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Case Report

The overreaction to intraoperative nociception associated with chemotherapy-induced peripheral neuropathy: case scenarios

Juan Gu[1,2], Chao Yu[1,2], Wenqin Zhou[1,2], Dong Luo[1,2]

[1]Department of Anesthesiology, West China Second University Hospital, Sichuan University, Chengdu, China; [2]Key Laboratory of Birth Defects and Related Diseases of Woman and Children, Sichuan University, Ministry of Education, Chengdu, China

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Abstract: Introduction: some patients receive many cycles of chemotherapy before undergoing surgery. Chemotherapy-induced peripheral neuropathy is a common adverse reaction to some chemotherapy agents. We report two cases of overreaction to intraoperative nociception correlated with chemotherapy-induced peripheral neuropathy. Case presentation: Two patients, approximately 50 years old, were scheduled for cytoreductive surgery. They had received three cycles of chemotherapy with cisplatin and paclitaxel. The patients' heart rates and blood pressures increased significantly throughout their operations. This situation could not be alleviated by deepening anesthesia or administering additional analgesics. However, it was partly improved by the intravenous infusion of lidocaine in one patient. In the postoperative interview, we found that the patients exhibited some symptoms of chemotherapy-induced peripheral neuropathy. Conclusions: Chemotherapy-induced neuropathy should be recognized by anesthesiologists, as it may lead to overreaction to intraoperative nociception during surgery, which is not easily controlled by opioid analgesics. Intravenous infusion of lidocaine may be a proper choice to administer in some situations. Therefore, it is advisable to administrate pregabalin or gabapentin preoperatively and combined intrathecal anesthesia with general anesthesia during operations in patients with chemotherapy-induced peripheral neuropathy.

Keywords: Chemotherapy induced peripheral neuropathy, pain, anesthesia, chemotherapy

Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a familiar side effect related to drug treatment. The incidence of CIPN is dependent on the drug used for chemotherapy and the duration of treatment. The overall incidence of CIPN is approximately 48%, but the incidence of CIPN is almost 68.1% within a month after chemotherapy [1]. Pain and paresthesia are the most common symptoms of CIPN, but dyskinesia and autonomic nervous system dysfunction are predominantly presented in some cases [2, 3]. A portion of patients with various types of malignant tumors are scheduled to undergo cancer surgery after receiving chemotherapy. We questioned whether there are characteristics specific to the intraoperative anesthetic management of patients with CIPN, which has been less considered by anesthesiologists. We present two cases of overreaction to intraoperative nociception that were associated with CIPN.

Cases presentation

A 46-year-old female patient, 61 kg, was scheduled for cytoreductive surgery. She was diagnosed with ovarian poorly differentiated adenocarcinoma IIIc by laparoscopy three months prior to surgery. To induce the optimal condition for surgery, she had received three cycles of chemotherapy: 240 mg paclitaxel and 500 mg carboplatin were intravenously infused in the first and second cycles of chemotherapy. The third cycle of chemotherapy was administered 26 days prior to surgery during which 210 mg paclitaxel and 90 mg cisplatin were intravenously infused, and 90 mg cisplatin was intraperitoneally infused. She had not previously

taken any opioids. There was no abnormal finding in the regular preoperative examination except for hyperglycemia (8.0 mmol/L). She had been diagnosed with diabetes for 3 months, which was controlled via her diet. When she arrived at the surgical room, her blood pressure was 124/70 mmHg, her heart rate was 82 beats/min, and oxygen saturation was 98%. General anesthesia was induced with 3 mg imidazole, 0.2 mg fentanyl, 100 mg propofol and 6 mg vecuronium. Anesthesia was maintained with 2% sevoflurane. Invasive blood pressure was monitored. An additional 0.2 mg fentanyl was injected intravenously before the incision. After the start of surgery, her blood pressure and heart rate persistently increased. Her blood pressure ranged from 130/90 mmHg to 160/100 mmHg, and her heart rate ranged from 120 beats per minute to 130 beats per minute. To enhance anesthesia, an additional 0.2 mg fentanyl was injected, and remifentanil was continually infused at a rate of 0.3 mg per hour. However, there was no significant change in blood pressure and heart rate. The inhalation concentration of sevoflurane was then increased to 4%. Five minutes later, her blood pressure decreased to 130/70 mmHg, but her heart rate was still approximately 120 beats per minute. Unfortunately, a bispectral index monitor was unavailable. One hour after the beginning of surgery, 2000 ml crystalloid solution had been infused, and urine output was 400 ml. The results of the blood-gas analysis indicated that there were no acid-base disturbances or electrolyte disorders. Her blood sugar concentration was 7.8 mmol/L. We suggested that the surgeons temporarily stop operating. Her heart rate then decreased to 80 beats per minute, and blood pressure decreased to 85/50 mmHg. When the surgeons operated again, her heart rate and blood pressure increased quickly. The heart rate and blood pressure of the patient fluctuated significantly following the activity of the surgeons, and alleviate these fluctuations with analgesics was difficult. We had to use esmolol to keep the heart rate and blood pressure essentially stable. Due to the difficulty in maintaining stable hemodynamics, the surgeons decided to terminate the operation without removing the lymph nodes. At the end of surgery, a total of 0.8 mg fentanyl and 1 mg remifentanil had been administered. The patient woke 30 minutes after surgery. We inquired about her medical history. Record of last hospitalization showed that chemotherapy induced neurotoxicity presented after her last chemotherapy treatment, and the main symptom was that normal walking could induce pain in the soles of her feet. The operation had lasted for three hours. Blood loss was 400 ml, the volume of infusion was 3500 ml, and urine output was 600 ml. The patient was discharged 5 days later and planned to continue chemotherapy. The next several chemotherapies also induce pain in the soles of her feet, and it relieved after she completed her chemotherapy.

Another 52-year-old female patient, 66 kg, was diagnosed with a pelvic malignant tumor two months prior to surgery. Because adenocarcinoma cells were found in her ascites, she was scheduled to undergo cytoreductive surgery after three rounds of chemotherapy. The patient received 240 mg paclitaxel and 90 mg cisplatin via intravenous infusion for the first and second cycles of chemotherapy. The third cycle of chemotherapy was carried out 20 days prior to surgery, and 210 mg paclitaxel and 100 mg cisplatin were intravenously infused. In the preoperative interview, she said that she had CIPN. She was sensitive to could touch, which could induce pain. Nerve conduction studies showed decreased sensory nerve conduction velocity in the limbs. She also had not previously taken any opioids. There was no obvious abnormality upon preoperative examination. Her blood pressure was 120/75 mmHg, heart rate was 82 beats/min, and oxygen saturation was 100% when she arrived at the surgical room. For general anesthesia induction, 3 mg imidazole, 20 μg sufentanyl, 100 mg propofol and 6 mg vecuronium were used, 3% sevoflurane and continuous infusion of remifentanil at a rate of 0.3 mg per hour were used for anesthesia maintenance. Invasive blood pressure was monitored. While the surgeon was doing intraperitoneal operation, her blood pressure increased to 170/100 mmHg, and her heart rate rose to 130 beats per minute. To deepen anesthesia, 10 μg sufentanil was intravenously injected. However, there was no marked change. Therefore, another 10 μg sufentanil was administered. Her heart rate remained increased throughout the operation and decreased upon cessation of operating. To attenuate the stress response to surgery, we infused lidocaine continuously at a rate of 2 mg/kg/h.

Five minutes later, her heart rate decreased to approximately 100 beats per minute, and her blood pressure was approximately 140/85 mmHg. The operation finished 5 hours later. Blood loss was 800 ml, the volume of infusion was 6500 ml, the volume of red blood cells was 300 ml, and urine output was 600 ml. The patient was discharged 6 days later and then resumed chemotherapy.

Discussion

CIPN is a side effect of some types of drugs that are used for chemotherapy, including platinum analogs, antitubulins, proteasome inhibitors, immunomodulatory agents, and some new biologics [3]. The chemotherapy agents used to treat the two patients in this report were cisplatin and carboplatin, which are platinum analogs, and paclitaxel, which is an antitubulin. The severity of CIPN depends on the chemotherapy agents, exposure duration, and individual sensitivity [4-6]. Patients who have medical comorbidities such as diabetes and vitamin B deficiencies or receive two or more neurotoxic drugs at the same time are more likely to develop CIPN [7]. In the patients in this report, administration of cisplatin and paclitaxel simultaneously increased the risk of having CIPN. In addition, diabetes predisposed the peripheral nerve of the first patient to CIPN.

Paranesthesia and pain are the most common symptoms of CIPN. The diagnosis of CIPN is based on complaints of the patient and examinations by a doctor. Questionnaires such as the Neurotoxicity questionnaire are the most widely used tools for assessing CIPN. However, these questionnaires are subjective, and obtaining consistency between the patient and the doctor is difficult [3]. Allodynia was the main symptom of the patients in this report characterized by sensitivity to walking or touching cold objects. During the surgery, there was an overreaction to intraoperative nociceptive stimuli in the pelvic region. Chemotherapy-induced neurotoxicity is systemic, the autonomic nerve in the pelvic region may be involved, although this is difficult to assess. The heart rate and blood pressure of the patients increased significantly during the surgical procedures. Such increases are typical results of light anesthesia and inadequate analgesia. However, the overreactions could not be alleviated by deepening anesthesia and administrating more opioid analgesics. Infusion of lidocaine partly eased the overreaction of the second patient, likely because lidocaine reduced the abnormal discharge of the neural system. In the past, lidocaine has been used to treat refractory pain induced by CIPN [8]. Whether infusion of lidocaine is an effective treatment for the overreaction to intraoperative nociception in patients with CIPN requires further investigation.

In the past, studies on the mechanism of CIPN have primarily focused on the peripheral nervous system. These studies showed that chemotherapy agents could induce degeneration of the mitochondria and dysfunction of ion channels in peripheral nerves [9-11]. However, more recent studies have found that chemotherapy agents not only injure the peripheral nervous system but also the central nervous system [12, 13]. Hyperalgesia could also be caused by central neuropathy [13]. Huang showed that there were increased responses of neurons in the spine within 1 hour after a single intraperitoneal dose of oxaliplatin [14]. In addition to CIPN, paclitaxel leads to acute nerve injury. The form of pain caused by acute nerve injury is usually described as myalgia or arthralgia, and it gradually subsides within a week [15]. The symptoms of the patients in this report were caused by CIPN rather than acute nerve injury because the date of surgery was more than 20 days later from their last chemotherapy. The American Society of Clinical Oncology suggests that clinicians use tricyclic antidepressants, pregabalin or gabapentin to treat the positive symptoms of CIPN [16]. Because hyperalgesia is a symptom of a neuropathological syndrome, nerve block therapy may be a reasonable choice. Intrathecal administration of morphine alone or bupivacaine and morphine in combination are recommended for the treatment of neuropathic pain [17]. For the patients in this report, we should have combined intrathecal anesthesia with general anesthesia to manage hyperalgesia during the operation because local anesthetics can decrease the abnormal discharges of neurons in the vertebral canal.

Conclusions

Chemotherapy-induced neuropathy should be recognized by anesthesiologists, as it may lead

to overreaction to intraoperative nociception. In addition, CIPN is not easily controlled by opioid. Intravenous infusion of lidocaine may be a proper choice to administer in some cases. The methods used to manage neuropathological syndromes may be effective. It is advisable to administer pregabalin or gabapentin preoperatively and combine intrathecal anesthesia with general anesthesia in operations of patients with CIPN.

Disclosure of conflict of interest

None.

Address correspondence to: Dong Luo, Department of Anesthesiology, West China Second University Hospital, Sichuan University, 20 Renmin Nan Road, Chengdu, Sichuan, 610041, China. Tel: +86-(028)85503753; Fax: +86-(028)85503753; E-mail: loveanesthesia@163.com

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