Original Research Article

Comparative evaluation of Ondansetron and Granisetron in combination with Dexamethasone for the prophylaxis of chemotherapy and radiation induced emesis in cervical cancer patients: A prospective study

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Abstract

Background: In advanced stages of cervical cancer, neoadjuvant chemoradiation have been used to improve the survival rates. Chemotherapy and radiotherapy induced emesis is severe adverse effect observed in cancer patients. There isstrong need to control nausea and vomiting, so that patients have better quality of life and adherence to treatment. **Objective:** present study plan to compare the efficacy of Ondansetron and Granisetron in combination with Dexamethasone in the prophylaxis of chemotherapy and radiation induced emesis in cervical cancer patients. **Methods:** This is a prospective study conducted from March 2019 to August 2020 in Jaya Arogya hospital, Gwalior. Cervical cancer patients were admitted for concurrent chemoradiation (Cisplatin monotherapy and half body irradiation). Total 100 cervical cancer patients included in study.Among them 50patients were administeredOndansetron and Dexamethasone and rest 50 patients were given Granisetron and Dexamethasone for prevention to chemothrapy or radiotherapy induced nausea and vomiting. Efficacy of antiemetics was assessed using multinational association of supportive care in cancer antiemesis tool and severity graded by Common Terminology Criteria for Adverse Events. **Results:** The study showed that 46% patients experienced nausea, 30% experienced vomiting who received Granisetron plus Dexamethasone whereas 64% experienced nausea, 46% experienced vomiting who received Ondansetron plus Dexamethasone. 36%, 20%, 8% patients in group1 and 30%, 12%, 4% patients in group2 experienced mild, moderate and severe nausea respectively whereas 28%, 14%, 4% patients in group1 and 22%, 6%,2% patients from group2 experienced mild, moderate and severe vomiting respectively. **Conclusion:** Present study showed that prophylactic use of Granisetron is more efficacious than Ondansetron for controlling chemotherapy and radiation induced nausea and vomiting.

Keywords: Antiemetics, Chemotherapy, Radiotherapy, Ondansetron, Granisetron.

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Introduction

Carcinoma cervix is the commonest malignancy in women in India yielding an incidence of 19.4 to 43.5 per 100,000. This rise has been mainly attributed to urbanization, industrialization, lifestyle changes, population explosion and increased life span. [1] In India, most patients present in advanced stage and the prognosis is directly related to the stage at presentation.To date, surgery and radiotherapy have been the mainstay of the treatment for carcinoma cervix, which is curative in early stage disease, but survival considerably decreases in advanced stage. In an effort to improve the survival rates, neoadjuvant chemotherapy in cancer cervix has been used. [2]

Chemotherapy and radiotherapy induced emesis is severe adverse effect observed in cancer patients which decreases patient compliance to drug therapy drastically. Different chemotherapeutic agents differ in their emetogenic potential. [3]

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Cisplatin monotherapy with concurrent radiotherapy is used in patients with advanced cervical carcinoma. Cisplatin known as a highly emetic drug. [4] Nausea and vomiting is also common when the mid- and upper-hemibody is exposed to radiation. If left untreated, vomiting can lead to various life threatening complications like discontinuation of therapy, aspiration of vomitus, dehydration and electrolyte imbalance. So prolonged vomiting has direct consequences and requires careful medical management. [5] Antiemetics are routinely administered before infusingCisplatin or irradiation.

The knowledge of the pathophysiology of chemotherapy induced nausea and vomiting (CINV) has advanced in the recent years. The important neurotransmitters said to be involved in CINV are serotonin, substance P and dopamine, and their receptors are located in the gastrointestinal tract and the central nervous system. Unlike CINV what causes radiation induced nausea and vomiting (RINV) is not very clear but scientists opine hypothetically that both share same related neurotransmitters and pathways. The other neurotransmitters involved in nausea and vomiting are cannabinoids, histamine, GABA and acetylcholine. It is postulated that there are a total of twenty

neurotransmitters and receptor systems involved in the vomiting reflex. Thus, agents which block the receptors of these neurotransmitters can be used pharmacologically totreat nausea and vomiting. [6]

Antiemetic management has been regulated by a standardized prophylactic antiemetic regimen which comprises of a serotonin antagonist and dexamethasone given to patients for prevention of acute and delayed nausea and vomiting. [7] Ondansetron was the first 5-HT3 antagonist, developed by Glaxo around 1984. Its efficacy was first established in 1987, in animal models. It blocks emetogenic impulses both at their peripheral and central origin. It also has a weak 5-HT4 antagonistic action. [8] Granisetron is a potent and highly selective 5-HT3-receptor antagonist that has little or no affinity for other 5-HT receptors. It was developed in 1995 and widely used for CINV. [9] Dexamethasone has adjuvant antiemetic action, can alleviate nausea and vomiting as it augment the efficacy of other primary antiemetic drugs. [10]On literature survey there is no scientific study available regarding efficacy of Granisetron over Ondansetron for prophylaxis of both CINV and RINV in patients of cervical cancer (stage IIA to IVB). Therfore present study is undertaken to compare the efficacy of Ondansetron and Granisetron in combination with Dexamethasone in the prophylaxis of chemotherapy and radiation induced emesis in cervical cancer patients.

Material and Methods

This was a prospective, randomized, single blind comparative study between Ondansetron and Granisetron on chemotherapy and radiation induced nausea and vomiting in cervical cancer patients. The study was conducted in department of Oncology at J.A. Group of hospitals and department of Pharmacology G.R. Medical College, Gwalior during March 2019 to August 2020, during 18 months duration total 100 patients (50 in each group) were enrolled in the study.

Inclusion criteria: In this study advanced cervical cancer patients (stage IIA to IVB) receiving Cisplatin chemotherapy & concurrent radiotherapy, age 18 years and above, who are on either Ondansetron or Granisetron as one of the antiemetic prophylaxis were included.

Exclusion criteria: In this study patients who are on antiemetics prophylaxis other than Ondansetron and Granisetron, or diagnosed with serious psychiatric conditions or suffering from serious liver and renal disorders were excluded

For this study ethical approval was obtained from institutional ethics committee, G R medical college, Gwalior (approval certificate no. 13/IEC-GRMC/2018). Written and informed consent from the patients were obtained prior to enrolment in study.

Study procedure

In this study, total 100 patients were included with diagnosis of advanced cervical cancer (stage IIB-IVA) who met the eligibility criteria and advised Cisplatin monotherapy (dose 40 mg/m^2) on 1st day and concurrent hemibody irradiation administered by using cobalt 60 teletherapy machine on 2nd day to 5th day. Patients were randomly allocated into 2 groups. Group I (n=50) received Ondansetron 8mg IV BD + Dexamethasone 4mg IV BD for 5 days and group II (n=50) received Granisetron 2mg IV BD + Dexamethasone 4mg IV BD for 5 days. Morning dose of antiemetic was given to patient, 30 minute before chemotherapy or radiotherapy.

Then Follow up was done every day upto five days to evaluate efficacy by no nausea and no vomiting (complete response). Data of nausea and vomiting were assessed using MASCC Antiemesis Tool (Multinational Association of supportive care in cancer). [11] Acute nausea & vomiting was defined when occurrence in first 24 hours after chemotherapy in case of CINV and acute nausea & vomiting after radiation was defined when occurrence was in period from a second day to fifth day after radiotherapy. The severity of nausea and vomiting assessed and graded by Common Terminology Criteria for Adverse Events (CTCAE version 4.03). [12]

Statistical Analysis Plan

All randomized patients who received prophylactic antiemetics for recommended duration included for analysis. Categorical data is expressed as a percentage and continuous data as mean ± standard deviation. Chi square test was performed to evaluate p value by statistical software SPSS20 and p value less than 0.05was considered as statistically significant.

Results

Demographic profile

The study was completed in 100 cervical cancer patients receiving chemotherapy and radiotherapy. The age of patients of cervical cancer in our study range from 43 to 74 years with a mean age of 57 ± 12.6 years and most common age group was 50-60 years. Marital status of patients, 88% were married and rest 12% were widow.. According to locality, 67% patients were from rural background and 33% patients were from urban areas. According to religion, 95% patients from hindu community and 5% patients from muslim community. Socio-economic status of patients, according to Kuppuswamy scale, maximum patients belong to lower middle class (53%) followed by 33% patients from upper lower class and some patients belong to upper middle, lower and upper class. Out of total 100 patients, 14% patients had co-morbidity (hypertension and diabetes mellitus). On the basis of FIGO staging of cervical cancer, maximum patients were of stage IIIB (34%), IIB (33%) & IIIA (28%) and some patients were of stage IVA (5%). (Table-1)

Table 1: Demographic distribution of the patients

Characters	Ondansetron + Dexamethasone group (n=50)	Granisetron + Dexamethasone group (n=50)
Age (years)		
1) <50	18 (36%)	13 (26%)
2) 50 to 60	24 (48%)	21 (42%)
3) >60	8 (16%)	16 (32%)
Marital status		
1) Unmarried	0	0
2) Married	46 (92%)	42 (84%)
3) Widow	4 (8%)	8 (16%)
Locality		
1) Rural	33 (66%)	34 (68%)
2) Urban	17 (34%)	16 (32%)
Religion		

1) Hindu	48 (96%)	47 (96%)
2) Muslim	2 (4%)	3 (6%)
Socio-economic status		
1) Upper	1 (2%)	0
2) Upper Middle	3 (6%)	7 (14%)
3) Lower Middle	33 (66%)	20 (40%)
4) Upper Lower	13 (26%)	20 (40%)
5) Lower	0	3 (6%)
Co-morbidity		
1) Hypertension	4 (8%)	5 (10%)
2) Diabetes mellitus	1 (2%)	3 (6%)
3) HTN + DM	1 (2%)	0
FIGO staging of advanced cervical cancer patients		
1) IIB	19 (38%)	14 (28%)
2) IIIA	12 (24%)	16 (32%)
3) IIIB	16 (32%)	18 (36%)
4) IVA	3 (6%)	2 (4%)

Outcome measures

(1) Occurrence of nausea (0-24 hrs) after chemothrapy,there were 30% cases in Ondansetron group as compared to 28% cases in Granisetron group. Incidence ofnausea for a period of 24 hrs following each radiation on second to fifth days were 16% cases in Ondansetron group as compared to 12% cases in Granisetron group. Incidence of nausea following both chemo and radiation were 18% cases in Ondansetron group as compared to 6% cases in Granisetron group. The incidence of nausea was maximum during the first twenty four hours and it was more in the Ondansetron group. P value is more than 0.05 (not significant). (Graph-1)

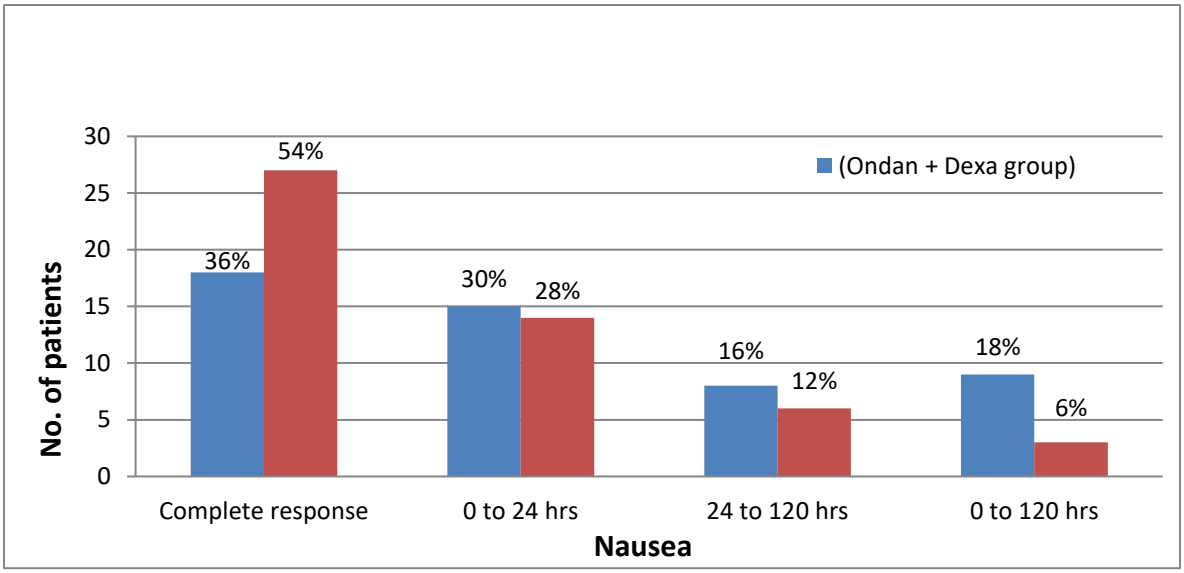

Fig. 1: Observed incidence rate of nausea after prophylaxis

(2) Incidence of vomiting (0-24 hrs) in Ondansetron group and Granisetron group after chemothrapy were 28% cases in Ondansetron group as compared to 20% cases in Granisetron group. Incidence ofvomiting for a period of 24 hrs following each radiation on second to fifth days were 10% cases in Ondansetron group as compared to 6% cases in Granisetron group. Incidence of vomiting following both chemo and radiation were 8% cases in Ondansetron group as compared to 4% cases in Granisetron group. The incidence of vomiting was maximum during the first twenty four hours and it was more in the Ondansetron group. P value is more than 0.05 (not significant). (Graph-2)

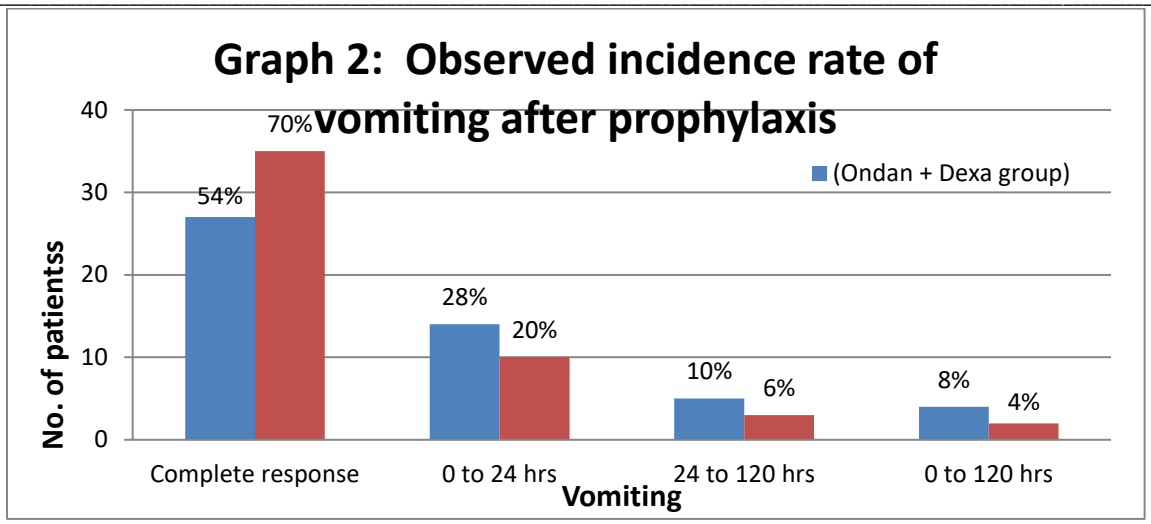

Fig. 2: Observed incidence rate vomiting after prophylaxix

(3)Severity rate of nausea in Ondanstron group and Granisetron groupshowed that mild nausea were in 36% cases in Ondansetron group as compared to 30% cases in Granisetron group, moderate nausea were in 20% cases in Ondansetron group as compared to 12% cases in Granisetron group and severe nausea were in 8% cases in Ondansetron group as compared to 4% cases in Granisetron group. The severity rate of nausea was minimum in Granisetron group than Ondansetron group. P value is more than 0.05 (not significant). (Table-2)

Table 2: Severity rate of nausea after prophylaxis

Nausea	Ondansetron + Dexamethasone group (n=50)	Granisetron + Dexamethasone group (n=50)	P value
Complete response	18 (36%)	27 (54%)	0.412
Mild nausea	18 (36%)	15 (30%)	
Moderate nausea	10 (20%)	6 (12%)	
Severe nausea	4 (8%)	2 (4%)	

(4) Severity rate of vomiting in Ondanstron group and Granisetron groupshowed that mild vomiting (1-2 episodes) were in 28% cases in Ondansetron group as compared to 22% cases in Granisetron group, moderate vomiting (3-5 episodes) were in 14% cases in Ondansetron group as compared to 6% cases in Granisetron group and severe vomiting (>=6 episodes) were in 4% cases in Ondansetron group as compared to 2% cases in Granisetron group. The severity rate of vomiting was minimum and complete response was maximum in Granisetron group than Ondansetron group. P value is more than 0.05 (not significant). (Table-3)

Table 3: Severity rate of vomiting after prophylaxis

Vomiting	Ondansetron + Dexamethasone group (n=50)	Granisetron + Dexamethasone group (n=50)	P value
Complete response	27 (54%)	35 (70%)	0.592
Mild vomiting(1-2 episodes/day)	14 (28%)	11 (22%)	
Moderate vomiting (3-5 episodes/day)	7 (14%)	3 (6%)	
Severe vomiting(>=6 episodes/day)	2 (4%)	1 (2%)	

Discussion

The present study was conducted to study and compare the efficacy of Ondansetron and Granisetron in combination with Dexamethasone used in chemotherapy and radiation induced nausea and vomiting in cervical cancer patients.

In this study, majority of the cases, age group was 50-60 years that included 45% patients followed by age group of <50 years, 31% cases and 24% cases were present in the age group >60 years. In Dahiya et al study, they also found that majority of the cases were in the age group of 50-60 years and Sharma et al in their study found that majority of the cases were in the age group of 60 years and above. [13,14] The mean age of development of cervical cancer in our study was 57.4 ± 12.6 years. Ambika Satija et al had lower mean age of development of cervical cancer in their studies. [15]

In present study, majority of the patients, 67% were from rural areas which was similar to Pragya Sharma et al study in which majority of the patients (73.9%) were from rural areas. In studies conducted in Bellary, Jammu, and North Karnataka, 74%, 55% and 67.34% patients, respectively, were from rural areas. The results were almost similar to our studies, this is because of lack of awareness, poor genital hygiene, poverty and lack of access to health services. [16]

In present study, most of the cases as Hindus i.e. 95% cases and only few cases were Muslims (5%). Dahiya et al found that, Majority of the subjects were Hindus (91.04 %) and only 8.96% were Muslims patients. Pragya Sharma et al also found majority of the Hindus in their studies showed the similar results in other studies also which were done previously. [16]

In the present study, 88% of the study patients were married and rest were widows. These results are comparable with the other studies which have been previously done by Dahiya et al showing that 23.79% cases were widows in their study. [13]

Maximum subjects in the present study were belonged to lower middle socioeconomic class i.e. 53% cases, followed by upper lower socioeconomic class (33%) cases of Kuppuswamy classification system. In other study done by Dahiya et al, maximum cases were present in lower middle socioeconomic class and subjects from the joint family. This may be due to low income suggesting that many were not able to afford the higher cost of cancer treatment.They have poor genital and menstrual hygiene, low nutrition and lack of awareness of health education. Inability to start treatment and lack of compliance will lead to lesser survival rates. [13]

In our study, we included cases from Stage llB to IVA and majority of the cases were of stage lllB followed by cases in stage llB. Only 5 cases were found in Stage IVA, as majority of the advanced cervical cancer in later stages died before they can be diagnosed. These results were similar to study of Dhamija S et al. [17]

In our study, a complete response (defined as no nausea and no vomiting) was attained in 54% of patients who received Granisetron plus Dexamethasone and in 36% of patients who received Ondansetron plus Dexamethasone for prophylaxis of chemoradiation induced nausea vomiting. In previous study, Andrews et al demonstrated that, 5HT3 receptor antagonist drug granisetron, is more potent and long acting than ondansetron against emesis associated with chemotherapy. Yoshitaka Fujii et al, in their study found that Granisetron administration was superior to Metoclopramide and placebo in the long term prevention of post operative nausea vomiting after anaesthesia. [18]

In our study, Granisetron group showed better efficacy than Ondansetron group to control of nausea and vomiting, but was not statistically significant. In previous study, Fujii et al, demonstrated that prophylactic therapy with combination of Granisetron plus Dexamethasone was more effective than each antiemetic alone for the prevention of post operative nausea vomiting after middle ear surgery. [18]Two study conducted by Poon & Chow, and Luisi et al, where observed the response to nausea and vomiting were achieved 70% in the patients who received Granisetron and value was significant. In our study the findings are also consistent with this study. [19,20]

Limitation of the study

Our study was conducted in limited number of patients and was for a short duration. Result of this study need to be confirmed by conducting studies on large number of patients at different centers for a long duration. This can help us to know exactly, which combination of our study is better for treatment.

Conclusion

This study concluded that the prophylactic intravenous administration of Granisetron is better drug than Ondansetron but was non significant statistically for controlling chemotherapy & radiation induced nausea and vomiting. Combination of Dexamethasone 4 mg with antiemetic 5HT3 receptor antagonists Granisetron (2 mg) or Ondansetron (8 mg) decreases the incidence of nausea and vomiting and Granisetron was more effective than Ondansetron to control acute nausea vomiting due to chemotherapy and irradiation.

The incidence of CINV was relatively high, than RINV and it indicates that more attention is needed for the treatment of both CINV and RINV. It also gives an idea for implementation of more efficient antiemesis guideline in the clinical practice.

Radiation-induced nausea and vomiting (RINV) is a frequent complication of radiation therapy. Its effect on patients quality of life should not be underestimated, especially as such effects may compromise or delay treatments. Therefore, patients at risk of RINV should always be offered the most effective antiemetic prophylaxis as suggested by the international guidelines.

References

1. Imran Ali, Waseem A. Wani and Kishwar Saleem. Cancer Scenario in India with Future Perspectives. Cancer Therapy Vol 8, 56-70, 2011.
2. Peters WA, Liu PY, Barrett RJ et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. J Clin Oncol 2000; 18: 1606-1613.
3. Lohr L. Chemotherapy-induced nausea and vomiting. Cancer J 2008; 4: 85-93.
4. National center for gynecological cancers. 2010. Treatment for cervical cancer; cancer Australia, pg 3-6.
5. Herrstedt J. Nausea and emesis: Still an unsolved problem in cancer patients? Support Care Cancer 2002;10:85-87.
6. Frame DG. Best practice management of CINV in oncology patients: I. Physiology and treatment of CINV. Multiple neurotransmitters and receptors and the need for combination therapeutic approaches. J Support Oncol 2010; 8(2 Suppl 1):5-9.
7. American Society of Clinical Oncology guideline for antiemetics in oncology: update 2006.J Clin Oncol. 2006 Jun 20;24(18):2932-47.
8. Butler A, Hill JM, Ireland SJ, Jordan CC, Tyers MB. Pharmacological properties of GR38032F, a novel antagonist at 5-HT3 receptors. Br J Pharmacol 1988;94:397–412.
9. Aapro M.Granisetron: An update on its clinical use in the management of nausea and vomiting. The Oncologist. 2004;9:6-73-86.
10. Ho CM, Ho ST, Wang JJ, et al. Dexamethasone has a central antiemetic mechanism in decerebrated cats. Anesth Analg 2004;99:734–739.
11. MASCC Antiemesis Tool. www.mascc.org
12. Common Terminology Criteria For Adverse Events (CTCAE version 4.03). 2009.
13. Dahiya et al. 1998. Cancer prevention and control research among Houma Indian women. Ethics in epidemiology and public health practices: colleted works. Library of congress catalog. No. 97-75537, 111. Consulted 6.10.2011
14. Sharma et al. 2010. Awareness screening programme reduces the risk of cervical cancer in women.African journal of pharmacy and pharmacology Vol. 4 No. 6, 314-323.
15. Ambika Satija et al. Cervical cancer in India. South Asia Centre for Chronic Disease. Available from: Http:// sancd.org/ uploads/ pdf/cervical-cancer.pdf
16. Pragya Sharma, Manju Rahi. Community-based Cervical Cancer Screening program. Indian J Community Medicine, 2010 January; 35(1): 86–88.
17. Dhamija S, Sehgal A, Luthra UK, Sehgal K. Et al. Factors associated with awareness and knowledge of cervical cancer in a community: implication for health education programmes in developing countries. 1993 Aug1; 13(4):184-6.
18. Yoshitaka Fujii H. Tanka MD, Hidenori Tiyooka. Prophylactic antiemetic therapy with a combination of Granisetron and Dexamethasone in patients undergoing middle ear surgery. Br J Anaesthesia 1998; 81: 754-756.
19. Poon RTP, Chow LWC. Comparison of antiemetic efficacy of granisetron and ondansetron in oriental patients. A randomized cross over study. Br J Cancer. 1998;77: 1683-1685.
20. Luisi FA, Petrilli AS, Tanaka C, Caran EM. Contribution to the treatment of nausea and emesis induced by chemotherapy in children and adolescents with osteosarcoma. Sau Paulo Med J. 2006;124:6-15.

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