In The Name Of God

ISFAHAN UNIVERSITY OF MEDICAL SCIENCES
SCHOOL OF MEDICINE
RADIOTHERAPY ONCOLOGY MEDICINE DEPARTMENT

Thesis for obtaining the specialty degree in Radiotherapy Oncology

Title:

Effect of increase in duration of Aprepitant consumption from 3 to 6 days on the prevention of nausea and vomiting in women receiving combination of Anthracycline/Cyclophosphamide chemotherapy: A randomized, crossover, clinical trial

NUMBER: 393449

Author:

Dr. Negah Chaabi Ahvazi

Supervisors:

Dr. Simin Hemati

(Assistant Professor of Radiotherapy Oncology)

Sep 2015

دانشکده پزشکی

بسمه تعالی

صورتجلسه هیأت داوران پایان نامه دکترای تخصصی

جلسه دفاع از پایان نامه تحقیقاتی خانم دکتر نگاه چعبی اهوازی

تحت عنوان: " بررسی اثر افزایش روزهای مصرف کپسول Abitant از سه روز به شش روز، در کنترل تهوع و استفراغ ناشی از شیمی درمانی با رژیم AC در بیماران مبتلا به سرطان پستان " برای دریافت دکترای تخصصی رشته پرتودرمانی در تاریخ ۱۳۹۴/۳/۴ با حضور امضاء کنندگان زیر تشکیل شد و مورد تصویب قرار گرفت.

۱- **اساتید راهنما:** دکتر سیمین همتی

معاون پژوهشی گروه: دکتر مهناز رعایایی

مدیر گروه: دکتر حمید امامی

مشاور آماری: مهندس اکبر حسن زاده

اعضای هیات داوران:

۲- دکتر حمید امامی

۳- دکتر سیمین همتی

۴- دکتر مینا تجویدی

۵- دکتر مهناز رعایایی

۶- دکتر علی اخوان

۷-

این قسمت توسط حوزه معاونت پژوهشی دانشکده پزشکی تکمیل می شود:

پایان نامه فوق در تاریخ ۹۴/۷/۱ در حوزه معاونت پژوهشی دانشکده با نمره ۱۹/۷۵ (بر مبنای ۲۰) و درجه عالی مورد تائید قرار گرفت.

معاون پژوهشی دانشکده پزشکی

all headers

Date: Mon, 17 Aug 2015 00:48:09 -0400
From: "Advanced Biomedical Research" <sh_haghjoo@med.mui.ac.ir>
Reply-To: <sh_haghjoo@med.mui.ac.ir>
To: <dr.n.ahazi@med.mui.ac.ir>
Subject: [abr]:Article provisionally accepted

all attachments

If you cannot see this page properly, please click here.

Dear Dr. chaabi ahazi,

NOTE: This e-mail is sent to you as one of the contributing authors. *If you are not corresponding author, you do not have to do anything. Please co-ordinate with the author designated by your group as the corresponding author for this manuscript*

Status of the manuscript titled "Effect of increase in duration of Aprepitant consumption from 3 to 6 days on the prevention of nausea and vomiting in women receiving combination of Anthracycline/Cyclophosphamide chemotherapy: A randomized, crossover, clinical trial" submitted by Dr. narges ahazi has been changed and a copy of the mail is as;

Dear Dr. Ahazi,

We are pleased to inform that your manuscript "Effec t of increase in duration of Aprepitant consumption from 3 to 6 days on the prevention of nausea and vomiting in women receiving combination of Anthracycline/Cyclophosphamide chemotherapy: A randomized, crossover, clinical trial" is provisionally accepted. You would receive an edited version of article in about 2-3 weeks from now for a final check and correction.

The journal does not charge for submission, processing or publication of manuscripts and except for color reproduction of photographs.
We thank you for submitting your valuable research work to Advanced Biomedical Research.
With warm personal regards,

Yours sincerely,
Shaghayegh Javanmard
Advanced Biomedical Research

Message sent on Monday, August 17, 2015

Please add sh_haghjoo@med.mui.ac.ir as a contact in your E-mail client to ensure that this mail is not considered a ss junk mail.

— END OF MESSAGE —

Effect of increase in duration of Aprepitant consumption from 3 to 6 days on the prevention of nausea and vomiting in women receiving combination of Anthracycline/Cyclophosphamide chemotherapy: A randomized, crossover, clinical trial

Abstract:

Background: Aprepitant is one of the effective antiemetic drugs that usually used for a period of 3 days for prevention of Anthracycline/ Cyclophosphamide (AC) induced nausea and vomiting. However many patients still experience nausea and vomiting on days 3 to 5.The aim of this study was evaluate the effect of increase in duration of Aprepitant consumption from 3 to 6 days on the prevention of nausea and vomiting in women receiving AC chemotherapy.

Methods: It was a randomized, cross-over, controlled clinical trial. Women with breast cancer and scheduled to receive AC regimens were enrolled in this study. Enrolled patients were randomized into 2 groups. Group I received 3 days regimen of Aprepitant in the first course of AC regimen chemotherapy and 6 days regimen of Aprepitant in the second course; Group II received 6 days regimen followed by 3 days regimen. For nausea and vomiting assessment, we used Eastern Cooperative Oncology Group (ECOG) questionnaire.

Results: forty nine patients were enrolled in this study. Sixty three percent achieved complete response (CR) with 6 day aprepitant regimen

compared with 39% with 3 day regimen (P <0.001).Ten percent had at least one vomiting episode during the 6 day regimen versus 15% with 3 day regimen (p=0.034). Nausea was significantly more sever in 3 days regimen of Aprepitant than in 6 days regimen.

Conclusion: Increase in duration of Aprepitant consumption through 6 days resulted significantly better prevention of nausea and vomiting than 3 day consumption for women receiving Anthracycline/ Cyclophosphamide chemotherapy.

Key word: Chemotherapy, Drug Related Side Effects, nausea, vomiting, Aprepitant, Anthracycline, Cyclophosphamide

Introduction:

Chemotherapy-induced nausea and vomiting (CINV) can be one of the most distressing problems for patients. This side effect impair patients 'quality of life, decline cognitive functions and physical ability and may eventually affect the patient's desire to continue further chemotherapy (1, 2).The mechanisms of CINV is seems to be depend on the cellular injury induced by chemotherapy, which may release neurotransmitters(3).Dopamine and serotonin (5-hydroxytryptamine) are the major excitatory neurotransmitters that are involved in emesis (3).

Several patient-related risk factors for CINV are generally assumed, including gender, age, alcohol use, and history of motion sickness(4). Patients less than 50 years old and women are more likely to suffer from CINV (5). Although, chemotherapy agents are vary in degrees of emetogenic potential and combinations of emetogenic agents may have additive effects on the overall CINV (6).

The combination of Anthracycline/ Cyclophosphamide (AC) chemotherapy are particularly high risk for inducing nausea and vomiting and considered as being highly emetogenic(7, 8).

Strategies for antiemetic prophylaxis have developed in recent years(9, 10). Some antiemetic guidelines for patients receiving highly emetogenic chemotherapy (HEC) recommend the use of the oral neurokinin-1 receptor(NK1) antagonists as part of a routine regimen that also includes a corticosteroid and a selective5-hydroxytryptamine-3 (5-HT3) receptor antagonist (11-13). Incidence of CINV in patients

receiving HEC , including breast cancer patients treated with 5-HT3–receptor antagonists is approximately 50% (14).

Aprepitant is the first commercially available drug of a new class of neurokinin-1 receptor
(NK1) antagonists with little or no affinity for other neurokinin receptors(15, 16).Approved by Food & Drug Administration (FDA) in 2003 for prevention of chemotherapy-induced emesis and usually administered for a period of 3 days(17). Recent studies reveal the efficacy of Aprepitantin preventing CINV in patients who received AC and non–AC-based HEC regimens (18-20).
However, despite these results, many cancer patients still experience CINV(18, 21);also the trend has now been reversed with increasing nausea and vomiting on days 3 to 5. Hence, there is clearly a need for more effective prevention of CINV in patients receiving HEC on delay phase, especially in patient, who are particularly susceptible to these symptoms such as women.

Here we present the study of Aprepitant duration for the management of nausea and vomiting associated with Anthracycline /Cyclophosphamide -containing chemotherapy in women with breast cancer. We hypothesized that addition of Aprepitant duration from 3 to 6 day will improve emetic symptoms in women receiving AC –based chemotherapy for breast cancer.

Methods and Materials:

Study Design:

This study was a randomized, cross-over, controlled clinical trial (IRCT2015040121574N1), and designed to evaluate the effect of increase in duration of Aprepitant usage from 3 days to 6 days on the prevention of nausea and vomiting in women receiving combination of Anthracycline/ Cyclophosphamide chemotherapy. This trial was conducted in referral university hospital in Isfahan (Iran's third largest city, located in the center of Iran), Iran. The Medical Ethics Committee of Isfahan University of Medical Sciences has approved the study design, protocols and informed consent procedure (The ethical code was 393449).

Participants:

Fifty patients with breast cancer were enrolled in this study through convenience sampling method. We included patients who were under 50 years of age, diagnosed with breast cancer and scheduled to receive 4 courses Anthracycline/ Cyclophosphamide (AC) regimens. The following general exclusion criteria were considered: previous history of gastritis, diabetes and brain tumor. In order to detect two-fifths standard deviation difference in the main outcome (nausea severity score), with $\alpha = 0.05$ and power= 80%. We considered 10% attrition rate and the final sample size was estimated 50 patients (25 per group). Patients served as their own controls for study cycles.

Intervention:

Enrolled patients were randomized to 1 of 2 groups. According to the crossover design of the study, Group I received Treatment A (3 days regimen) in the first course of one day AC regimen chemotherapy and Treatment B (6 days regimen) in the second course of one day AC regimen chemotherapy; Group II received Treatment B followed by Treatment A. Treatment A (3 days regimen) consisted of Aprepitant(ABITANT ,Abidi, Iran)125 mg orally plus dexamethasone 8 mg injected Intravenous (IV)on day 1fallowed by 80 mg dexamethasone once per day on days 2 and 3 administered orally (PO). Treatment B (6 days regimen) consisted of Aprepitant125 mg orally plus dexamethasone 8 mg injected Intravenous (IV) on day 1 fallowed by 80 mg dexamethasone once per day on days 2 through 6 administered orally (PO). There was a 30-day washout between the first and second courses.

Measurement:

Patients were followed from first day of chemotherapy for a total of 7 days.

For nausea and vomiting assessment, we used Eastern Cooperative Oncology Group (ECOG) COMMON TOXICITY CRITERIA questionnaire, asking patients to answer 2 specific questions about any nausea and vomiting symptoms. First question was about nausea severity on a 0–3 scale (0= being no nausea, 1=able to eat reasonable intake, 2=intake significantly decreased but can eat, 3=no significant

intake) and second question was about vomiting (0=none, 1=1 episode in 24 hours, 2= 2-5 episodes in 24 hours, 3=6-10 episodes in 24 hours, 4=>10 episodes in 24 hours or requiring parenteral support). Complete response (CR) was defined as no nausea and no episodes of vomiting during the study period.

All patients were given this questionnaire on cycle 1 and cycle 2, at baseline (prior to each chemotherapy treatment course), and after 7 days. Only patients with no symptom of nausea and vomiting (score of zero) at baseline (before chemotherapy) were eligible for entering to each cycle of this study.

Statistical Analyses:

All statistical analysis was performed by using SPSS version 20 (Release 2011, SPSS Inc., Chicago, IL) for windows. Findings had shown as relative frequencies, mean and standard deviation. The Comparisons were performed by McNemar's tests, Wilcoxon signed-rank tests, paired Student's t-test. A mixed General lineal model was used to adjust for age and order of interventions (Treatment B followed by Treatment A or Treatment A followed by Treatment B) for all comparisons. All tests were two-sided and P values less than 0.05 are considered significant. The statistical approach was based on an intention to treat.

Result:

A total of 50 patients were enrolled in the study. One patient declined to continue participating in the study on his decision with no reason. A consort diagram illustrates patient flow through each cycle of the study (figure 1).

All of participants were women with breast cancer and were free from nausea and vomiting before entering to each cycle. The mean age of the 49 subjects analyzed was38.7 ± 6.5 years.

Thirty one (63%) of 49 patients achieved a complete response (CR was defined as no nausea and no episodes of vomiting) with 6 days regimen of Aprepitant compared with nineteen (39%) on 3 days regimen of Aprepitant ($P < 0.001$) (table 1). Overall 19(38.6%) patients achieved a complete response with both of two regimens, 12(24.4%) experienced complete response with 6 days regimen but not attended CR when they cross over to the 3 days regimen and 18(37%) not achieved CR with both of two regimens (table 1).

As present in figure 2, Ninety percent in the 6 days regimen of Aprepitant versus 85% in the 3 days regimen of Aprepitant experienced no vomiting episode. In the 6 days regimen, one vomiting episode was experienced for 10.2% of patient compare with 6.1% in the 3 days regimen. no one experienced more than 1 episode of vomiting with 6 days regimen , but 8.2% of patient experienced 2-5 vomiting episodes with 3 days regimen .The number of vomiting episodes was

significantly lower during the 6 days regimen than during the 3days (P =0.034) (figure 2). No one experienced more than 5 episode of vomiting during the study.

The proportion of patient that remained free from nausea in 6 day regimen was 63% compere with 39% in 3 day regimen(P <0 .001) . Nausea was significantly more sever in 3 days regimen of Aprepitant than in 6 days regimen of Aprepitant (figure 3).
The order of treatment regimens (consumption of each regimen in first cycle or second cycle) was not affected the results of study.
Both treatment regimens were tolerable for patient and no one was complaining of side effects.

Discussion:

Chemotherapy-induced nausea and vomiting (CINV) is a strong and dreaded side effect of chemotherapy that can limit the efficacy of cancer treatments and has a potent negative effect on patient quality of life.
Antiemetic therapy should aim to overcome this problem in all cancer patients receiving chemotherapy. Substantial development has been made in improving the control of CINV, largely because of the introduction of antiemetic agents. But, this trend has now been reversed with increasing nausea and vomiting on days 3 to 5.
This cross over clinical trial in women with breast cancer addressed the potential efficacy of increase in duration of Aprepitant consumption from 3 to 6 days for the prevention of nausea and vomiting induced by

combination of Anthracycline/ Cyclophosphamide (AC) chemotherapy. The advantage of this cross over clinical trial design is less need for samples, similarity of participant in two intervention group and the least Bayes.

In the current setting, we found that consumption of Aprepitant for 6 day was superior to 3 day consumption in the proportion of patients achieving a complete response overall after one day AC regimen chemotherapy (63% versus 39%).As seen in previous trials CINV is well controlled on days 1 and 2 with Aprepitant regimen. However, loss of control on days 6 through 8 in the delayed phase remains a challenge , therefore adding Aprepitant to the standard antiemetic prophylaxis for 6 day provides a significant improvement in complete control for CINV from 43% to 63%(22-24).Madsen et al. report that a 5-day dosing regimen of Aprepitant is highly effective for preventing CINV , Although, single doses of oral Aprepitant 40 mg or oral Aprepitant 125 mg alone were effective for the prevention of post-operative nausea and vomiting (25). However, other studies demonstrate 60-80% complete response to 3 day administration of Aprepitant-containing regimen (19, 20). Badar T et al. represent that more than75%ofpatients were free from nausea on day 1 and day 2 after use of Aprepitant but This fraction decreased from day 3 to day 7(19). This discrepancy may be due to differences in the underlying disease, the patient characteristics, and the chemotherapy regimens the patients received; thus judgments should be made with caution.

We have shown in this study that the number of vomiting episodes is significantly lower during the 6 days Aprepitant regimen than during the 3 days regimen. In agreement with our finding, other studies show significant effect of Aprepitant in the episodes of vomiting reduction, in patients treated with HEC regimens(26, 27).

The main limitation of our study is lack of placebo group to identify the placebo effect. We cannot allocate placebo group because not to treat nausea and vomiting in patient who received chemotherapy is unethical.

The present study provides an experimental evidence of increase duration of Aprepitant consumption can decline nausea severity. Patient who cannot significant intake due to severe nausea is 12% with 3 days regimen, versus 2% with 6 days regimen. A similar trend was seen in the previous studies where patient who received 5 days of Aprepitant had less nausea on day 6 and day 7(28, 29)

Hence, we can provide superior prevention of CINV in women with breast cancer only with increasing in duration of Aprepitant consumption.

Conclusion:

In conclusion, increase in duration of Aprepitant consumption through 6 days resulted in significantly better prevention of CINV than 3 day consumption and provides adequate antiemetic therapy for patient receiving Anthracycline/ Cyclophosphamide chemotherapy.

References:

1. Fernandez-Ortega P, Caloto M, Chirveches E, Marquilles R, San Francisco J, Quesada A, et al. Chemotherapy-induced nausea and vomiting in clinical practice: impact on patients' quality of life. Supportive Care in Cancer. 2012;20(12):3141-8.

2. Grunberg SM. Obstacles to the implementation of antiemetic guidelines. Journal of the National Comprehensive Cancer Network. 2009;7(5):601-5.

3. Navari RM. Prevention of emesis from multiple-day and high-dose chemotherapy regimens. Journal of the National Comprehensive Cancer Network. 2007;5(1):51-9.

4. Warr DG, Street JC, Carides AD. Evaluation of risk factors predictive of nausea and vomiting with current standard-of-care antiemetic treatment: analysis of phase 3 trial of aprepitant in patients receiving adriamycin–cyclophosphamide-based chemotherapy. Supportive Care in Cancer. 2011;19(6):807-13.

5. Aapro M. Optimising antiemetic therapy: what are the problems and how can they be overcome? Current Medical Research and Opinion®. 2005;21(6):885-97.

6. Hesketh PJ. Chemotherapy-induced nausea and vomiting. New England Journal of Medicine. 2008;358(23):2482-94.

7. Roila F, Herrstedt J, Aapro M, Gralla R, Einhorn L, Ballatori E, et al. Guideline update for MASCC and ESMO in the prevention of chemotherapy-and radiotherapy-induced nausea and vomiting: results of

the Perugia consensus conference. Annals of Oncology. 2010;21(suppl 5):v232-v43.

8. Basch E, Prestrud AA, Hesketh PJ, Kris MG, Feyer PC, Somerfield MR, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. Journal of Clinical Oncology. 2011;29(31):4189-98.

9. Jordan K, Jahn F, Aapro M. Recent developments in the prevention of chemotherapy-induced nausea and vomiting (CINV): A comprehensive review. Annals of Oncology. 2015:mdv138.

10. Gao H, Liang Y, Zhou N, Zhang D, Wu H. Aprepitant plus palonosetron and dexamethasone for prevention of chemotherapy-induced nausea and vomiting in patients receiving multiple-day cisplatin chemotherapy. Internal medicine journal. 2013;43(1):73-6.

11. Rey J, Launay-Vacher V, Scotté F, Krakowski I, Aapro M. Guideline update for MASCC and ESMO in the prevention of chemotherapy-and radiotherapy-induced nausea and vomiting: results of the Perugia consensus conference. Oncologie. 2012;14(5):329.

12. Chan A, Low XH, Yap K. Assessment of the relationship between adherence with antiemetic drug therapy and control of nausea and vomiting in breast cancer patients receiving anthracycline-based chemotherapy. J Manag Care Pharm. 2012;18(5):385-94.

13. Kris MG, Hesketh PJ, Somerfield MR, Feyer P, Clark-Snow R, Koeller JM, et al. American Society of Clinical Oncology guideline for

antiemetics in oncology: update 2006. Journal of Clinical Oncology. 2006;24(18):2932-47.

14. Grunberg SM, Deuson RR, Mavros P, Geling O, Hansen M, Cruciani G, et al. Incidence of chemotherapy-induced nausea and emesis after modern antiemetics. Cancer. 2004;100(10):2261-668.

15. Laumann AE, Derick AJ. Tattoos and body piercings in the United States: a national data set. Journal of the American Academy of Dermatology. 2006;55(3):413-21.

16. Uchida M, Ikesue H, Kato K, Ichinose K, Hiraiwa H, Sakurai A, et al. Antiemetic effectiveness and safety of aprepitant in patients with hematologic malignancy receiving multiday chemotherapy. American Journal of Health-System Pharmacy. 2013;70(4):343-9.

17. Aprepitant FDA Advisory Committee Background Package. Available at: http://www.fda.gov/ ohrms/dockets/ac/ 03/briefing/ 3928B1_01_Merck%20 Backgrounder.pdf. Accessed December 1, 2011.

18. Rapoport BL, Jordan K, Boice JA, Taylor A, Brown C, Hardwick JS, et al. Aprepitant for the prevention of chemotherapy-induced nausea and vomiting associated with a broad range of moderately emetogenic chemotherapies and tumor types: a randomized, double-blind study. Supportive care in cancer. 2010;18(4):423-31.

19. Badar T, Cortes J, Borthakur G, O'Brien S, Wierda W, Garcia-Manero G, et al. Phase II, Open Label, Randomized Comparative Trial of Ondansetron Alone versus the Combination of Ondansetron and Aprepitant for the Prevention of Nausea and Vomiting in Patients with

Hematologic Malignancies Receiving Regimens Containing High-Dose Cytarabine. BioMed Research International. 2015;2015.

20. Badar T, Mattiuzzi G, Kantarjian HM, Ravandi F, Daver NG, Manero GG, et al. Phase II, Open Label, Randomized Comparative Trial Of Ondansetron Alone Versus The Combination Of Ondansetron Plus Aprepitant For The Prevention Of Nausea and Vomiting In Patients (Pts) With Hematological Malignancies Receiving Regimens Containing High Dose Cytarabine. Blood. 2013;122(21):3887-.

21. Warr DG, Hesketh PJ, Gralla RJ, Muss HB, Herrstedt J, Eisenberg PD, et al. Efficacy and tolerability of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in patients with breast cancer after moderately emetogenic chemotherapy. Journal of Clinical Oncology. 2005;23(12):2822-30.

22. Albany C, Brames MJ, Fausel C, Johnson CS, Picus J, Einhorn LH. Randomized, double-blind, placebo-controlled, phase III cross-over study evaluating the oral neurokinin-1 antagonist aprepitant in combination with a 5HT3 receptor antagonist and dexamethasone in patients with germ cell tumors receiving 5-day cisplatin combination chemotherapy regimens: a hoosier oncology group study. Journal of Clinical Oncology. 2012;30(32):3998-4003.

23. Celio L, Bonizzoni E, Bajetta E, Sebastiani S, Perrone T, Aapro MS. Palonosetron plus single-dose dexamethasone for the prevention of nausea and vomiting in women receiving anthracycline/ cyclophosphamide -containing chemotherapy: meta-analysis of

individual patient data examining the effect of age on outcome in two phase III trials. Supportive Care in Cancer. 2013;21(2):565-73.

24. Sachin H, Nirmal R. Open-label observational study to assess the efficacy and safety of aprepitant for chemotherapy-induced nausea and vomiting prophylaxis in Indian patients receiving chemotherapy with highly emetogenic chemotherapy/moderately emetogenic chemotherapy regimens. South Asian Journal of Cancer. 2015;4(1):7.

25. Madsen JL, Fuglsang S. A randomized, placebo-controlled, crossover, double-blind trial of the NK1 receptor antagonist aprepitant on gastrointestinal motor function in healthy humans. Alimentary pharmacology & therapeutics. 2008;27(7):609-15.

26. Aapro MS, Schmoll HJ, Jahn F, Carides AD, Webb RT. Review of the efficacy of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in a range of tumor types. Cancer treatment reviews. 2013;39(1):113-7.

27. Stiff PJ, Fox-Geiman MP, Kiley K, Rychlik K, Parthasarathy M, Fletcher-Gonzalez D, et al. Prevention of nausea and vomiting associated with stem cell transplant: results of a prospective, randomized trial of aprepitant used with highly emetogenic preparative regimens. Biology of Blood and Marrow Transplantation. 2013;19(1):49-55. e1.

28. Aapro M, Carides A, Rapoport BL, Schmoll H-J, Zhang L, Warr D. Aprepitant and Fosaprepitant: A 10-Year Review of Efficacy and Safety. The oncologist. 2015;20(4):450-8.

29. Nasu R, Nannya Y, Kurokawa M. A randomized controlled study evaluating the efficacy of aprepitant for highly/moderately emetogenic chemotherapies in hematological malignancies. International journal of hematology. 2015:1-10.

Table 1.Comparison of complete response (CR) between two Aprepitant regimens after cross over

		3 days regimen of Aprepitant		TOTAL
		CR	NOT CR	
6 days regimen of Aprepitant	CR	19	12	31(63%)
	NOT CR	0	18	18(37%)
TOTAL		19(39%)	30(61%)	49

NOTE: of 31 patients achieving a complete response (CR) with 6 days regimen of Aprepitant, 19 subsequently attained a CR when they cross over to the 3 days regimen of Aprepitant .Conversely, all of 19 CRs with 3 days regimen of Aprepitant had a CR with 6 days regimen of Aprepitant .McNemar's test P <0 .001.Complete response (CR) was defined as no nausea and no episodes of vomiting.

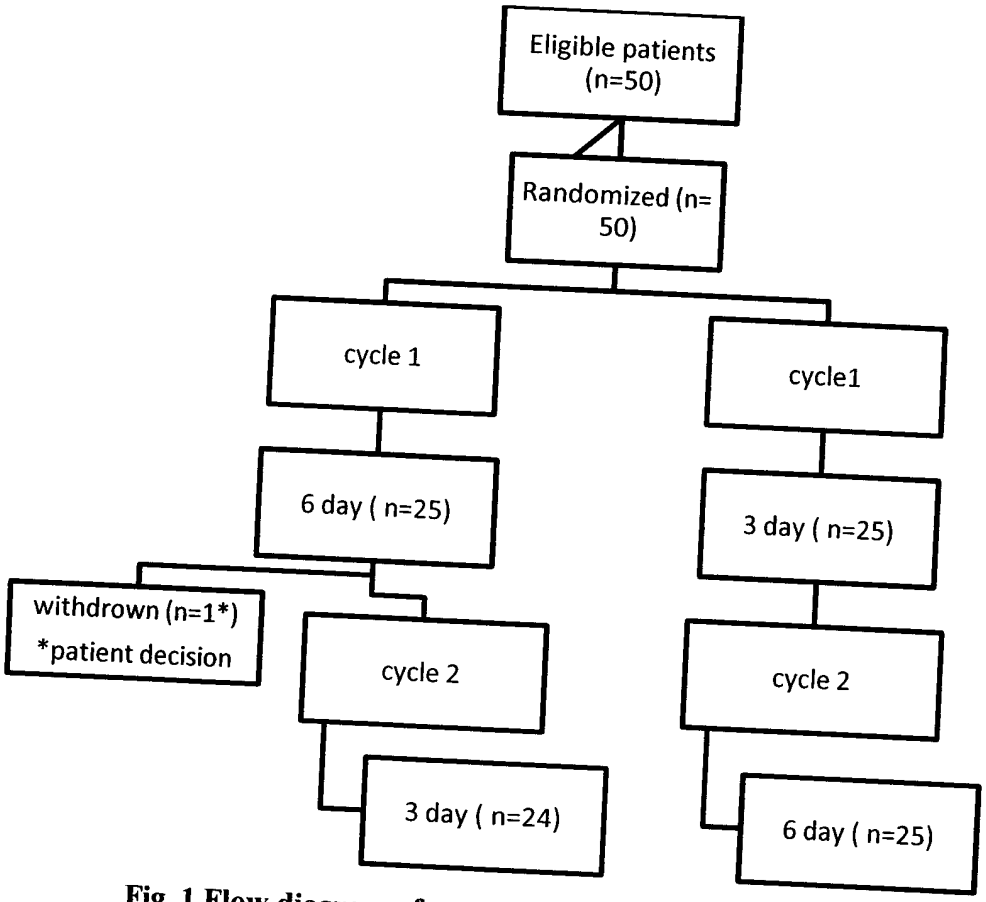

Fig. 1.Flow diagram of participants through each cycle of the study.

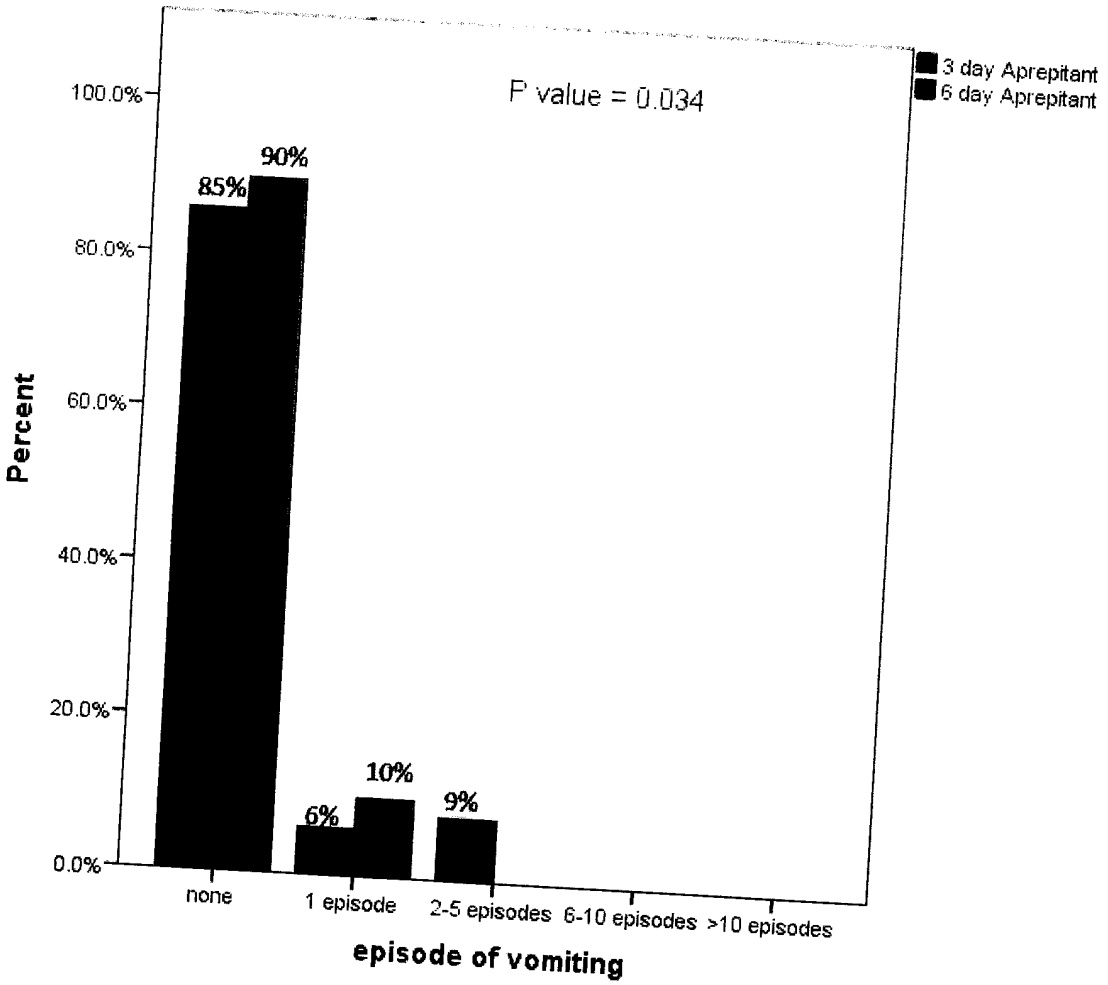

Fig 2.Percentage of patients experiencing different episode of vomiting

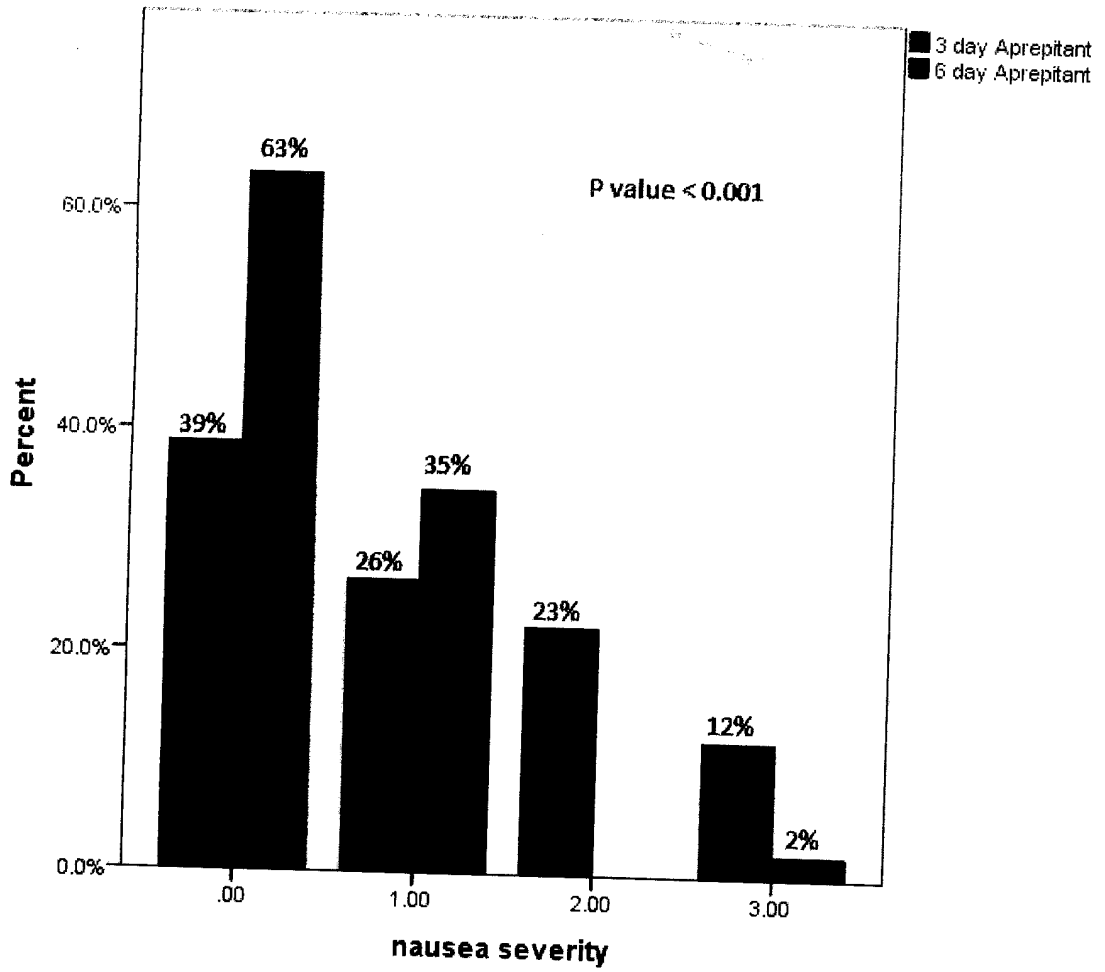

Fig 3.Percentage of patients experiencing different nausea severity (0= being no nausea, 1=able to eat reasonable intake, 2=intake significantly decreased but can eat, 3=no significant intake)