J Anesth (2012) 26:864–869
DOI 10.1007/s00540-012-1443-1

ORIGINAL ARTICLE

Penehyclidine enhances the efficacy of tropisetron in prevention of PONV following gynecological laparoscopic surgery

Zhiming Zhang · Yuehong Zhuang · Fang Ouyang · Ansheng Zhang · Bin Zeng · Miaoning Gu

Received: 16 February 2012 / Accepted: 19 June 2012 / Published online: 10 August 2012

Abstract
Purpose Postoperative nausea and vomiting (PONV) are common complications after gynecological laparoscopic surgery. Because monotherapy with antiemetics is insufficient, combinations of various antiemetics are often recommended by experts. In this study, our purpose was to find out whether penehyclidine could enhance the efficacy of tropisetron in preventing PONV.
Methods With hospital ethics committee approval, we investigated 120 women undergoing gynecological laparoscopic surgery receiving prophylactic tropisetron (0.1 mg/kg; maximal dose, 5 mg) (group T) or tropisetron (0.1 mg/kg; maximal dose, 5 mg) plus penehyclidine (0.01 mg/kg; maximal dose, 1 mg) (group TP), or penehyclidine (0.01 mg/kg; maximal dose, 1 mg) (group P). The incidence of vomiting, the intensity of nausea (assessed by a visual analogue scale [VAS]), antiemetic rescues, and adverse effects were recorded at 2, 6, 12, and 24 h after surgery in the gynecological ward by a visiting nurse anesthetist who was unaware of the treatments. Collected data were analyzed using analysis of variance (ANOVA) and the χ^2 test. Continuous variables were expressed as means ± SD, and non-continuous variables were expressed as *n* (%).
Results The overall incidence of vomiting was 28.3 % (34/120) in our study. The incidence of vomiting was significantly lower in group TP (4 cases, 10 %) than that in group T (12 cases, 30 %) and group P (18 cases, 45 %). The incidence of vomiting in group TP was also significantly lower than that in group T at 0–2 h and 2–6 h postoperatively and it was also significantly lower than that in group P at 0–2 h, 2–6 h, 6–12 h, and 12–24 h postoperatively. The incidence of vomiting was significantly lower in group T than that in group P at 12–24 h postoperatively. The VAS of nausea was significantly lower in group TP than that in group T and group P at 2 and 6 h after surgery. It also showed a significant higher score in group P than that at group T and group TP at 12 and 24 h. Within group P, the VAS of nausea was significantly lower at 2 h postoperatively than that at 24 h.
Conclusions Penehyclidine showed less efficacy in preventing PONV than tropisetron; however, compared with tropisetron or penehyclidine monotherapy, prophylactic medication with tropisetron plus penehyclidine significantly reduced the incidence of vomiting and decreased the intensity of nausea in women undergoing gynecological laparoscopic surgery.

Keywords Gynecological laparoscopic surgery · Postoperative nausea and vomiting · Antiemetics · Tropisetron · Anticholinergic agent · Penehyclidine

Z. Zhang and Y. Zhuang contributed equally to this article, and are co-first authors.

Z. Zhang · F. Ouyang · A. Zhang · B. Zeng
Department of Anesthesiology, The First People's Hospital of Chenzhou, Institute of Translation Medicine, Chenzhou 423000, Hunan, People's Republic of China

Z. Zhang · M. Gu (✉)
Department of Anesthesiology, Nanfang Hospital, Southern Medical University, 1838 Guangzhou Avenue North, Guangzhou 510515, Guangdong, People's Republic of China
e-mail: etee@qq.com

Y. Zhuang
Anatomical Department, Fujian Medical University, Fuzhou 350108, Fujian, People's Republic of China

Introduction

The incidence of postoperative nausea and vomiting (PONV) in women undergoing gynecological laparoscopic surgery

has been reported to be between 54 and 92 % [1]; PONV is sometimes regarded as a 'minor' problem, and patients may be willing to forego effective PONV prophylaxis in preference for better analgesia [2, 3], a choice which, however, would deprive the patients of satisfaction and comfort during hospitalization. Prophylactic medication to avoid or reduce PONV in these patients is therefore highly needed. Selective serotonin 5-hydroxytryptamine subtype 3 (5-HT3) receptor antagonists can safely and effectively prevent PONV. Consensus guidelines for managing PONV suggest that 5-HT3 receptor antagonists should be viewed as the first-line antiemetics in high-risk patients [4]. But 5-HT3 receptor antagonists alone were reported to be insufficient for these high-risk patients [4–6]; consequently, combination with other antiemetics, such as dexamethasone or droperidol, to prevent or treat severe PONV was recommended [4, 5]. Because of the high risk of severe adverse effects of droperidol, the United States Food and Drug Administration issued a black-box warning about its use in clinical practice, though some scholars claimed that this was a subjective decision [7]. And it has been reported that dexamethasone may increase the risk of infection [8], further justifying the search for other effective drugs to prevent PONV. Anticholinergics, such as atropine and scopolamine, have been used in clinical practice as premedication for the inhibition of glandular secretion, which can also reduce the incidence of postoperative vomiting [9–11], and this action is enhanced when 5-HT3 receptor antagonists are combined with anticholinergics.

Tropisetron, a long-acting 5-HT3 receptor antagonist with a long-established effect in reducing PONV in laparoscopic cholecystectomy, is less effective than ondansetron in the first 3 h after surgery [12]. Penehyclidine hydrochloride is a novel anticholinergic agent developed in China [13, 14], and has been widely used as a preoperative anticholinergic in China owing to its stronger selective antagonistic action for M3/M1 receptors, and fewer adverse effects compared with other anticholinergics [14].

Does penehyclidine have similar efficacy to that of other anticholinergics in treating PONV? We hypothesized that penehyclidine could enhance the effect of tropisetron in preventing PONV in women undergoing gynecological laparoscopic surgery. This study was conducted to verify this hypothesis.

Patients, materials, and methods

With the local hospital ethics committee approval and written informed consent from the patients, 120 patients aged between 18 and 43 years whose weight was between 40 and 72 kg were enrolled in this study. These patients were scheduled for gynecological laparoscopic surgery, with an anticipated duration of 1.5–2.5 h, under general anesthesia. Exclusion criteria included: pregnancy, hepatic or renal dysfunction, presence of gastrointestinal disease, smoking, being allergic to theresearch drugs, and duration of surgery longer than 2.5 h.

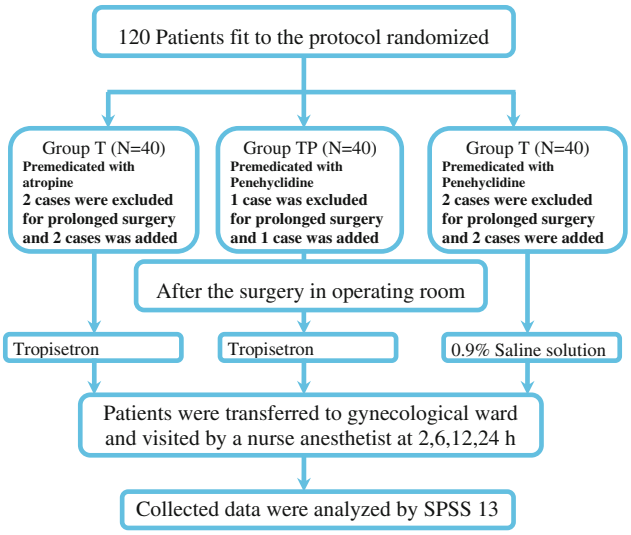

Fig. 1 Flow chart of study protocol

Patients were allocated to three groups equally (40 patients in each group) with the random numbers generated using the Rand function of Excel 2003 (Microsoft, Redmond, WA, USA). Patients in group T were treated with tropisetron alone; patients in group TP were treated with tropisetron plus penehyclidine; and patients in group P were treated with penehyclidine alone. Patients in group T received atropine (0.01 mg/kg, maximal total dose, 0.5 mg) as premedication, while patients in groups TP and P were received penehyclidine (0.01 mg/kg, maximal total dose, 1 mg) as premedication, administered via intramuscular injection 20–40 min before anesthesia induction. All patients were monitored cyclically with continuous electrocardiogram (ECG), pulse oximetry, and non-invasive blood pressure (NIBP) of the left arm every 5 min. End-expiratory carbon dioxide was monitored immediately after endotracheal intubation and ventilation was adjusted to maintain a range between 30 and 35 cmH_20. Hydration was maintained with lactated Ringer's solution (LRS) administered via a venous cannula in the right cephalic vein of the forearm at the speed of 15–25 ml/kg/h. The following steps of this research are shown in Fig. 1.

Protocol

Patients were fasted for at least 6 h even for emergency surgery. Anesthesia was induced intravenously in the same sequence in each group: midazolam 0.08 mg/kg, fentanyl 5 μg/kg, and etomidate 0.3 mg/kg, plus cisatracurium besilate 0.2 mg/kg to facilitate tracheal intubation.

Anesthesia was then maintained with target-controlled infusion (TCI) of propofol at a plasma concentration of 3–4 μg/ml and remifentanil at 3 ng/ml; muscle relaxation was achieved by continuous infusion of atracurium besilate at 0.08 mg/kg/min. Ventilation was maintained with an anesthesia machine with intermittent positive-pressure ventilation (IPPV): O_2 at 1.5 l/min, tidal volume at 6 ml/kg, and frequency at 12 bpm. During the surgery, fluctuations of blood pressure and heart rate were kept within 20 % of the preanesthesia value. Pain control was achieved with 0.5 % levobupivacaine administered by the gynecologist through local infiltration anesthesia in the surgical wound. Intramuscular tramadol was used for postoperative pain relief if necessary. Patients were transferred to the postanesthesia recovery unit (PACU) for recovery at the end of the surgery and muscle blockade was reversed with atropine 15 μg/kg and neostigmine 60 μg/kg injected intravenously when autonomous respiration occurred.

Anti-vomiting prophylaxis was achieved with the following steps: 10 ml diluted tropisetron solution (0.1 mg/kg, maximal total dose, 5 mg) was administered intravenously at a speed of 5 ml/min just after the surgery in both groups T and TP, while 10 ml 0.9 % saline solution was administered in group P.

On complete recovery, patients were transferred to the gynecological ward and, to assess nausea and vomiting, they were visited at 2, 6, 12, and 24 h after the surgery by a nurse anesthetist who was unaware of the drugs involved in the study. Vomiting was defined as the forceful expulsion of gastric contents through the mouth, or dry-retching, and was assessed by the patient's response of yes or no to questioning; nausea was defined as a subjective sensation of an unpleasant feeling associated with awareness of wanting to vomit, and was assessed by a VAS [10, 15, 16]; patients were asked to record the degree of severity on a 100-mm VAS, with the left end of the line representing no nausea and the right end of the line representing the worst possible nausea [10]. Tropisetron (1 mg) was administered intravenously as the postoperative rescue medication when the nausea was insufferable or when more than two emetic episodes occurred within 15 min, or at any time at the patient's request; the incidence of antiemetic rescue was defined as the ratio of the number of patients who had received tropisetron (regardless of how many times the patient had received it) divided by the total number of patients. Data including age, gender, duration of surgery, and anesthesia were recorded for each patient. Adverse effects such as dry mouth and headache were also recorded if patients complained about these effects.

We examined the hypothesis that approximately 48 % of the patients treated with penehyclidine alone would suffer from nausea and vomiting; and tropisetron combined with penehyclidine would reduce the incidence of nausea and vomiting by approximately 16 %. A sample size of 38 patients in the pre-treatment group would provide 90 % (1-β) validity to detect a difference between the treatments in group P and TP at a significance level of $\alpha = 0.05$. In this study, 40 patients were enrolled in each treatment group.

Statistical analysis was performed with SPSS for Windows version 13 (SPSS Chicago, IL, USA). Continuous variables were expressed as means ± SD and tested with one-way analysis of variance (ANOVA). The VAS of nausea was tested with two-way ANOVA, and multiple comparisons were tested with the least significant difference (LSD) test or the Dunnett T3 according to the homogeneity of variance. Non-continuous variables were expressed as the number of cases (%) and tested with Pearson's χ^2 test and Fisher's exact test.

Results

All patients (40 in each treatment group) enrolled in the study recovered from anesthesia after surgery. The characteristics of the patients and the durations of surgery and anesthesia are shown in Table 1. There were no significant differences in these characteristics among the three groups. The prophylactic consumption of tropisetron in groups T and TP was not significantly different. The consumption of penehyclidine as premedication in groups P and TP also showed no significant difference.

The overall incidence of vomiting (patients who vomited once or more) in the study was 28.3 % (34/120), and the incidence was significantly lower in group TP (4 cases, 10 %) than that in groups T (12 cases, 30 %) and P (18 cases, 45 %); no significant difference was found between groups T and P, although tropisetron was more efficacious

Table 1 The demographic data of patients and durations of surgery and anesthesia (mean ± SD)

Items	Group T ($n = 40$)	Group P ($n = 40$)	Group TP ($n = 40$)
Age (years)	33 ± 7	31 ± 8	30 ± 8
Weight (kg)	52 ± 6	51 ± 7	50 ± 5
Duration of surgery (min)	118 ± 18	122 ± 16	120 ± 18
Duration of anesthesia (min)	138 ± 20	134 ± 18	135 ± 23
Consumption of tropisetron (mg)	4.84 ± 0.299	–	4.77 ± 0.327
Consumption of penehyclidine (mg)	–	0.508 ± 0.071	0.497 ± 0.054

Group T patients treated with tropisetron alone, *group TP* patients treated with tropisetron plus penehyclidine, *group P* patients treated with penehyclidine alone

Table 2 Patients with nausea and vomiting in the first 24 h after the operation stratified by treatment group [mean ± SD, or number (%)]

	Group T ($n = 40$)	Group P ($n = 40$)	Group TP ($n = 40$)
0–2 h			
Cases of vomiting	5 (12.5 %)	5 (12.5 %)	0 (0)[a]
VAS of nausea	39 ± 9	41 ± 11	31 ± 11[a]
2–6 h			
Cases of vomiting	6 (15 %)	6 (15 %)	1 (2.5 %)[a]
VAS of nausea	40 ± 18	42 ± 8	27 ± 11[a]
6–12 h			
Cases of vomiting	5 (12.5 %)	6 (15 %)	2 (5 %)
VAS of nausea	37 ± 7	54 ± 13[b]	33 ± 15
12–24 h			
Cases of vomiting	5 (12.5 %)	13 (32.5 %)[b, c]	3 (7.5 %)
VAS of nausea	38 ± 9	63 ± 11[b, c]	33 ± 13

VAS visual analogue scale, *Group T* patients treated with tropisetron alone, *group TP* patients treated with tropisetron plus penehyclidine, *group P* patients treated with penehyclidine alone

[a] $P < 0.05$ versus groups T and P

[b] $P < 0.05$ versus groups T and TP

[c] $P < 0.05$ versus 0–2 h within group P

Table 3 The overall incidences of vomiting, antiemetic rescue, and adverse effects in the three treatment groups [number (%)]

	Group T ($n = 40$)	Group P ($n = 40$)	Group TP ($n = 40$)
Overall vomiting	12 (30 %)	18 (45 %)	4 (10 %)[a]
Antiemetic rescue	13 (32.5 %)	21 (55 %)	5 (12.5 %)[a]
Dry mouth	1 (2.5 %)[b]	14 (35 %)	13 (32.5 %)
Headache	6 (15 %)	4 (10 %)	7 (17.5 %)

Group T patients treated with tropisetron, *group TP* patients treated with tropisetron plus penehyclidine, *group P* patients treated with penehyclidine, *antiemetic rescue* patients treated with tropisetron 1 mg

[a] $P < 0.05$ versus groups T and P

[b] $P < 0.05$ versus groups TP and P

than penehyclidine (Table 3). During the first 2 h after the operation, there was no patient vomiting in group TP, demonstrating a lower incidence of vomiting than that in the groups treated with tropisetron alone or penehyclidine alone. The incidence of vomiting during 12–24 h postoperatively was significantly higher than that during 0–2 h in group P, and this incidence was also higher than those in group T (5 cases) and group TP (3 cases). The data are shown in Table 2.

The intensity of postoperative nausea was assessed with the VAS when the patients were aware of a desire to vomit. The VAS values of patients who were treated with tropisetron plus penehyclidine were significantly lower than the values for those who were treated with tropisetron alone at 2 and 6 h after surgery and the values were also significantly lower than the values for those who were treated with penehyclidine alone at 2, 6, 12, and 24 h after surgery. The difference in VAS between groups T and P was not significant at 2 and 6 h after the surgery, but significance was found at 12 and 24 h after the surgery (Table 2).

Tropisetron rescue was performed as planned preoperatively. The overall incidence of antiemetic rescue in the study was 32.5 %; patients in group TP needed significantly less rescue than those in group T and P; although the need for rescue in group T was less than that in group P, the difference between these two groups was not significant ($P = 0.07$) (Table 3).

There were no serious adverse events attributable to the study drugs and only 10 patients complained of pain (the pain was easy to bear and no analgesics were needed); none of the patients were treated with analgesics in the first 12 h. Two adverse effects were noted and recorded in our study: dry mouth and headache, which were associated with penehyclidine and tropisetron, respectively. The incidence of dry mouth in group T was significantly less than that in group TP ($P < 0.01$) and that in group P ($P < 0.01$), and there was no difference between groups TP and P. Headache was found in each group and there was no significant difference among the groups ($P = 0.68$), although the incidence of headache in was higher in group TP than that in the other two groups.

Discussion

Postoperative nausea and vomiting occur frequently after laparoscopic gynecological surgery, with an incidence of up to 50–88 % [17, 18]. Even when patients were treated with antiemetics, the incidence of PONV was still very high [6]. PONV is one of the factors that most frequently deprive patients of satisfaction and comfort during hospitalization. The research of Myles et al. [3] showed that much attention should be paid to PONV rather than it being regarded as a 'minor' complication. Combinations of antiemetics to achieve more effective results are common and recommended [4, 5, 9–11]. Droperidol in combination with 5-HT3 antagonists and dexamethasone was viewed as a very effective method to treat patients with a high risk of PONV [4]. However, the application of droperidol in clinical practice is limited because of its severe adverse effects on the cardiovascular system [7]; also, the intraoperative administration of dexamethasone is controversial in that an antiemetic dose of the agent (8 mg) could markedly suppress plasma cortisol in the first 24 h postoperatively, and cause a minor elevation of blood glucose [19], leading to the possibility of an increased risk of

postoperative infection [8]. Anticholinergic agents with an antiemetic effect, such as atropine [20] and especially scopolamine [11, 21–23], are administered to prevent PONV. Penehyclidine, as a novel anticholinergic and a highly selective antagonist of M3/M1 receptors with lower adverse effects than other anticholinergics [14], has been proven to have a protective function against septicopyemia and liver injury in rats, as do other anticholinergics; however, to our best knowledge, research of its effect in preventing PONV has not yet been reported.

Our study indicates that tropisetron and penehyclidine have comparative effects in the prevention of vomiting in the 24 h after surgery (incidence of 30 vs. 45 %, $P > 0.05$) and tropisetron combined with penehyclidine significantly reduced the incidence of vomiting in the first 24 h (10 %) compared with monotherapy with either agent. 5-HT3 antagonists have been reported to be effective for the reduction of PONV in women following gynecological laparoscopic surgery, and these agents are also reported to have minimal adverse effects [17, 18]. In spite of prophylaxis with intravenous 5-HT3 antagonists, the incidence of postoperative vomiting is still too high (30–60 %) [6, 12] to accept. Anticholinergics, especially scopolamine, can reduce the incidence of PONV significantly. Like scopolamine, penehyclidine is an anticholinergic, and in our study it showed an effect on prevention of PONV similar to that of tropisetron in the first 12 h postoperatively. The incidence of vomiting increased dramatically in the 12–24 h after surgery in patients treated with penehyclidine only, and was significantly higher than that in patients treated with tropisetron or tropisetron plus penehyclidine. This phenomenon could be explained by the pharmacodynamic characteristics of the agent: the half life of penehyclidine in humans is 10.4 ± 1.22 h [24], while tropisetron is a long-acting 5-HT3 antagonist with an efficient antiemetic effect in the first 24 h, and the effect can last for 2–6 days, although its mean elimination half-life following intravenous administration was 7.3 h [25], and it could be administered once daily for prevention of chemotherapy-induced nausea and vomiting [25]. In our study, tropisetron plus penehyclidine showed better efficacy in preventing PONV than monotherapy with tropisetron or penehyclidine, and this finding could be explained by an additive or synergistic effect of the two drugs, similar to the effect of 5-HT3 plus scopolamine [10, 23].

Analgesia in all the patients in our study was performed with levobupivacaine by local infiltration anesthesia in the surgical wound. Because of the efficacy of levobupivacaine in infiltration anesthesia and the minimally invasive wound of laparoscopic surgery, the postoperative pain was well tolerated. In clinical practice, headache was reported as an adverse effect of tropisetron and other 5-HT3 antagonists [6, 12, 25], but it was mild. In our study the patients treated with tropisetron showed a higher incidence of slight headache than those treated with penehyclidine alone, but the difference was not statistically significant. However, our patients receiving penehyclidine had a significantly higher incidence of dry mouth than those receiving tropisetron monotherapy, this being attributable to the longer-lasting effect of the new anticholinergic compared with that of atropine.

In summary, the main results of our study showed that combination therapy of tropisetron and penehyclidine was superior to monotherapy with either tropisetron or penehyclidine, and the combination did not increase the adverse effects significantly; our study also showed that penehyclidine had an antiemetic effect similar to that of tropisetron in the first 12 h postoperatively. In other words, the hypothesis we put forward was tested very well by our clinical study and was shown to be true. However, further investigation of the dosage-effect of penehyclidine and a comparison of the antiemetic effects of scopolamine and penehyclidine should be undertaken. We note that penehyclidine is a drug that was developed in China and that it has been exclusively used in China to date, leading to its efficacy being unable to be appraised by anesthesiologists worldwide.

Acknowledgments The authors gratefully acknowledge the co-operation of the anesthetists, the nurse anesthetists, gynecological surgeons, and the staff of the gynecological ward of the First People's Hospital of Chenzhou City. Revision of this manuscript by Zhenlong Zhao Ph.D., and Henan Deng M.D., is also appreciated.

Conflict of interest Drs. Zhiming Zhang, Yuehong Zhuang, Fan Ouyan, Ansheng Zhang, and Miaoning Gu have no conflicts of interest or financial ties to disclose. The authors have no affiliation or relationship with any company or organization that has a potential interest in the outcome of the study.

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