# Olanzapine (5 mg) Plus Standard Triple Antiemetic Therapy for the Prevention of Multiple-Day Cisplatin Chemotherapy-Induced Nausea and Vomiting: A Prospective Randomized Controlled Study

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# Abstract

**Objective** A prospective randomized controlled trial was conducted to compare 5 mg olanzapine plus standard triple antiemetic therapy for the prevention of nausea and vomiting induced by multiple-day cisplatin chemotherapy.

**Methods** Patients received 3-day cisplatin-based chemotherapy(25mg/m2/d) were given either 5mg olanzapine quadruple therapy (aprepitant, tropisetron, dexamethasone) or 5mg olanzapine-based triplet therapy. The primary end-point was the complete response(CR) in the overall phase(OP)(0-120h) between quadruple regimen group and triplet regimen group. The secondary end-points were the CR in the acute phase(AP)(0-24h), delayed phase(DP)(25-120h) between two groups. The first time of vomiting was also compared by Kaplan-Meier curves. The impact of chemotherapy induced nausea and vomiting(CINV) on the quality of life was assessed by the Functional Living Index-Emesis(FLIE). Aprepitant-related adverse effects (AEs) was also recorded.

**Results** (1) The primary end-point CR during overall phase was 76.0% (45/59) vs 67.0% (41/61) between the quadruple regimen group and triplet regimen group(*P* =0.271). The secondary end-point CR during the AP was significantly higher in the quadruple group than in the triple group, which was 100.0%(59/59) vs 93.0%(57/61)(*P*=0.045). The difference between the groups was especially greater in the delayed phase(quadruple group 76.0% (45/59) vs triple group 67.0%(41/61)(*P*=0.271)). The rate of patients who achieved total protection in the overall phase was also larger in the quadruple group than in the triple group(28.8% (17/59) vs 23.0%(14/61)(*P*=0.463)). During the OP, the incidence of no vomiting in quadruple group and triple group was 93.2%(55/59) vs 80.3%(49/61)(*P*=0.038)respectively.(2) Kaplan-Meier curves of time to first emesis were obviously longer in the quadruple group than in the triple group(*P*=0.031). According to FLIE, no impact of CINV on daily life was defined as total score of questionnaire >108, this study exhibited identical life quality in quadruple group and the triplet group.(3) The most common aprepitant- and olanzapine-related AEs included sedation, fatigue and constipation. The occurrences between two groups were identical.

**Conclusion** It may been recommended that combined 5mg olanzapine with aprepitant, tropisetron, dexamethasone quadruple therapy for the prevention of multiple-day cisplatin induced nausea and vomiting due to the better CINV control rate and safety.


# Introduction

Patients receiving multiple-day cisplatin chemotherapy are at risk of both acute and delayed nausea and vomiting for each day, as acute and delayed emesis may overlap after the initial day chemotherapy until the last day of chemotherapy[1, 2]. Although the combination of aprepitant, 5-HT3 receptor antagonist(5-HT3RA) and dexamethasone(DXM) had showed higher complete response than the combination of 5-HT3RA plus dexamethasone in cisplatin multiple-day chemotherapy clinical studies, nausea remains a major problem for many patients[3, 4, 5]. The activity of olanzapine on multiple receptors, particularly the

D2, 5-HT2c and 5-HT3 receptors, may be involved in nausea and vomiting. A single-institution phase 3 trial showed that olanzapine was comparable to aprepitant in the control of CINV, and nausea was better controlled with olanzapine in delayed period and overall period[6] .Somnolence is a major side effect when olanzapine was administered at a dose of 10 mg. In a phase 2 study, 5mg olanzapine has shown equivalent activity to 10mg olanzapine and a favourable safety in relation to somnolence[7]. Guidelines suggest that a dose reduction to 5 mg should be considered to prevent sedation, and a randomised, double-blind, placebo-controlled phase 3 study showed that 5mg olanzapine combined with aprepitant, palonosetron and dexamethasone could be a new standard antiemetic therapy for patients undergoing cisplatin single-day chemotherapy[8]. Aprepitant is an oral neurokinin-1 receptor antagonist[9]. A randomized controlled trial was conducted to compare the efficacy of 5 mg olanzapine plus triplet therapy (aprepitant, tropisetron, dexamethasone) versus 5 mg olanzapine-based triplet therapy in preventing CINV in patients receiving multiple-day cisplatin chemotherapy(chiCTR1800018424).

# Methods

## Patients

This study was approved by the local Institutional Review Board, and all patients provided written informed consent before the start of study procedures. A randomized, clinical trial (chiCTR1800018424) was conducted to compare the effectiveness of 5 mg olanzapine plus triplet therapy (aprepitant, tropisetron, dexamethasone) (Quadruple group ) versus 5 mg olanzapine-based triplet therapy(Triplet group) in preventing CINV in patients receiving multiple-day cisplatin chemotherapy.

## End points

We chose the CR rate, defined as the absence of emetic episodes and no use of rescue medications during the overall phase after the initiation of cisplatin, as the primary end-point. Secondary end-points are the CR rate in the acute phase and the delayed phase . The total control(TC) rate is defined as the absence of nausea and emetic episodes and no use of rescue medications for the acute, delayed, and overall phase. We used a 100mm categorical scale to stratify nausea and chose ≤5mm to define the total control. The time of treatment failure is defined as the time of first emetic episode or the use of rescue medication. AEs were graded according to Common Terminology Criteria for Adverse Events (CTCAE) V.4.0.

## Randomization

After confirming that the patients fulfills the eligibility criteria, the patients are randomized by random digits table.

## Eligibility criteria

Inclusion criteria

(1) Patients older than 18 years who will receive 3-day cisplatin-based chemotherapy (25 mg/m2/d) enrolled in the study. All patients had histologically confirmed, (2) Karnofsky Performance Scale≥70, (3) There is no abnormality in liver and kidney function, blood routine and electrocardiogram before chemotherapy, including: White Blood Cell Couct >3.5×10^9/L, Absolute neutrophil count >1.5×10^9/L, Platelet count >85×10^9/L, Alkaline phosphatase<2.5 upper limit of normal (ULN), alanine transaminase <2.5 upper limit of normal (ULN), Bilirubin <1.5 ULN, Creatinine <1.5 ULN, (4) Patients without chemotherapy contraindications after CT and MRI examination, (5) No episodes of nausea and vomiting occurred during last 1 week before enrollment, and no aprepitant or olanzapine was used for pretreatment, (6) Patients are able to understand and describe patient-reported outcomes.

### Exclusion criteria

Patients were excluded if they meet any of the following criterias: (1)Symptomatic brain metastases, (2) Requiring treatment for ascites or pleural effusion, (3) Requiring radiotherapy in the abdominal or pelvic field, (4) Requiring anticonvulsant medication, (5)History of hypersensitivity or allergy to the study drugs or similarcompounds, (6) Severe complications (pulmonary fibrosis, heart failure, myocardialinfarction, unstable angina, cerebral vascular disorder, psychiatricdisease, renal dysfunction, liver dysfunction, intestinalparesis, ileus, uncontrol lable diabetes mellitus, active peptic ulceretc), (7)History of using any of the following drugs within 48h, opioids, aprepitant, 5-HT3 receptor antagonists, dexamethasone, dopamine receptor antagonists, antihistamines, benzodiazepines and phenothiazine antipsychotics, (8)Pregnant or lactating women or women with child bearing potential, or men wishing to be the father of children, (9) Partial/complete bowel obstruction, (10) Malignant tumor of digestive tract,

### Treatments

The study antiemetic administrations are shown in Table 1. Patients in quadruple antiemetic regimen group received: Aprepitant 125 mg po day 1, 80mg po days 2-3(EMEND, MSD Sharp & Dohme, Haar, Germany), Olanzapine 5mg po days 1-3, tropisetron 5mg iv days 1-3 (Beijing Shuanglu Pharmaceutical Co. Ltd., China), dexamethasone 5mg iv days 1-3. Patients in triple antiemetic regimen group received: Olanzapine 5mg po days 1-3 , tropisetron 5mg iv days 1-3 , dexamethasone 10mg iv days 1-3. The aprepitant group had a half dosage of dexamethasone besides tropisetron hydrochloride and aprepitant, since the function of CYP3A4 in DXM pharmacokinetics could be exhibited by aprepitant[10].

Table 1 Antiemetic administrations

| | Day1 | Day2 | Day3 |
|---|---|---|---|
| Quadruple antiemetic regimen | Aprepitant 125mg po | Aprepitant 80mg po | Aprepitant 80mg po |
| | Olanzapine 5mg po | Olanzapine 5mg po | Olanzapine 5mg po |
| | Tropisetron 5mg iv | Tropisetron 5mg iv | Tropisetron 5mg iv |
| | Dexamethasone 5mg po | Dexamethasone 5mg po | Dexamethasone 5mg po |
| Triple antiemetic regimen | Olanzapine 5mg po | Olanzapine 5mg po | Olanzapine 5mg po |
| | Tropisetron 5mg iv | Tropisetron 5mg iv | Tropisetron 5mg iv |
| | Dexamethasone 10mg po | Dexamethasone 10mg po | Dexamethasone 10mg po |

### Follow-up

Patients recorded and self-reported the times and dates of vomiting or retching episodes, and the use of rescue therapy from time of chemotherapy infusion(0 h) until day 5. Patients were contacted in the mornings of days 2-5 to ensure compliance with nausea categorical scale. Functional Living Index-Emesis(FLIE) questionnaire scoring was self-administered early on the day5, directly following completion of final self-reports[11]. Notably, FLIE is a validated emesis- and nausea-specific questionnaire with nine nausea domain questions(items) and nine vomiting domain questions(items) and“no impact of CINV on daily life”represented means scores >6 on a 7-point scale(>108 in total)[12,13].

All patients underwent post-treatment examination on days 6-8 and follow-up at days 19-21, and AEs related to aprepitant and olanzapine were recorded.

### Statistical analysis

The sponsor managed the data and performed the analyses for this study. The hypothesis of this study was that the CR rate of 5 mg olanzapine in quadruple group would be significantly higher than that of 5 mg olanzapine-based triplet group. Other trials have shown that the CR rate of triple antiemetic therapy was about 65%[14,15]. According to the previous studies, CR rates of antiemesis treatment by olanzapine combined aprepitant, tropisetron and dexamethasone were 86%[14]. We believed that an improvement of more than 15% in the CR rate would be clinically meaningful. Therefore, assuming that the null hypothesis of the CR rate is 65% and the alternative hypothesis is 80%, we calculated that a minimum of 82 patients were required to achieve a one-sided type I error of 0.1% and 80% of power, based on the exact binomial distribution. Because some dropouts were expected, we set the target sample size to 104, and the sample size calculation was performed by SASV.9.4 (Cary, NC, USA).

Treatment comparisons were made using logistic regression models that included terms for treatment, gender, age, alcohol use, history of motion sickness etc. All comparisons used a two-sided significance level of 5%. Tests of siginificance were based on the logistic regression models, and the norminal *P* values were reported. Kaplan-Meier curves of time to first emesis were constructed to both groups. Fisher's exact test was used to compare the percentage of patients who got CR or experienced aprepitant-related AEs between the two groups.

# Results

## Patients

From March 2018 to March 2019, this prospctive, randomized, controlled study was conducted at the Medical Oncology Department of Ordos Central Hospital in Inner Mongolia, China. A total of 132 patients assigned to a study group with the use of random digits table. Six patients did not receive treatment (because of the cancellation of chemotherapy), and six patients dropped out of the study because of lacking of nausea data and FLIE questionnaires. Thus, 59 patients in the Quadruple group and 61 in the Triple group were completely assessed. The baseline characteristics were comparable between two groups(Table 2).

Table2　Patients’baseline characteristics [n(%)]

| Characteristics | Quadruple Group (n=59) | Triple Group (n=61) | *P* |
|---|---|---|---|
| Age(years) | | | |
| ≥55 | 60.39±9.22 | 58.11±7.80 | 0.104 |
| Gender | | | 0.708 |
| Female | 27(45.76) | 30(49.18) | |
| Male | 32(54.24) | 31(50.82) | |
| History of motion sickness | 9(15.25) | 14(22.95) | 0.284 |
| History of nausing with pregnancy in female | 14(51.85) | 20(66.67) | 0.271 |
| Alcohol use | | | 0.881 |
| No Consumption | 32(54.24) | 32(52.46) | |
| <4 drinks per week | 19(32.20) | 22(36.07) | |
| ≥4drinks per week | 8(13.56) | 7(11.48) | |
| Smoking Index | | | 0.144 |
| No Smoking | 15(25.42) | 22(36.07) | |
| 0~400 | 10(16.95) | 4(6.56) | |
| ≥400 | 34(57.63) | 35(57.38) | |
| Type of malignance | | | 0.850 |
| Lung cancer | 31(52.54) | 31(50.82) | |
| Others | 28(47.46) | 30(49.18) | |
| Chemotherapy Cycle | | | 0.109 |
| First- Cycle | 25(42.37) | 17(27.87) | |
| Second to Third- Cycle | 22(37.29) | 22(36.07) | |
| ≥Fouth- Cycle | 12(20.34) | 22(36.07) | |

## Efficacy

The primary end-point of CR rate during the overall phase in the quadruple group(76.0% (45/59)) was higher than those in the triple group (67.0% (41/61))(*P*=0.271), but there was no statistic significance. During AP, the CR of quadruple group(100.0%(59/59)) was significantly higher than triple group(93.0% (57/61))(*P*=0.045). The difference between the groups was especially greater in the delayed phase (24-120 hours) (quadruple group 76.0% (45/59) vs triple group 67.0%(41/61) (*P*=0.271))(Figure 1). The total

protection rates of quadruple group(28.8% (17/59)) in the overall phase were also larger than triple group(23.0%(14/61) (*P*=0.463)). During the OP, the incidence of no vomiting in quadruple group and triple group was 93.2%(55/59) vs 80.3%(49/61)(P=0.038), respectively. In the no-rescue treatment, few cases were reported in the quadruple group(16.9%(10/59)) than in the triple group group(27.9 %(17/61) (P=0.152)) during the OP.

### Comparison of FLIE Index

According to FLIE, reports of no impact of CINV on daily life were exhibited by 47.5%(28/59) of the quadruple group and 44.3%(27/61) of the triple group (*P*=0.035). The comparison of FLIE index of nause or vomiting between two groups was listed below in Table 3.

Table 3 Comparison of FLIE Index

| Items | Quadruple Group | Triple Group | *P* |
|---|---|---|---|
| Nausea FLIE Score | 48.92±12.32 | 48.66±12.15 | 0.907 |
| Vomiting FLIE Score | 52.91±11.49 | 50.67±13.05 | 0.322 |
| FLIE Score | 101.83±22.46 | 99.33±24.70 | 0.563 |

Notes：FLIE: functional living index-emesis

### Comparison of time to first vomiting

Kaplan–Meier curves of time to first emesis were obviously longer in the quadruple regimen group than that in the triple regimen group(*P*=0.031).

### Tolerability

The most common aprepitant- and olanzapine-related AEs of the total patients were recorded. AEs included sedation, fatigue and constipation. The occurrences were observed in 57.6%(34/59), 54.2% (32/59)and 22.0%(13/59) of patients in the quadruple regimen group vs 50.8%(31/61), 52.5%(32/61)and 13.1%(8/61)in the triple regimen group(*P* =0.454, *P* =0.854, *P* =0.199). The difference of AEs between two groups did not reach statistic significance. No grade 3 or 4 adverse events were obseaved in this study and no patients interrupted the study because of undesired sedation.

## Discussion

Navari et al. conducted a Phase III study revealing that olanzapine(10 mg) combined with standard therapy was superior at overall phase after chemotherapy, both at the primary endpoint (no nausea) and the secondary endpoint (CR rate)[14]. Olanzapine (10 mg) combined with NK-1RA, 5HT3-RA and dexamethasone quadruple therapy has been recommended antiemetic therapy for HEC in clinical guidelines of the Multinational Association of Supportive Care in Cancer/European Society for Medical

Oncology(MASCC/ESMO), the American Society of Clinical Oncology(ASCO), and the National Comprehensive Cancer Network(NCCN)[16]. However, the majority of trials involved antiemetic research have investigated patients receiving single-day cisplatin chemotherapy, and multiple-day chemotherapy(MDC) is one of the most neglected and challenging areas of antiemetic research due to the overlap of acute phase and delayed phase[1].

We conducted this randomized, controlled, clinical trial enrolled patients who received 3-day cisplatin-based chemotherapy. It is more effective for combine 5 mg olanzapine to triplet therapy (aprepitant, tropisetron, dexamethasone) versus 5 mg olanzapine based triplet therapy in the early, later, and overall assessment phases. However, the primary and secondary end-points (CR rate) of OP and DP did not reach statistic significance, the secondary end-point CR rate in AP or no vomiting in OP was significantly higher in the quadruple group. The primary end-point did not reach statistic significance in this study which was inconsistent with previous reports of Navari et al[14]. The possible explanations for those differences may be complex. On the one hand, we designed 5 mg olanzapine rather than NK-1 receptor antagonist based triplet therapy as the control group because a phase 3 trial showed that olanzapine 10 mg was comparable to aprepitant in the control of CINV ,but somnolence is a major side effection[6]. And olanzapine 5 mg has shown equivalent activity to olanzapine 10 mg and a favourable safety in relation to somnolence in phase 2 study, thus it is reasonable for this clinical design[7]. On the other hand, we adopted CR as primary end-point that was different from previous quadruple regimen clinical studies which adopted no nausea or TC as primary end point[14, 15]. As we know, nausea was better controlled by olanzapine in delayed period and overall period, so it may explained that the TC rates were identical in both groups in our study[6]. Besides these, a randomized, double-blind, placebo-controlled, phase 3 study enrolled 710 patients to evaluate the efficacy of olanzapine 5 mg with triplet antiemetic therapy adopted CR in the delayed phase as primary endpoint. The proportion of patients who achieved a complete response was 79% vs 66% ($P < 0.0001$)[8],and our clinical results of 76% vs 67% were highly accordence with this phase 3 study, and a relative smaller sample size in this study than those in phase III trial maybe one of the reasons of not reaching statistic significantly in OP and DP[8, 14]. Furthermore, the different doses of 5-HT3RA, DXM, olanzapine and given number of days in the study also affected the results of those quadruple vs triplet regimen comparison studies[8, 14]. This study and J-FORCE both adopted 5 mg olanzapine achieved higher CR rate compared with a phase III study which adopted 10 mg olanzapine[8, 14]. The different time cut-off points between acute phase and delayed phase in multiple-day cisplatin-induced chemotherapy may affect the CR rate, as shown by H.F.Gao that CR declined about 20% when acute phase cut-off point switched from 24 hour to 72 hour[17] .We defined 24 hour as acute phase in this study and 25% enrolled patients received < 70 mg/m²cisplatin in J-FORCE study may explained the higher CR in some degree. This also supports the previously conclusion that olanzapine 5 mg has equivalent activity to 10 mg in CINV prevention[7, 8]. The superiority of 5 mg olanzapine-based quadruple regimen in the study was also support its clinical advantages for prevention of CINV induced by cisplatin multiple-day chemotherapy.

According to FLIE, no impact of CINV on daily life was defined as questionnaire total score > 108, this study exhibited identical life quality in quadruple regimen group to the triplet regimen group. Kaplan-Meier curves of time to first emesis in the quadruple regimen group were obviously longer than the triple regimen group($P$ = 0.031) and this was in accordance with no vomiting in OP which was significantly higher in the quadruple group. This supports the superiority of control of chemotherapy-induced vomiting(CIV) by 5mg olanzapine-based quadruple regimen induced by cisplatin multiple-day chemotherapy.

The most common aprepitant- and olanzapine-related AEs included sedation, fatigue and constipation.The occurrences between two groups were identical and it were consistent with other studies examining aprepitant and olanzapine-related AEs[4, 8, 14]. In general, the tolerability in the study was safe, no grade 3 or 4 adverse events were observed in this study, and no patients discontinued the study because of undesired sedation.

# Conclusion

In summary, 5 mg olanzapine plus triplet therapy (aprepitant, tropisetron, dexamethasone) is more effective than 5-mg olanzapine-based triplet therapy for the prevention of CINV induced by multiple-day cisplatin chemotherapy. Clinical studies with larger sample sizes were needed to further confirm it and 5mg olanzapine combined with new generation of 5-HT3RA palonosetron and NK-1RA fosaprepitant for the prevention of CINV induced by multiple-day cisplatin chemotherapy clinical study is ongoing.

# Declarations

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**Conflicts of interest/Competing interests:** The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

**Availability of data and material:** All data generated or analysed during this study are included in this published article [and its supplementary information files]

**Code availability:** Not applicable.

**Authors' contributions:** Gaowa Jin participated in supervision,project administration and funding acquisition.Quanfu Li participated in writing - original draft,conceptualization,methodology,funding acquisition,software.Jiali Gao participated in investigation,formal analysis and data curation.Researchers of the study investigation included Jun Zhao,Caihong Jiang,Feng Chen,Lanzhen Zhao,Ying Jiang,Hui Li,Wenjuan Wang,Yungaowa Wu,Yilan Jin,Lenggaowa Da,Yajuan Zhang and Hongxia Li.Zewei Zhang was responsible for Software

**Ethics approval:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Bioethics Committee of the Ordos Central Hospital.

**Consent to participate:** Informed consent was obtained from all individual participants included in the study.

**Consent for publication:** Written informed consent was obtained from the patient for publication of this article and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

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# Figures

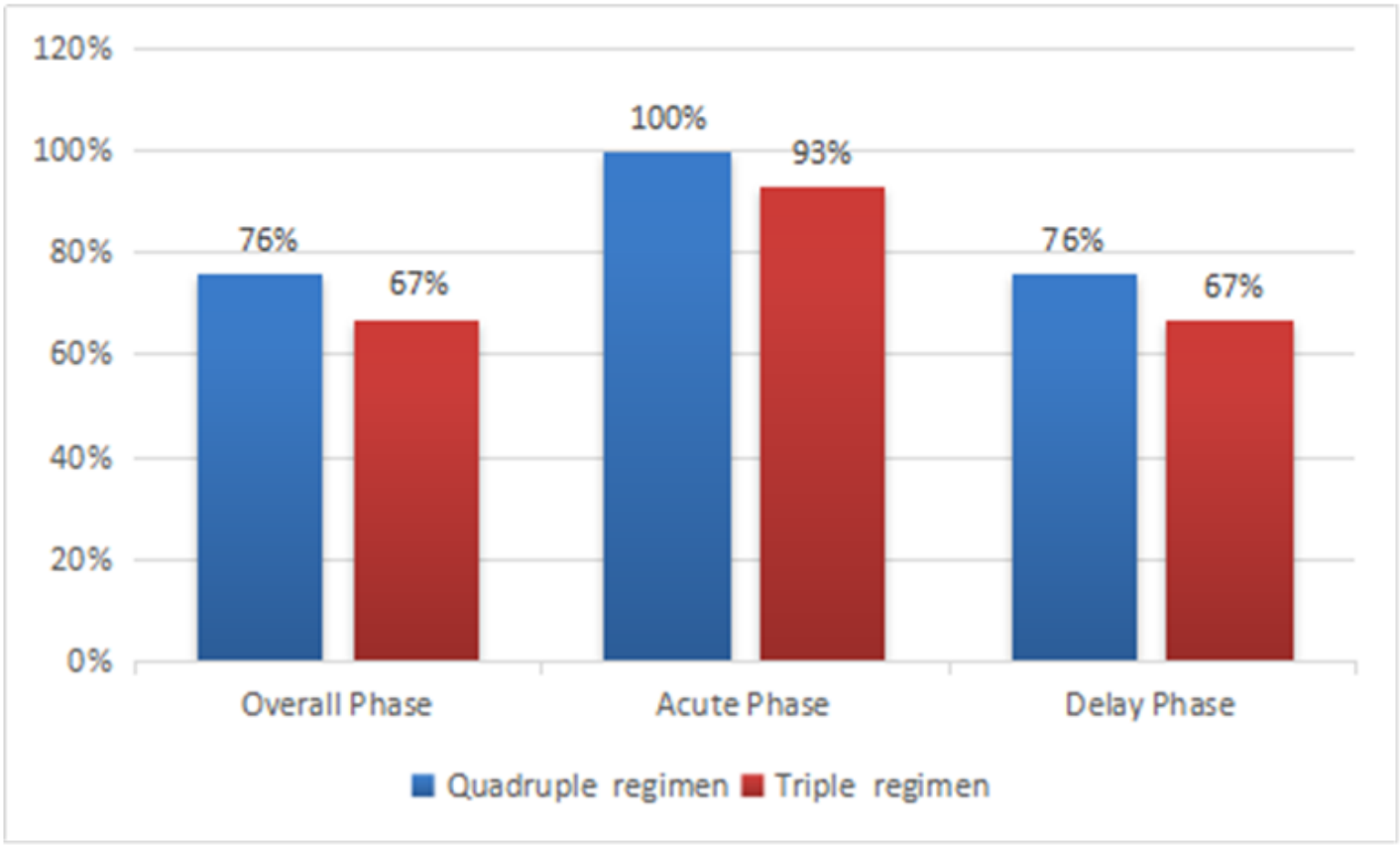
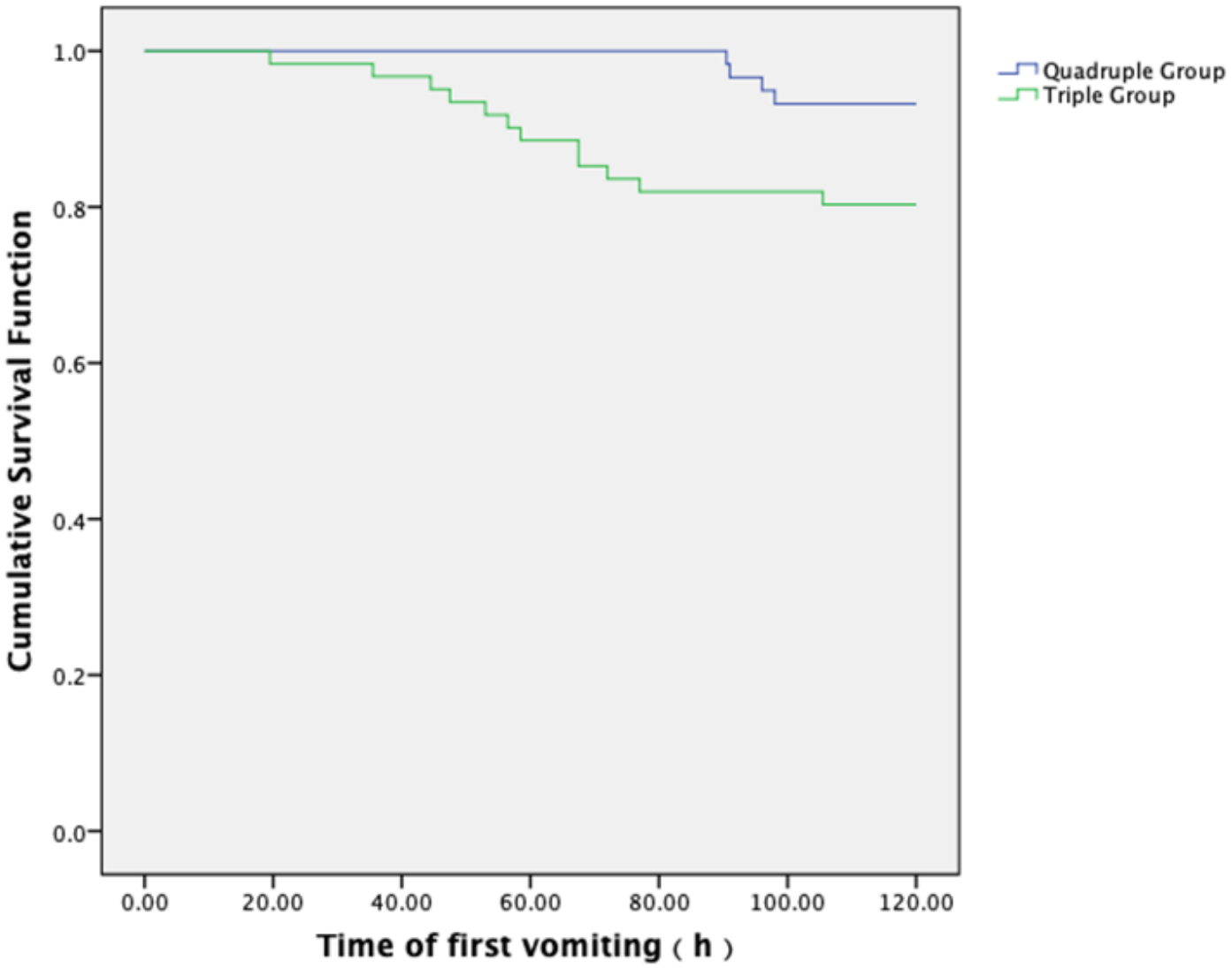



**Figure 1**

Comparison of Complete Response Between Two Groups




## Figure 2

Comparison of time to first vomiting between two groups