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Decreased pain tolerance before surgery and increased postoperative narcotic requirements in abstinent tobacco smokers

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HIGHLIGHTS

- Abstinent smokers exhibited lower pain thresholds before surgery.
- Abstinent smokers required higher quantity of postoperative morphine equivalent.
- Smokers have an increased risk of perioperative pain.

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ABSTRACT

Introduction: The clinical influence of smoking cessation on pain tolerance before surgery and postoperative pain perception is not fully understood. This clinical study investigated the effect of smoking cessation on pain threshold during the perioperative period in patients undergoing hepatic resection.

Methods: We enrolled 148 male patients (68 non-smokers and 80 abstinent smokers) who underwent hepatic resection and received postoperative patient-controlled intravenous analgesia. Patients were tested for preoperative pain thresholds in response to electrical stimuli. We recorded the cumulative amount of extra morphine equivalent required during the first 48 h after surgery. Pain intensity was evaluated at 1 h, 6 h, 24 h and 48 h after surgery using the visual analogue scale (VAS). Additionally, button-pressing consumption was recorded by a patient-controlled analgesia (PCA) pump.

Results: The groups did not differ with respect to baseline clinical characteristics. Compared with non-smokers, abstinent smokers exhibited lower pain thresholds before surgery and demanded a larger quantity of extra morphine equivalent during the first 48 h after surgery. Abstinent smokers also exhibited more severe postoperative pain than non-smokers. Postoperative complications, such as nausea, vomiting, dizziness, sedation, and respiratory depression, did not significantly differ between the two groups.

Conclusions: In this study, smokers deprived of cigarettes exhibited decreased pain tolerance before surgery and required a larger quantity of postoperative extra morphine equivalent than non-smokers. Health care providers must be aware of the potential for increased narcotic requirements in smokers.

1. Introduction

According to the 2015 Chinese Adults Tobacco Survey Report, approximately 27.7% of Chinese adults are current smokers, and approximately 57.1% non-smokers are exposed to second-hand smoke at home (Li, Ma, & Xi, 2016). Smoking cigarettes poses a number of relevant medical and social problems. In China, approximately 235,000 new cases of hepatocellular carcinoma occur each year, and liver resection or hepatic resection is widely accepted as a first-line surgical approach (Yang et al., 2011; Zhu, Huang, Liao, & Zeng, 2016). Analgesia plays a pivotal role in the management of patients undergoing open abdominal surgery. Therefore, an increased emphasis has been placed on postoperative pain management (Fawcett & Baldini, 2015). Patients cannot smoke while hospitalized. Accordingly, there is a pressing need to understand the correlation between smoking cessation and the increased risk of perioperative pain during hospitalization.

Smokers generally cannot smoke during hospitalization, which can induce nicotine withdrawal. The association between smoking

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cessation and postoperative pain is a priority for anaesthesiology research. A retrospective clinical-based review of postoperative pain medications administered to coronary artery bypass graft patients revealed that smokers who are not allowed to smoke during hospitalization might require more postoperative opiate analgesics than non-smokers during the first 48 h after surgery (Creekmore, Lugo, & Weiland, 2004). In a small prospective study, smokers consumed more opioids via the use of patient-controlled analgesia (PCA) pumps during the first 24 h after surgery than non-smokers (Steinmiller et al., 2012). In addition, a prospective observational study on 848 patients who underwent elective surgery under general anaesthesia found that male smokers required more morphine during the first 72 h after surgery than non-smokers and past-smokers (Chiang, Chia, Lin, & Chen, 2016).

However, previous clinical studies have not examined the relationship between smoking abstinence and the preoperative pain threshold. This relationship is important because preoperative sensitization to pain may already exist in the patient subgroup, and may be related to an increased risk of postoperative chronic pain (Kalso, 2013; Kampe et al., 2016). In addition, conventional methods of assessing exposure to tobacco smoke have intrinsic limitations. Self-reported smoking questionnaires are often inaccurate, and the misrepresentation rate ranges from 2% to 50% (Connor Gorber, Schofield-Hurwitz, Hardt, Levasseur, & Tremblay, 2009). Recently, nicotine and cotinine levels have become commonly regarded as reliable markers of recent nicotine exposure (Metz-Favre, Donnay, & de Blay, 2005). However, cotinine concentrations may remain stable in smokers over a longer term. Unfortunately, many studies have failed to accurately test nicotine and cotinine concentrations.

We enrolled 148 Chinese male patients (68 non-smokers and 80 abstinent smokers) who underwent hepatic resection in our hospital in this study. Salient variables, such as age, body mass index (BMI), tumour size, alcohol consumption, duration of surgery, and pre- and intra-operative medications were controlled. Patients were tested for their preoperative pain threshold in response to electrical stimuli. We recorded the cumulative amount of extra morphine equivalent required during the first 48 h after surgery. Additionally, pain intensity and PCA consumption were recorded at 1 h, 6 h, 24 h and 48 h after surgery. The study was specifically conducted to determine the relationship between smoking cessation and pain sensitivity during the perioperative period.

2. Material and methods

2.1. Patients

This study was approved by the Institutional Ethics Committee (Eastern Hepatobiliary Surgery Hospital, Shanghai, China) and was conducted from 1 May 2014 to 10 October 2015. We obtained informed consent from patients who were sufficiently competent to understand the recruiter's description of the trial. The study included 148 Chinese male patients who underwent hepatic resection under general anaesthesia in our hospital. All patients had an American Society of Anesthesiology (ASA) physical status of I or II. Patients were excluded if they met the following criteria: age > 70 yrs. or < 30 yrs.; body mass index (BMI) > 30 kg/m^2; hypertension, diabetes mellitus, or cardiovascular diseases; hepatic encephalopathy or serious renal dysfunction; history of acute or chronic pain; and medications known to affect pain thresholds or a history of drug abuse. We also excluded patients who received intraoperative blood transfusion or experienced massive haemorrhaging during the operation.

Eighty abstinent tobacco smokers were defined as patients who had smoked ≥ 10 cigarettes per day for at least one year and discontinued smoking < 1 month before surgery. Sixty-eight subjects were non-smokers (defined as patients who had no history of smoking, had smoked < 100 cigarettes during their lifetime or had discontinued smoking > 3 months prior to assessment). Smoking and non-smoking statuses were confirmed by cotinine and cotinine levels in plasma and urine, respectively.

2.2. Cutaneous electrical pain threshold

During the preoperative anaesthetic assessment, the patients were tested for preoperative pain thresholds in response to electrical stimuli. A constant current stimulator (EP601C; Scientific and Educational Instrument Factory, Shanghai, China) was used to measure the pain threshold in our human subjects in response to electric stimulation. Surface skin electrodes were placed caudal to the lateral malleolus at the innervation area of the sural nerve (Neziri et al., 2011). The intensity of the electrical stimuli was increased (0.2 mA/s) until the subject reported feeling pain. This stimulus intensity was adopted as the pain threshold. Measurements were recorded three times during a 5-min interval, and the mean values were used for analysis.

2.3. Induction and maintenance of anaesthesia

No analgesics or sedatives were used preoperatively. On the patient's arrival in the operating room, we began monitoring with non-invasive blood pressure, pulse oximetry and electrocardiography. The intraoperative anaesthetic management was standardized in all patients. Propofol was administered via a target-controlled infusion (TCI) to achieve and maintain the desired plasma concentration (Cp). General anaesthesia was induced with intravenous propofol (targeted Cp at 5 μg/ml), sufentanil (0.3–0.5 μg/kg), and cisatracurium (0.15–0.2 mg/kg). Anaesthesia was maintained with propofol (targeted Cp at 3–4 μg/ml), remifentanil (5–10 μg/kg/h) and cisatracurium (0.03 mg/kg) when necessary. The infusion rate of remifentanil was adjusted according to patient heart rate and blood pressure. These variations were controlled within 20% of the preoperative values. End-tidal carbon dioxide was maintained between 35 and 45 mm Hg. The propofol TCI was stopped at the time of the last surgical suture. At the end of the operation, 2 mg of neostigmine and 1 mg of atropine were administered intravenously.

2.4. Postoperative analgesia management

During the preoperative anaesthetic assessment, researchers instructed the patients how to use the PCA pump and visual analogue scale (VAS) pain measurement (0 signifying no pain and 10 being the worst possible pain). After anaesthesia, patients were sent to a post-anaesthesia care unit for further care. All patients were provided with sufentanil (1.2 μg/ml, Humanwell Pharmaceutical, Yichang, China) via PCA. The PCA device was set to deliver 2 ml of analgesics as an intravenous bolus with a lockout time of 10 min and no background infusion or limits. The maximum permitted amount of sufentanil was 10 μg/h. If patients exhibited poor response to sufentanil or serious sufentanil-associated adverse effects, supplemental rescue analgesics were used to relieve the postoperative pain. The analgesics administered in this study included injectable morphine, meperidine and oxycodone. All of them were opiate analgesics and converted to the dosage of morphine based on equianalgesic dose ratios (Creekmore et al., 2004). No nicotine was used as an analgesic during the perioperative period.

2.5. Measurement of plasma and urine cotinine levels

On each surgery day, blood and urine specimens were obtained prior to surgery. The samples were labelled and centrifuged at room temperature and promptly frozen at − 80 °C. After completion of the study, all samples were sent to the Pharmacy Department for analysis. Cotinine and nicotine levels in the serum and urine were determined using ultra-pressure liquid chromatography-tandem mass spectrometry (UPLC-MS/MS, 1290 Infinity II series LC system, G6470 QQQ mass