RESEARCH ARTICLE

Phase II Study on EANI Combined with Hydrochloride Palonosetron for Prevention of Chemotherapy-induced Nausea and Vomiting Following Highly Emetogenic Chemotherapy

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Abstract

Objective: To investigate the electronic anti-nausea instrument (EANI) combined with hydrochloride palonosetron for prevention of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. Methods: Patients who received highly emetogenic chemotherapy were randomly assigned to a treatment group (60 patients) treated with EANI combined with hydrochloride palonosetron, and control group (also 60 patients) given only hydrochloride palonosetron. Chemotherapy related nausea and vomiting were observed and recorded in both groups of patients from the start till the end of chemotherapy. Results: Complete control rates of vomiting in treatment and control group were 40%, and 35%, respectively, without any statistical ly significant difference ($p > 0.05$); however the response rates are 95.0%, 78.3%, respectively, with statistical difference ($p < 0.05$). Complete control rates of nausea in treatment and control group were 36.7%, 30%, respectively, without statistical difference ($p > 0.05$); but the response rates are 90.0%, 76.7%, respectively, with statistical difference ($p < 0.05$). Conclusion: EANI combined with hydrochloride palonosetron for prevention of nausea and vomiting induced by chemotherapy could be more effective than hydrochloride palonosetron alone, and can be recommended for use in prevention and treatment of chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy.

Keywords: Electronic anti-nausea instrument - palonosetron - chemotherapy - nausea/vomitting

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Introduction

At present, Chemotherapy is still an effective methods for treating patients with advanced and metastatic cancer. However, chemotherapy - induced nausea and vomiting (CINV) is one of the most common gastrointestinal side effects of chemotherapy, especially for patients who were treated with highly emetogenic chemotherapy (Akyuz et al., 2013; Baykara et al., 2013; Fu et al., 2013; Huang et al., 2013; Keat et al., 2013; Keat et al., 2013; Kubota et al., 2013; Abe et al., 2014; Akkuzu et al., 2014; Li et al., 2014; Tas et al., 2014). It is estimated that more than 90% of patients will suffer nausea and vomiting, repeatedly, and persistent nausea, vomiting, or unbearable pain, will makes patients not tolerable to chemotherapy and fear, further even reject chemotherapy. Hydrochloride palonosetron is a new type of 5-HT3 receptor antagonist with high selectivity, good affinity, and curative effect due to long half-life (about 40 H), as well as good safety profile. But when hydrochloride palonosetron is used to prevent acute nausea/vomiting caused by chemotherapy, there are still some patients presenting with severe gastrointestinal reaction, and even led to suspension of chemotherapy. Electronic anti-nausea instrument (EANI) is a new therapy apparatus that effects through a particular low frequency electric stimulus percutaneously, reduces 5-HT3 release in gastrointestine and brain, so as to prevent the occurrence of nausea and vomiting. From June 2013 to March 2014, we conducted clinical trial using EANI combined with hydrochloride palonosetron to prevent acute gastrointestinal reaction induced by chemotherapeutic regimens, and presented the main results here.

Materials and Methods

Patients

From June 2013 to March 2014, cancer patients hospitalized and scheduled to be treated by highly emetogenic chemotherapy containing adriamycin, cisplatin and epirubicine, aged 23 to 74 years old, and randomly assigned to control group (hydrochloride palonosetron) and treatment group (EANI combined with hydrochloride palonosetron). Hydrochloride palonosetron

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Table 1. A comparison on the Response Rate of Anti-vomiting Effect Between Two Groups

	Case number	0° N(%)	I° N(%)	II° N(%)	III° N(%)	Response rate (%)	*P* value
Treatment group	60	24(40.0)	33(55.0)	2(3.3)	1(1.7)	95.0	<0.05
Control group	60	21(35.0)	26(43.3)	8(13.3)	5(8.3)	78.3	

Table 2. A Comparison on the Response Rate of Anti-nausea Effect Between Two Groups

	Case number	0° N(%)	I° N(%)	II° N(%)	III° N(%)	Response rate (%)	*P* value
Treatment group	60	22(36.7)	32(53.3)	4(6.7)	2(3.3)	90.0	<0.05
Control group	60	18(30.0)	28(46.7)	10(16.7)	4(6.7)	76.7	

injection (0.25 mg/unit) was provided by Jiangsu Zhengda Tianqin Pharmaceutical co., LTD. EANI was provided by Kunming Luo Shi Technology co., LTD.

Other eligibility criteria: (1) all patients had CT, MRI, cytological or pathological diagnosis (2) with normal liver and renal function before chemotherapy (3) no nausea, vomiting, and 24 h before chemotherapy and did not use anti-nausea medications before chemotherapy. (4) emotionally stable.

Exclusion criteria: with a clear brain metastases or intracranial hypertension; with epilepsy; with vomiting caused by digestive tract obstruction or due to a variety of causes; pregnant women and nursing mothers; allergic to metal contact; skin damage around wrist; with a pacemaker, with an implanted glucose meter or with an artificial cochlear.

Treatment Methods

Control group: hydrochloride palonosetron at a dose of 0.25 mg (5 ml) was injected for no less than 5 minutes before chemotherapy.

Treatment group: hydrochloride palonosetro at a dose of 0.25 mg (5 ml) was injected for no less than 5 minutes before chemotherapy, and on the contralateral wrist of infusion, to wear an EANI.

Vomiting classification: without vomiting (degree 0); 1 ~ 2 vomiting per day (degree 1); 3 ~ 5 vomiting per day (degree 2); vomiting for more than five times per day (degree 3). Response rate = (degree 0 + degree 1)/total number of cases.

Nausea classification: no change (level 0); loss of appetite, but no obvious change in food intake, eating habits and food species (level 1); II, obviously reduction in food intake (level 2); almost can't eat, need nutritional support intravenously (level 3). Response rate = (level 0 + level 1)/total number of cases.

Statistical Analysis

SPSS19.0 software was used for data analysis. Chi-square test was used to detect change in nausea and vomiting in two groups. $P< 0.05$ is considered to be statistically significant.

Results

The results showed that during chemotherapy, complete control rates of vomiting were 40%, and 35% in treatment and control respectively, no statistical difference was detected between two groups ($p > 0.05$), however response rates were 95.0% and 78.3%, respectively, with statistically significant difference ($p< 0.05$) (Table 1). Complete control rates of nausea were 36.7% and 30% respectively in treatment and control group without statistical difference ($p >0.05$), but response rates were 90.0% and 76.7%, respectively, statistically significant difference ($p< 0.05$) (Table 2).

Some patients in this study presented anti-nausea treatment related adverse reactions (headache, dizziness, vertigo, diarrhea, constipation, etc.), but were mild (less than degree 2). No significant difference was detected between two groups. No severe adverse reactions were diagnosed, and no patients suspended treatment due to adverse reactions suggesting EANI, and hydrochloride palonosetron both has statisfactory safety profile.

Discussion

According to 2014 national comprehensive cancer network guideline on anti-nausea treatment, highly emetogenic chemotherapeutic regimen including carmustine (> 250 mg/m^2), cisplatin, doxorubicin (≥60 mg/m^2), dacarbazine, cyclophosphamide (> 1500 mg/m^2), epirubicine (> 90 mg/m^2), and ifosfamide (≥2 g /m^2/d or higher), etc. The mechanism of vomiting is not yet fully elucidated, supposing that serotonin (5 – HT3) plays an important role in CINV (Richard et al., 2002),

Nausea caused by chemotherapy, could be divided into acute, delayed and anticipatory based on the time of onset (Jordan et al., 2005). Acute nausea and vomiting: refers to nausea or vomiting, occurring within 24 hours of administration of chemotherapeutic drugs, and usually 5 to 6 hours, and could sustain for 18 hours (Jordan et al., 2005). The delayed nausea and vomiting: refers to nausea or vomiting, occurring after 24 hours of administration of chemotherapeutic drugs, and usually 40% - 50% of delayed nausea and vomiting occurring within 24 to 48 hours after administration of chemotherapeutic drugs, sometimes sustainable for 5 ~ 7 days (Dranitsaris et al., 2001).

Since the mid of 1980s, a variety of selective 5 - HT receptor antagonists were developed, eg., ONDANSETRON, Tropisetron, Ramosetron, etc. because of the short half-life, affinity is not high, vomiting is difficult to fully control (Uygun et al., 2013; Wang et al., 2013; Wang et al., 2013; Wang et al., 2013; Wu et al., 2013; Xu et al., 2013; Yan et al., 2013; Yusuf et al., 2013; Wei et al., 2014). Hydrochloride palonosetron is an efficient, second generation of 5-HT3 receptor antagonist, with 5-HT3 receptor binding affinity of about 100 times stronger than ONDANSETRON (Ingersoll et al., 2010). Hydrochloride palonosetron is reported to have a long half-life plasma clearance, about 40 h (Ingersoll et al.,

2010), significantly longer than other 5-HT3 antagonists.

EANI is a newly developed therapeutic apparatus functioning by percutaneously electric stimulus. EANI is a pulse generator with the appearance similar to a wristwatch, and is usually weared around the wrist. EANI has two metal plate and should be pressed to the radial side of wrist flexor. it is functioning by producing a low frequency electric pulse and then transfering the pulse through wrist median nerve to the brain cortex, to adjust a variety of biological and physical activities, including mechanism that controls nausea and vomiting. This electric pulse could also adjust signals to and from stomach transferred by vagus nerve, prevent or delay signal transmission inducing vomit from brain to stomach. EANI could significantly reduce the release of 5-HT3 from gastrointestinal tissue and brain tissue, and down-regulate 5-HT3 receptors. Therefore, EANI could inhibite vomiting center through both peripheral and central ways.

This study suggests that in the acute phase of chemotherapy, the control rate of nausea and vomiting in treatment group was higher than that in control group, and was statistically significant. In terms of complete control rate, although no statistical difference in both groups, it is higher in treatment group than that in control group. Suggesting that EANI and hydrochloride palonosetron combined could achieve better effects in controlling chemotherapy related acute gastrointestinal reactions, eg., nausea, vomiting, than hydrochloride palonosetron alone. The mechanism may be associated with above mentioned description. Hydrochloride palonosetron is a new generation 5-HT3 receptor antagonist, functioning by 5-HT3 receptors; and EANI functioning through a low frequency pulse to stimulate cerebral cortex, and to reduce the release of 5-HT3 from gastrointestinal and brain tissue, thereby, could synergistically inhibite vomiting center through both peripheral and central ways, and enhance the anti-nausea effect. And in the aspect of adverse reaction, this study shows that when hydrochloride palonosetron and EANI were used together, toxic reactions were similar to hydrochloride palonosetron used alone, the most common degree I to II toxic reactions were constipation, headache, fatigue and abdominal distention. No degree III toxic effects occurred. All adverse reactions could be alleviated after symptomatic treatment, and part of patients could recover without any special treatment.

In conclusion, EANI combined with hydrochloride palonosetron is associated with curative effect of gastrointestinal reaction induced by chemotherapeutic drugs and the control effectiveness is better than hydrochloride palonosetron alone. Thus, could be used as the prevention and treatment for chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy. However, further study should be encouraged to investigate if EANI combined with hydrochloride palonosetron is effective in prevention and treatment of delayed and anticipatory vomiting.

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References

Abe H, Mori T, Kawai Y, et al (2013). Feasibility study of docetaxel and cyclophosphamide six- cycle therapy as adjuvant chemotherapy for Japanese human epidermal growth factor receptor 2-negative breast cancer patients. *Asian Pac J Cancer Prev*, **14**, 4835-8.

Akkuzu G, Talas MS, Ortac F (2014). Functional status in Turkish women with gynecological cancer. *Asian Pac J Cancer Prev,* **15**, 2045-9.

Akyuz RG, Ugur O, Elcigil A (2013). Sleep quality in lung cancer patients. *Asian Pac J Cancer Prev,* **14**, 2909-13.

Baykara M, Buyukberber S, Ozturk B, et al (2013). Efficacy and safety of concomitant chemoradiotherapy with cisplatin and docetaxel in patients with locally advanced squamous cell head and neck cancers. *Asian Pac J Cancer Prev,* **14**, 2557-61.

Dranitsaris G, Leung P, Ciotti R, et al (2001). A multinational study to measure the value that patients with cancer place on improved emesis control following cisplatin chemotherapy. *Pharmacoeconomics*, **19**, 955-67.

Fu JH, Gao Z, Ren CC, et al (2013). Comparison of clinical efficacy of three different neoadjuvant approaches (chemotherapy combined vaginal intracavitary irradiation, neoadjuvant chemotherapy alone or radiotherapy) combined with surgery for patients with stage Ib2 and IIa2 cervical cancer. *Asian Pac J Cancer Prev,* **14**, 2377-81.

Huang XE, Wei GL, Huo JG, et al (2013). Intrapleural or intraperitoneal lobaplatin for treatment of patients with malignant pleural effusion or ascites. *Asian Pac J Cancer Prev,* **14**, 2611-4.

Ingersoll GL, Wasilewski A, Haller M, et a1 (2010). Effect of concord grape juice on chemotherapy-induced nausea and vomiting results of a pilot study. *Oncol Nurs Forum*, **37**, 213-21.

Jordan K, Kasper C, Schmoll HJ (2005). Chemotherapy-induced nausea and vomiting: Current and new standards in the antiemetic prophylaxis and treatment. *Eur J Cancer*, **41**, 199.

Keat CH, Ghani NA (2013). Cost-effectiveness analysis of granisetron-based versus standard antiemetic regimens in low-emetogenic chemotherapy: a hospital-based perspective from Malaysia. *Asian Pac J Cancer Prev,* **14**, 7701-6.

Keat CH, Phua G, Abdul Kassim MS, et al (2013). Can granisetron injection used as primary prophylaxis improve the control of nausea and vomiting with low- emetogenic chemotherapy? *Asian Pac J Cancer Prev,* **14**, 469-73

Kubota H, Taguchi K, Kobayashi D, et al (2013). Clinical impact of palliative treatment using octreotide for inoperable malignant bowel obstruction caused by advanced urological cancer. *Asian Pac J Cancer Prev,* **14**, 7107-10.

Li CH, Liu MY, Liu W, et al (2014). Randomized control study of nedaplatin or cisplatin concomitant with other chemotherapy in the treatment of advanced non-small cell lung cancer. *Asian Pac J Cancer Prev,* **15**, 731-6.

Rabasseda X.Ramosetron (2002). 5-HT3 receptor antagonist for the control of nausea and vomiting. *Drugs Today (Barc)*, **38**, 75-89.

Tas D, Uncu D, Sendur MA, et al (2014). Acupuncture as a complementary treatment for cancer patients receiving chemotherapy. *Asian Pac J Cancer Prev,* **15**, 3139-44.

Uygun K, Bilici A, Kaya S, et al (2013). XELIRI plus bevacizumab compared with FOLFIRI plus bevacizumab

as first-line setting in patients with metastatic colorectal cancer: experiences at two-institutions. *Asian Pac J Cancer Prev,* **14**, 2283-8.

Wang JY, Cai Y (2013). Clinical observation and prognostic analysis of pemetrexed plus platinum as first-line treatment in patients with advanced non-small cell lung cancer. *Asian Pac J Cancer Prev,* **14**, 6267-71.

Wang M, Gu J, Wang HX, et al (2013). Retrospective study of gemcitabine based chemotherapy for unresectable or recurrent esophagus squamous cell carcinoma refractory to first line chemotherapy. *Asian Pac J Cancer Prev,* **13**, 4153-6.

Wang SY, Zhu WH, Vargulick S, et al (2013). Nausea and vomiting after transcatheter arterial chemoembolization for hepatocellular carcinoma: incidence and risk factor analysis. *Asian Pac J Cancer Prev,* **14**, 5995-6000.

Wei G, Nie MM, Shen XJ, et al (2014). Experimental study on sustained-release 5-Fluorouracil implantation in canine peritoneum and para-aortic abdominalis. *Asian Pac J Cancer Prev,* **15**, 407-11.

Wu XY, Huang XE, You SX, et al (2013). Phase II study of pemetrexed as second or third line combined chemotherapy in patients with colorectal cancer. *Asian Pac J Cancer Prev,* **14**, 2019-22.

Xu X, Wang L, Xu HQ, et al (2013). Clinical comparison between paclitaxel liposome (Lipusu®) and paclitaxel for treatment of patients with metastatic gastric cancer. *Asian Pac J Cancer Prev,* **14**, 2591-4.

Yan HA, Shen K, Huang XE (2013). Clinical study on mannan peptide combined with TP regimen in treating patients with non-small cell lung cancer. *Asian Pac J Cancer Prev,* **14**, 4801-4.

Yusuf A, Ahmad Z, Keng SL et al (2013). Quality of life in Malay and Chinese women newly diagnosed with breast cancer in Kelantan, Malaysia. *Asian Pac J Cancer Prev,* **14**, 435-40.