British Journal of Anaesthesia **112** (3): 485–90 (2014)
Advance Access publication 22 October 2013 · doi:10.1093/bja/aet340

BJA

CLINICAL PRACTICE

Efficacy of palonosetron for the prevention of postoperative nausea and vomiting: a randomized, double-blinded, placebo-controlled trial

H. R. Chun[1], I. S. Jeon[2], S. Y. Park[1], S. J. Lee[1], S. H. Kang[1] and S. I. Kim[1]*

[1] Department of Anesthesiology and Pain Medicine, Soonchunhyang University Hospital Seoul, 657, Hannam-dong, Yongsan-gu, Seoul, Republic of Korea
[2] Department of Anesthesiology and Pain Medicine, Soonchunhyang University Hospital Gumi, 250, Gongdan-dong, Gumi, Gyeongsangbuk-do, Republic of Korea

* Corresponding author. E-mail: soonnim@schmc.ac.kr

Editor's key points

- Effective long-acting anti-emetic treatment should help improve postoperative recovery and early discharge.
- Palonosetron, a new 5-HT_3 receptor antagonist, may offer advantages with a prolonged duration of action.
- This study found that palonosetron showed benefit over placebo mainly in the first 24 h.
- Further work is needed to establish the place of palonosetron in the management of postoperative nausea and vomiting.

Background. The aim of this study was to evaluate the efficacy of palonosetron, the latest 5-HT_3 receptor antagonist, for the prevention of postoperative nausea and vomiting (PONV) during the first 72 h after operation.

Methods. In this randomized, double-blinded, placebo-controlled study, 204 healthy inpatients who were undergoing elective surgery with general anaesthesia were enrolled. Patients were divided into two groups: the palonosetron group (palonosetron 0.075 mg i.v.; $n=102$) and the placebo group (normal saline i.v.; $n=102$). The treatments were given after the induction of anaesthesia. The incidence of nausea, vomiting, severity of nausea, and the use of rescue anti-emetics during the first 72 h after surgery were evaluated.

Results. The incidence of PONV was lower in the palonosetron group compared with the placebo group during the 0–24 h (33% *vs* 47%) and 0–72 h period (33% *vs* 52%) ($P<0.05$), but not during the 24–72 h postoperative period (6% *vs* 11%). The incidence of nausea was also significantly lower in the palonosetron group than in the placebo group during the 0–24 and 0–72 h period ($P<0.05$), but not during the 24–72 h postoperative period. However, there were no significant differences in the incidence of vomiting, and the use of rescue anti-emetics between the groups.

Conclusions. Palonosetron 0.075 mg i.v. effectively reduced the incidence of PONV during the first 72 h after operation, with most of the reduction occurring in the first 24 h.

Keywords: anti-emetics; palonosetron; postoperative nausea and vomiting

Accepted for publication: 6 July 2013

Postoperative nausea and vomiting (PONV) is one of the most common and distressing complications after anaesthesia and surgery. PONV may result in wound dehiscence, bleeding, dehydration, electrolyte imbalance, pulmonary aspiration of gastric contents, and delayed hospital discharge.[1] Despite advances in the prevention of PONV and development of new drugs, the overall incidence of PONV has been reported to be between 20% and 30%, and can increase up to 80% in high-risk patients.[2]

For the prevention of PONV, several anti-emetics of different pharmacological classes are available. Currently, selective 5-hydroxytryptamine type 3 (5-HT_3) receptor antagonists are frequently used for the prevention of PONV because of their efficacy and fewer side-effects compared with other anti-emetics.[3 4]

Palonosetron, the latest 5-HT_3 receptor antagonist, exhibits significantly different characteristics from older 5-HT_3 receptor antagonists because of its unique chemical structure. Palonosetron has a greater receptor binding affinity and a much longer half-life, conferring a prolonged duration of action, exceeding 40 h, compared with other 5-HT_3 receptor antagonists.[5 6] In addition, palonosetron exhibits allosteric interactions and triggers receptor internalization resulting in a long-lived inhibition of receptor function.[7]

Given these pharmacological differences, palonosetron provides better protection against chemotherapy-induced nausea and vomiting (CINV) compared with older 5-HT_3

receptor antagonists (ondansetron, dolasetron, granisetron) throughout the 5 day post-chemotherapy period.[8–10]

For the prevention of PONV, two identically designed multicentre, double-blind, placebo-controlled phase III efficacy trials were published.[11 12] One study showed that palonosetron effectively prevented PONV during the 0–72 h postoperative period.[11] However, another study showed that palonosetron effectively prevented PONV during the 0–24 h period after operation, but not during the 24–72 h postoperative period.[12] As a result, more clinical evidence is needed before palonosetron can be routinely used in the prevention of PONV.

This randomized, double-blind, placebo-controlled study was designed to further evaluate the efficacy of palonosetron for preventing PONV during the first 72 h after operation.

Methods

The study was approved by the IRB of Soonchunhyang University Hospital (Ref: 2010-106) before study commencement and registered with CRiS (Ref: KCT0000537). After receiving written informed consent, 204 healthy inpatients with an ASA physical status of I–II, aged 20–70 yr, who were undergoing elective surgery, were enrolled in this randomized, double-blinded, placebo-controlled study. The patient underwent laparoscopic cholecystectomy or herniorrhaphy, minor orthopaedic surgery, plastic surgery, mastoidectomy and/or tympanoplasty, thyroidectomy, or tonsillectomy. Exclusion criteria included pregnancy, body weight more than 30% above the ideal body weight, vomiting or retching within 24 h before the operation, administration of anti-emetics or steroids or psychoactive medications within 24 h before the operation, or patients who electively requested an i.v. patient-controlled analgesia (i.v. PCA) using fentanyl for postoperative pain control or received an i.v. PCA using fentanyl after operation.

Patients were randomly allocated to one of the two groups: palonosetron group (palonosetron 0.075 mg i.v.) or placebo group (normal saline i.v.). Randomization was performed before surgery using a computer-generated randomized number table. The envelopes were opened before induction of anaesthesia by a trained nurse not involved in the study. The nurse then prepared the appropriate study medication as an injectable solution (1.5 ml) placed in identical syringes, for i.v. administration after the induction of anaesthesia. All patients and investigators collecting the postoperative data were blinded to the randomization. A standardized anaesthesia regimen was followed. All patients received midazolam 3–5 mg i.m. for premedication 30 min before surgery. General anaesthesia was induced with propofol 2 mg kg^{-1} and fentanyl 2 $\mu g\ kg^{-1}$. Rocuronium 0.6 mg kg^{-1} was administered to facilitate tracheal intubation. Anaesthesia was maintained with sevoflurane or desflurane combined with nitrous oxide (50%). At the end of surgery, residual neuromuscular block was reversed with pyridostigmine and glycopyrrolate in all patients. Ketorolac (0.5–1.0 mg kg^{-1}) was administered for postoperative pain control. After surgery, patients were observed in the post-anaesthetic care unit for 1 h before ward transfer. The incidence of nausea and vomiting, severity of nausea, and use of rescue anti-emetics were evaluated at 1, 6, 24, 48, and 72 h after operation. An episode of vomiting was defined as either vomiting (expulsion of stomach contents) or retching (an involuntary attempt to vomit but not productive of stomach contents). The severity of nausea was assessed using a four-point verbal rating scale (none, mild, moderate, severe). Metoclopramide 10 mg was administered i.v. as rescue medication for PONV upon patient's request or complaint of nausea ($\geq$ moderate nausea) or vomiting. For postoperative pain control, non-steroidal anti-inflammatory drugs (ketorolac, etc.) were given. Adverse events were evaluated and recorded by the investigator during the entire observation period. Patients were asked to rate their overall satisfaction with the anaesthetic experience on a three-point scale (satisfied, neutral, and dissatisfied) at 72 h after operation.

The primary outcome measured in this study was the incidence of PONV 0–24 h after operation, and the secondary outcome measured included the incidence of PONV 24–72 h after operation, the severity of nausea, use of rescue medication, and patient satisfaction.

The sample size was predetermined using power analysis based on the following assumptions: (i) the incidence of PONV would be 60% in the placebo group[13]; and (ii) a 34% reduction in the incidence of PONV[11] (from 60% to 40%) by palonosetron would be of clinical relevance using α=0.05 and β=0.2. The sample size was estimated at 97 patients per group. A larger number of patients, 102 patients per group, were enrolled to allow for possible incomplete data collection or patient dropout.

Statistical analysis was performed using SPSS for Windows (version 14, SPSS Inc., Chicago, IL, USA). Student's *t*-test was used to compare the continuous variables between the groups. Categorical variables were analysed using the χ^2 test or Fisher's exact test, as appropriate. A *P*-value of $<$0.05 was considered statistically significant. Data are presented as mean [standard deviation (SD)], numbers, or percentages.

Results

Among the 204 patients enrolled in this study, 15 patients were withdrawn from the study due to receiving i.v. PCA using fentanyl for pain control after being transferred to the ward. Therefore, only data obtained from the remaining 189 patients were analysed, 94 patients in the palonosetron group and 95 in the placebo group (Fig. 1).

There were no significant differences between the groups with respect to patient characteristics, Apfel's risk score, duration of surgery, duration of anaesthesia, and type of surgery (Table 1).

The incidence of PONV was significantly lower in the palonosetron group than in the placebo group during the 0–24 h (33% *vs* 47%) and the 0–72 h postoperative period (33% *vs* 52%) ($P<0.05$), but not during the 24–72 h postoperative period (6% *vs* 11%) (Table 2).

The incidence of nausea was significantly lower in the palonosetron group than in the placebo group during the 0–24 h