting pruritus; preeclampsia; diabetes mellitus; or

neurological disease. All patients received combined spinal and epidural anesthesia. Epidural catheterization was performed using an 18-gauge epidural needle and a 19-gauge epidural catheter at the Th11–12 or Th12–L1 level. Spinal anesthesia was performed at the L3–4 level with 10 mg of 0.5% hyperbaric bupivacaine, 10 μg of fentanyl, and 100 μg of morphine. After delivery of the baby and placenta, the parturient women were randomized to intravenously receive 15 mg (1 mL) of pentazocine or 1 mL of saline. All women received postoperative analgesia with the epidural infusion of 0.15% levobupivacaine. The infusion rate was 4 mL/h with 3-mL patient-controlled bolus administration. the primary outcome was the incidence of pruritus within 24 hours. We also determined the time until the first postoperative itching presented. Other variables included the severity of pruritus, the pain score, and other adverse effects and complications. The severity of pruritus, pain score, and other adverse effects were evaluated at just after arrival on the ward and 3, 6, 12, and 24 hours after intrathecal administration of opioids.

Statistical analysis was performed using the open source statistical software R version 3.1.2. The incidence of pruritus within 24 hours was compared by using the Fisher exact test. The time from intrathecal administration of opioids until first complaint of postoperative itching was analyzed using time to event analysis by the Kaplan-Meier method and log rank test. Secondary outcomes, including the severity of pruritus, postoperative nausea and vomiting (PONV), and the number of patients with more than a moderate degree of pruritus, were compared using the Fisher exact test. The pain score at each time point was examined by 2-way repeated-measure analysis of variance. Continuous data were analyzed by using Student t test. $P < .05$ was considered significant.

RESULTS AND DISCUSSION

A total of 119 women completed the study. data were collected from 58 patients in the pentazocine group and 61 patients in the saline group. IV pentazocine prolonged the median time until the first report of postoperative itching from 392 minutes to 1460 minutes after intrathecal opioid administration ($P = .003$). IV pentazocine reduced the overall incidence of pruritus within the first 24 hours compared to IV saline, with an estimated relative risk of 69% (95% confidence interval [CI], 52%, 90%; $P = .007$). IV pentazocine also reduced the number of patients with more than a moderate degree of pruritus, with an estimated relative risk of 9.6% (95% CI, 2, 54; $P = .004$) The incidence of PONV was not significantly different. There were no significant differences in postoperative Numerical Rating Scale (NRS) scores.

Our results show that a single 15-mg dose of IV pentazocine reduced the incidence of pruritus from 77% to 53%, attenuated the severity of pruritus, and prolonged the median time until the first report of postoperative itching. Recent basic research suggested that opioid-induced pruritus occurs via the activation of gastrin-releasing peptides receptor (GRPR) signaling by μ-opioid receptor (MOR) isoform MOR1D heterodimerzation in the dorsal horn. Moreover, an endogenous opioid peptide dynorphin possessing a strong affinity for KOR may inhibit

pathologic pruritus via the B5-I neurons in the dorsal horn. Pentazocine is widely used as an analgesic in Japan. In a randomized trial that compared pentazocine with ondansetron for the treatment of morphine-induced pruritus, pentazocine was almost uniformly effective. Our study confirmed the effectiveness of pentazocine for the prophylaxis of morphine-induced pruritus. There was a limitation in this study design. We did not study the dose-response effect of pentazocine or the optimal timing of administration. The incidence of pruritus was still more than 50% in the pentazocine group. Additional studies are needed to optimize the dosage and timing of pentazocine administration.

CONCLUSIONS

A single 15-mg dose of IV pentazocine after delivery can reduce both the incidence and severity of pruritus in women who have received subarachnoid opioids during cesarean delivery.