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ORIGINAL ARTICLE

No Superiority of Granisetron Over Metoclopramide in Prevention of Post-operative Nausea and Vomiting: A Randomized Clinical Trial

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Abstract
Purpose Post-operative nausea and vomiting (PONV) is considered as one of the most disturbing sequels of surgeries under general anesthesia, which if not controlled appropriately increases post-operative morbidity, nursing burden, and general healthcare costs. In this study, we compared granisetron with its brand Kytril® and also with metoclopramide regarding PONV management.
Methods A total of 180 obstetrics and gynecology patients who underwent surgeries under general anesthesia participated in this prospective study at the Dr. Shariati Teaching Hospital, Tehran, Iran. The patients were randomly assigned to single-dose generic granisetron (40 mcg/kg), Kytril® (40 mcg/kg), or metoclopramide (0.2 mg/kg) at the end of the surgery. Two episodes of emetic symptoms (nausea and vomiting) were recorded by a gynecologist who had no knowledge of which treatment each patient had received. This gynecologist observed the patients at three different intervals: 0–6, 6–12, and 12–18 h post-surgery.
Results One hundred and thirty-seven patients (76.1 %) underwent hysterectomy and 40 patients (22.2 %) underwent myomectomy. Each group consisted of 60 patients (33 %). The incidence of vomiting in the first 6, 12, and 18 h post-surgery was 22, 15.2, and 13.3 % for granisetron; 18.6, 10, and 8.3 % for Kytril; and 22, 11.9, and 5 % for generic metoclopramide, respectively. There was no significant difference in the incidence of PONV with any of these agents.
Conclusions All three anti-nausea and vomiting agents, granisetron, its brand (Kytril), and generic metoclopramide, have a similar effect to manage PONV in obstetrics and gynecological surgeries. *Trial registration* This trial is registered with www.irct.ir, number IRCT201010134927N1.

Keywords Post-operative nausea and vomiting · Granisetron · Kytril · Metoclopramide

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Introduction

Post-operative nausea and vomiting (PONV) is still one of the most disturbing sequels and a common patient's

complaint after general anesthesia. PONV can increase the length of both recovery room and hospital stay and the overall health care cost. Even after the introduction of newer anti-emetic agents to the market, shorter surgical procedure techniques, and shorter acting anesthetics, the incidence of PONV is still high [1]. The vomiting center (VC) in the medulla, chemoreceptor trigger zone (CTZ), and higher cortical centers are all involved in vomiting. There are dopamine, serotonin, histamine, muscarinic, and opioid receptors located in these regions and most anti-emetic agents, including 5HT (serotonin) antagonists and dopamine antagonists, act by blocking these receptors. The incidence of PONV with volatile anesthetics is between 20 and 30 %, which in high-risk patients can go up to 80 %. Besides the type of anesthetic agent, there are other factors which affect the incidence and severity of PONV including age, female sex, non-smoking status, surgical technique and duration, and history of previous PONV or motion sickness [2–4].The PONV prophylaxis would be necessary considering the potential risks associated with PONV including suture opening, esophageal rupture, and increasing the risk of aspiration pneumonia due to post-operative vomiting. In this prospective study, we compared the efficacy of generic granisetron with its brand Kytril and also with generic metoclopramide for prevention of PONV in gynecological surgeries.

Materials and Methods

This 11-month randomized study was conducted at the Dr.Shariati Teaching Hospital, affiliated to Tehran University of Medical Sciences. Participants were randomized by parallel computer selection. Approval of our institutional ethics committee was obtained. Ethical approval for this study (Ethical Committee N° 90-130-208) was provided by the Ethical Committee of Tehran University Hospitals, Tehran, Iran (Chairperson Prof. Akbar Fotoohi), on February 2, 2010. This trial is registered with www.irct.ir, number IRCT201010134927N1.

A total of 180 obstetrics and gynecology patients who had undergone myomectomy and hysterectomy surgeries were allocated randomly into one of three 60-patient groups (1:1:1) via a computer-generated random selection (Block randomization) to be treated with generic granisetron (40 mcg/kg, by Aburaihan Pharmaceuticals), Kytril® (40 mcg/kg by Roche Laboratories Inc.), or generic metoclopramide (0.2 mg/kg by Caspian Tamin Pharmaceuticals) at the end of the operation.

As the two studies were identical, data were combined and analyzed as a single trial. The planned sample size of 180 patients was sufficient to detect a 15 % difference between groups at the nominal, two-sided, 0.05 level of significance and 80 % power. Sample size was predetermined using a power analysis based on the following assumptions: (1) The total incidence of nausea and vomiting in the saline group would be 60 % [5]; (2) a 30 % reduction in the total incidence of nausea and vomiting (from 60 to 42 %) in the treatment groups would be of clinical relevance; and (3) $\alpha = 0.05$ and $\beta = 0.2$ [6].

Patients with medical histories including gastrointestinal diseases, motion sickness, and who received any anti-emetics within 24 h of their surgeries were excluded from this study. All included patients signed a consent form provided to them regarding the content of this study with details in patient information.

The anesthesia induction was done with 0.1–0.3 mcg/kg sufentanil, 5 mg/kg sodium thiopental, 0.5 mg/kg atracurium, and 1 mg/kg lidocaine intravenously. For each patient, an envelope containing the group assignment was prepared, sealed, and sequentially numbered. On the morning of the surgery and before induction of anesthesia, a nurse who was not involved in the patient's evaluation opened the envelope and prepared generic granisetron, Kytril®, or generic metoclopramide syringes for administration. The investigator involved in patient management and data collection was also not aware of the group assignment.

All patients were evaluated at 6, 12, and 18 h post-surgery for the incidence rates of nausea and vomiting (primary outcome) by a gynecological specialist. Also, as the defined secondary outcomes, each patient was asked for her satisfaction with PONV prevention and also drug-induced sedation in 2 ranking scales at 18 h post-operation. For the PONV prevention, a 1–5 scale was used, with 1 meaning no satisfaction with the treatment and 5 meaning the highest satisfaction rate. Regarding sedation, 1 means no sedation and 5 means the highest sedation effect [7].

A series of one-way analyses of variance was conducted to examine differences among the three groups with respect to parametric variables. The Kruskal–Wallis test was used to determine differences among the three groups with respect to nonparametric variables, followed by the Mann–Whitney *U*-test for intergroup differences.

Results

Demographic Data

Three patients were excluded from the study because of short a follow-up period. One hundred and thirty-seven patients (76.1 %) underwent hysterectomy and 40 patients (22.2 %) underwent myomectomy between February 2010 and January 2011. All patients received allocation interventions with no loss to follow-up or discontinuation of intervention, and there was no exclusion from study

Table 1 Patients' demographic information

Variable	Kytril®	Metoclopramide	Granisetron	*p* value
Age (Mean)—year	43.4 ± 7.9	46.7 ± 9.6	43.7 ± 7.9	0.066
Weight (Mean)—year	72.3 ± 12.7	74.5 ± 12.6	73.1 ± 12.5	0.617
Duration (Mean)—day	2.5 ± 4.4	2.3 ± 4.1	2.3 ± 2.9	0.943
Allergy existing (Yes/No)—n	4/52	7/49	8/51	0.507

statistical analysis. Mean age in patients who received Kytril®, generic granisetron, and generic metoclopramide was 43.3, 40.3, and 40.9 (years), respectively, and mean duration of post-operative hospitalization was 2.4 days for all patients. As shown in Table 1, demographic information among the three allocated groups was statistically comparable.

Nausea and Vomiting

The incidence of vomiting in the first 6, 12, and 18 h post-surgery was 22, 15.2, and 13.3 % for the generic granisetron; 18.6, 10 and 8.3 % for granisetron brand Kytril®; and 22, 11.9, and 5 % for generic metoclopramide, respectively. Results regarding the rate of both nausea and vomiting with each of these three agents within the first 6, 12, and 18 h poet-surgery are shown in Table 2. Considering the *p* values, there was no significant difference in the incidence of PONV with any of these agents. (Table 2).

Sedation Score and Treatment Satisfaction

Sedation score was 1.48, 1.69, and 1.43 out of 5 in the Kytril®, generic metoclopramide, and generic granisetron groups, respectively. Also, treatment satisfaction rates were 3.95, 3.81, and 3.84 out of 5 in the Kytril®, generic metoclopramide, and generic granisetron groups, respectively. (Table 2).

Discussion

Nausea and vomiting is still one of the major complaints by patients post-operation under general anesthesia. The incidence of PONV is about 20–30 % and in high-risk patients up to 80 %. Peri-operative opiate use, volatile anesthetic agents, and duration of the surgery are among the major surgery- and anesthesia-related factors. Each 30 min added to surgery duration increases the risk of PONV by 60 %. Using newer agents like propofol rather than volatile anesthetics reduces the incidence of PONV [8].

The drugs used for either PONV prophylaxis or treatment are mostly serotonin and dopamine antagonists. These medications work both directly on the gastrointestinal tract and on the central nervous system to block the related receptors and inhibit the process of vomiting. Major drug classes in this regard are butyrophenones (e.g., droperidol), benzamides (e.g., metoclopramide), muscarinic receptor antagonists (e.g., scopolamine), corticosteroids (e.g., dexamethasone), and serotonin antagonists (e.g., granisetron). [9].

Metoclopramide antagonizes dopamine effects in CTZ and VC, also facilitates the gastric emptying time, and increases the lower esophageal sphincter tone. It reverses the post-operative gastric stasis induced by morphine and other opiates. Major side effects include abdominal cramping, dizziness, extrapyramidal symptoms, and sedation. In a meta-analysis on 54 studies including a total number of 7,324 patients by Domino et al., in 1999,

Table 2 Rate of nausea and vomiting at 6, 12, and 18 h post-operation

Variable	Kytril®	Metoclopramide	Granisetron	*p* value
Existence of vomiting				
6 h after operation, n (%)	11 (18.3)	13 (21.7)	13 (21.7)	0.872
12 h after operation, n (%)	6 (10.0)	7 (11.7)	9 (15.0)	0.695
18 h after operation, n (%)	5 (8.3)	3 (5.0)	8 (13.3)	0.272
Existence of nausea				
6 h after operation, n (%)	19 (31.7)	19 (31.7)	21 (35.0)	0.903
12 h after operation, n (%)	11 (18.3)	17 (28.3)	16 (26.7)	0.392
18 h after operation, n (%)	11 (18.3)	6 (10.0)	12 (20.0)	0.329
Sedation score				
18 h after operation—Mean	1.48	1.69	1.43	0.359
18 h after operation—Mean rank	84.81	96.92	88.38	
Treatment satisfaction score				
18 h after operation—Mean	3.95	3.81	3.84	0.366
18 h after operation—Mean rank	92.50	84.94	86.61	

metoclopramide was not as effective as either ondansetron or droperidol for prevention of PONV. In the majority of studies, metoclopramide was dosed as 10 mg intravenous at the end of surgery.

On the other hand, 5HT3 (serotonin) antagonists act by blocking the serotonin receptors both in the brainstem and the gastrointestinal tract. Major side effects of this family include headache which may be dose dependent, flushing, and light-headedness. The advantage of less frequent dosing may be seen with granisetron with longer elimination half-life (2.5 times longer than ondansetron elimination half-life) [10–13].

Fujii and his colleagues also performed a number of comparative studies on the efficacy profiles of granisetron, metoclopramide, and droperidol in the prevention of PONV. In one of these studies in 1994, the efficacy of granisetron versus metoclopramide on 60 female patients who underwent gynecologic surgeries was evaluated. The doses of granisetron and metoclopramide were 3 and 10 mg, respectively, intravenous at the end of the surgery. The incidence of PONV between 3 and 24 h post-operation was 0.5 with metoclopramide and 0.1 with granisetron [14].

Gan et al., [15–17] in their study in 2009 showed that a single dose of 0.1 mg intravenous granisetron versus 6.25 mg intravenous promethazine at the end of surgery was more effective to prevent PONV (53.3 vs 36.2 % response rate, p value $= 0.0079$). Another study in 1998 on 90 patients was done to compare the efficacy of granisetron, metoclopramide, and droperidol in PONV prevention. They concluded on the superiority of granisetron to reduce the incidence of PONV within 24 h post-surgery (incidence of 20, 57, and 60 %, respectively).

In our study, the granisetron dose was 0.04 mg/kg with the mean weight of 73 kg (2.5–3 mg dose) and the metoclopramide dose was 0.2 mg/kg (10–15 mg dose), which are comparable with the above studies. However, different from previous studies in this regard, we concluded that no significant difference exists between granisetron and metoclopramide in reducing the incidence of PONV, which makes it unique to show no superiority of 5HT3 with relatively longer half-life versus metoclopramide. Another notable result of this study was that both brand Kytril and its generic granisetron by a local pharmaceutical company showed equivalent efficacy in PONV prevention. It should be taken into consideration that the results of our study might be due to inter-individual pharmacogenetic variables as well as the types of gynecological procedures included in this study. So, further studies in this regard are recommended.

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Conflict of interest There is no conflict of interest in our study.

Disclosure All of the authors state that they do not have any relationships with companies that may have a financial interest in the information contained in the manuscript and they have nothing to disclose.

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