The Effect of Pentazocine on Nausea and Vomiting Following Catheter Ablation

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Abstract: Pentazocine is an intravenously administered preoperative analgesic, but patients occasionally experience nausea and vomiting as an adverse reaction to this drug. As nausea and vomiting may interfere with the patient’s postoperative rest, prevention of the reaction is necessary. This study aimed to survey postoperative nausea and vomiting (PONV) caused by pentazocine administered for catheter ablation. Patients receiving catheter ablation often experience pain during venipuncture and radiofrequency application, thus they are frequently placed under mild to deep sedation. Patients who underwent catheter ablation between February and July 2016 were analyzed retrospectively. The preoperative analgesic dose and PONV were assessed. In total, 256 subjects (177 males, mean age: 65.3 ± 12.9 years) were analyzed of which 185 (72.3%) underwent atrial fibrillation ablation. Of these, 134 subjects (52.3%) were administered 15 mg pentazocine and 122 subjects (47.7%) were administered 30 mg pentazocine, preoperatively. Patients who required additional sedative administration, as determined by the physician, during the procedure received either dexmedetomidine (205 subjects; 80.1%) or thiopental (218 subjects; 85.2%). Investigation of postoperative nausea revealed that 8 subjects in the 15 mg group (6.0%) and 21 subjects in the 30 mg group (17.2%) experienced nausea, a significantly higher percentage in the 30 mg group (p = 0.005). Analysis of postoperative vomiting shows that 6 subjects in the 15 mg group (4.5%) and 14 subjects in the 30 mg group (11.5%) experienced postoperative vomiting, indicating a higher percentage in the 30 mg group (p = 0.04). Furthermore, the data indicate that being female is also an independent indicator of PONV. The results of this study suggest a relationship between pentazocine dose and PONV and that the incidence of PONV is directly related to an increased pentazocine dose.

Key words: catheter ablation, atrial fibrillation, pentazocine, postoperative nausea and vomiting (PONV)

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Introduction

Catheter ablation is the widely chosen method as a curative treatment for various arrhythmias\(^1-3\). However, catheter ablation treatment is invasive and patients may experience pain or discomfort during venipuncture and radiofrequency (RF) application. Inadequate sedation can result in patient movement due to pain or discomfort during the procedure, which can affect the accuracy of the 3-dimensional mapping and negatively affect the outcomes of the ablation treatment\(^4\). To minimize patient movement, appropriate management of sedation is required\(^5-8\). Current catheter ablation treatment strategies use a combination of sedatives, such as propofol, midazolam, and dexmedetomidine, in conjunction with opioid analgesics, such as fentanyl and pentazocine.

To reduce the effects of bodily movements during atrial fibrillation (AF) ablation, patients at the Japan Red Cross Yokohama City Bay Hospital (our institution) undergo deep sedation during the procedure. Until April 2016, the conventional method of sedation, at our institution, for catheter ablation used was intravenous injection of 15 mg pentazocine as a preoperative analgesic. After April 2016, the dose of pentazocine was increased to 30 mg, which allows for better intraoperative management of body movement during the procedure. However, opioid analgesics are known to cause nausea and vomiting\(^9\) and this postoperative nausea and vomiting (PONV) can interfere with the patient’s postoperative rest, a factor in the recovery process, thus, prevention and management PONV is essential for patient care and comfort.

Although previous studies have examined nausea and vomiting associated with catheter ablation\(^5, 10, 11\), the status of PONV onset with different doses of pentazocine has not been investigated. In the present study, we retroactively compared the status of PONV onset caused by 2 dosages of the analgesic pentazocine, 15 mg versus 30 mg, when used during catheter ablation.

Materials and Methods

2.1. Patients

This single-center retrospective study analyzed the medical records of patients who had undergone catheter ablation for arrhythmia during the study period from February 2016 to July 2016. The selection criteria stipulated that only patients who received intravenous administration of pentazocine preoperatively were included in the study; patients who received additional intraoperative intravenous administration of pentazocine were excluded. In cases where the same patient underwent multiple catheter ablation procedures during the study period, only data from the first procedure was included in our analysis. This study was approved by the Institutional Review Board of Japan Red Cross Yokohama City Bay Hospital (approval number: 2017-3, dated November 2016 to July 2017).

2.2. Anesthesia management

Patients received preoperative intravenous pentazocine administration prior to catheter ablation between February and April 2016, the pentazocine dose was 15 mg, and between May and July 2016, the pentazocine dose was 30 mg. Sedative administration was managed as follows: in cases
of ablation for supraventricular tachycardia (SVT) and premature ventricular contraction (PVC), thiopental was administered as an additional sedative when necessary. In cases of ablation for AF, common atrial flutter (AFL), and ventricular tachycardia (VT), dexmedetomidine was continuously added intravenously and thiopental was administered intravenously as an additional sedative when necessary. Medication dosages were delivered at the physician’s discretion.

2.3. Procedure

Each patient provided written informed consent prior to the ablation procedure. Antiarrhythmic drugs were generally discontinued for at least 5 half-lives before the ablation procedure in all patients with SVT, PVC, and VT. All patients with AF were orally administered an anticoagulant, either warfarin or direct oral anticoagulants, for at least one month before AF ablation. Transesophageal echocardiography or enhanced computed tomography was performed just prior to AF ablation to rule out left atrial thrombus.

Three or four vascular sheaths were inserted into the right femoral vein and internal jugular vein under lidocaine local anesthesia. Heparin, 50–100 IU/kg of body weight, was administered after the insertion of vascular sheaths. In addition, heparinized saline was also infused to maintain the activated clotting time at 300–400 seconds. A multi-electrode mapping catheter was inserted through the right internal jugular vein and positioned in the coronary sinus for pacing, recording, and internal cardioversion. During catheter ablation for SVT, PVC, and VT, two or three sheaths were inserted through the right femoral vein and positioned in the right atrium, the bundle of His site, and the right ventricular apex. During AF ablation, two long sheaths were inserted through the right femoral vein for left atrial mapping and ablation. In all patients, the luminal esophageal temperature was measured with a thermocouple catheter inserted into the esophagus. A single transseptal puncture was performed with a RF needle. Pulmonary vein isolation was mainly performed using a cryoballoon catheter. Left atrial ablation was performed with a RF catheter with a 3.5 mm irrigation tip under the guidance of a 3-dimensional mapping system. An esophageal temperature probe was advanced into the esophagus and later adjusted to its closest proximity with the ablation sites along the left atrial (LA) posterior wall. The RF power was limited to 20–25 W on the LA posterior wall and the RF application was truncated when the esophageal temperature increased to 40°C. Similarly, cryoablation was stopped when the esophageal temperature dropped below 15°C. During SVT, PVC, and VT, RF-guided catheter ablation with an irrigated tip was primarily performed. Cryoablation was occasionally performed if the iatrogenic risk of an atrioventricular block was highly suspected during slow pathway ablation or para-Hisian accessory pathway ablation.

2.4. PONV

Nausea and vomiting symptoms were assessed if they appeared within 24 h following surgery. Presence of nausea was defined as an uncomfortable, sickly, or nauseated feeling. Vomiting was defined as at least one instance of an oral charging of the stomach contents. Data regarding nausea and vomiting episodes were extracted from medical records spanning the study period and utilized in our analysis.
2.5. Statistical analysis

Statistical analysis was performed using JMP® Pro13.0 software (SAS Institute, Tokyo, Japan). Continuous variables are shown as the mean ± standard deviation (SD), and then compared using the Student’s t-test. Categorical variables were analyzed using either Fisher’s exact test or chi-squared test. Independent variables associated with PONV were analyzed using univariate and multivariate analysis. Significant differences were set at a p-value < 0.05.

Results

3.1. Patient background

Table 1 shows the patient background characteristics for the 256 patients included in the study. The mean age of patients was 65.3 ± 12.9 years with 177 males (69.1%). One-hundred thirty-four patients (52.3%) received 15 mg and 122 patients (47.7%) received 30 mg of intravenously administered pentazocine, respectively. No other significant differences were found between the two groups, including the number of patients who underwent catheter ablation for AF (p = 0.82) or intergroup differences for any other parameter.

3.2. PONV

Overall, there were 29 cases (11.3%) of postoperative nausea and 20 cases (7.8%) of postoperative vomiting. The frequencies of nausea and vomiting, as a result of the dosage of pentazocine, are shown in Figure 1. The frequency of postoperative nausea was 6% in the 15 mg group and 17.2% in the 30 mg group, indicating a significantly higher frequency (p = 0.005) in the 30 mg group. The frequency of postoperative vomiting was 4.5% in the 15 mg group and 11.5% in the 30 mg group, again indicating a significantly higher frequency (p = 0.04) in the 30 mg group.
Univariate analysis of the factors that affected the onset of postoperative nausea indicated that there were four such factors: female, pentazocine dose of 30 mg, without administration of dexmedetomidine, and without administration of thiopental. We then performed multiple logistic regression analyses with these four factors as explanatory variables and postoperative nausea onset as the objective variable. The results of multivariate analysis indicated that being female (OR, 3.58; 95% CI, 1.54–8.29; $p = 0.003$) or in the pentazocine 30 mg group (OR, 3.86; 95% CI, 1.57–9.48; $p = 0.003$) were statistically independent risk factors (Table 2).
The following five factors were found to influence the onset of postoperative vomiting: female, AF patients, administration of pentazocine 30 mg, without administration of dexmedetomidine, and without administration of thiopental. As with nausea, multivariate analysis showed that being female (OR, 5.32; 95% CI, 1.88–15.1; p = 0.002) or administration of pentazocine 30 mg (OR, 3.46; 95% CI, 1.19–10.0; p = 0.02) were statistically independent risk factors (Table 3).

**Discussion**

We found that the overall frequency of postoperative nausea following catheter ablation was 11.3% and the frequency of postoperative vomiting was 7.8%, inclusive of both pentazocine dosages. However, administration of pentazocine 30 mg was significantly associated with increased PONV, with the postoperative nausea frequency at 17.2% and the postoperative vomiting frequency at 11.5%. Being a female patient was also demonstrated to be an independent risk factor for PONV.

PONV is one of the most frequently occurring postoperative complications following general anesthesia. Overall, it has been reported that the frequency of postoperative nausea is 36% (18%–45%) and that the frequency of postoperative vomiting is 25% (16%–25.5%)\(^2\). Risk factors related to the onset rate of PONV in patients include type of anesthesia and type of surgery. Patient-related risk factors for PONV are female patients, history of PONV and motion sickness, being a nonsmoker, and age\(^2\)\(^3\)\(^4\)\(^5\). Anesthesia-related risk factors include use of volatile anesthetics, anesthetic duration, postoperative opioid use, and use of nitrous oxide\(^2\)\(^6\). Surgery-related risk factors include long procedure time, cholecystectomy, endoscopic surgery, and gynecological surgery\(^2\)\(^4\)\(^5\).
In this study, we identified “the female sex” as a patient-related risk factor for PONV onset. Similarly, Honkavaara et al.\textsuperscript{17} and Beattie et al.\textsuperscript{18} reporting that menstruation increases the risk of PONV. However, there have also been conflicting studies reporting that there is no relationship between the menstrual cycle and PONV\textsuperscript{19, 20}. Thus, the relationship between PONV and female hormones remains unclear. Finally, low body weight was not found to be related to the onset of PONV.

Damage caused to the periesophageal vagal nerve during ablation of the posterior wall of the left atrium is thought to cause periesophageal vagal nerve paralysis\textsuperscript{21-23}. It is believed that this damage results in pyloric spasms and reduces gastric motility that may result in nausea and vomiting. However, in the present study, there were no significant differences found in AF patients receiving 15 mg or 30 mg pentazocine.

According to a report described by Tyndall et al., the frequency of nausea following RF ablation is 22% and the frequency of vomiting is 13%\textsuperscript{10}. These results show even higher frequencies than those found in our study. We postulate that these differences are due to differences in anesthesia-related risk factors, as the study by Tyndall et al. included fentanyl in anesthesia management\textsuperscript{10}. A retrospective study of PONV associated with the combined use of fentanyl or pentazocine and general venous anesthesia with propofol reported that there was no significant difference in the frequency of PONV between fentanyl and pentazocine\textsuperscript{24}. However, the authors attributed the non-significant difference to the high percentage of female patients in the fentanyl group. Fentanyl might lead to higher PONV frequency than that caused by pentazocine.

Pentazocine is easier to use than fentanyl because of pharmaceutical regulations regarding its administration. Use of pentazocine in catheter ablation for AF has been previously reported\textsuperscript{6, 8}\textsuperscript{8}. However, these studies did not include data for nausea and vomiting frequency. To our knowledge, the present study is the first to report the frequency of PONV caused by pentazocine in patients who underwent catheter ablation.

The mechanism of nausea and vomiting due to opioids remains unknown, but it is thought that they cause direct stimulation of the chemoreceptor trigger zone, inhibit gastrointestinal tract motility, and stimulate the vestibular apparatus\textsuperscript{25-27}. Pentazocine causes delayed emptying of gastric contents and delayed gastrointestinal transit in rats, but selective kappa agonists do not cause these side effects. Therefore, it is assumed that pentazocine affects gastrointestinal functions through an off-target mechanism other than the opioid receptors and occurrence of PONV is a result of pentazocine’s effect on these other sites\textsuperscript{28}. Currently, there are no high-quality clinical studies on antiemetics for opioid-induced nausea and vomiting, dopamine receptor antagonists and prokinetic agents, or antihistamines based on mechanism of action. One of the limitations of our study was the fact that it was a retrospective study that utilized patient medical records; thus, we have been not able to evaluate the analgesic effect of pentazocine dose.

The results of the present study suggest a relationship between PONV onset and pentazocine. It was found that the onset frequency of PONV with pentazocine is dose dependent. In conclusion, the dosage of pentazocine should be carefully selected according to the degree of surgery and addition of antiemetic drugs should be considered for female patients receiving more than 30 mg pentazocine.
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Conflict of interest

The authors have no conflicts of interest to declare.

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