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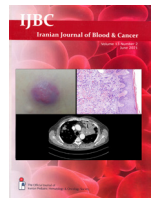

ORIGINAL ARTICLE

A Prospective Triple-blind Randomized Trial on Safety and Efficacy of Abitant in the Prevention of Chemotherapy-Induced Nausea and Vomiting

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ABSTRACT

Background: Oral Aprepitant, a neurokinin-1 receptor antagonist, is suggested in combination with other antiemetic agents in preventing chemotherapy-induced nausea and vomiting(CINV) associated with emetogenic chemotherapeutic regimens in adolescents, but its efficacy and safety in pediatric patients more than six months are unknown. in this study, we used abitant drug (a generic name of Aprepitant produced by Exir pharmaceutical company) for preventing CINV in children.

Methods: In this triple-blind clinical trial, patients aged between 6 months to 15 years were randomly assigned to receive 3 mg/kg (maximum of 120 mg per dose) Abitant 60 minutes before receiving moderate to highly emetogenic chemotherapy and 2 mg/kg (maximum 80 mg per dose) in days 2 and 3 or placebo plus ondansetron. The primary efficacy endpoint was the percentage of patients who obtained complete response (stated as no retching, no vomiting, and no urge for rescue medication) during 25–120 hours (delayed phase) after initiation of emetogenic chemotherapy. The secondary endpoint was the proportion of children who attained complete response throughout the acute (0–24 h) and the total phase(0-120 h). Efficacy and safety analyses were done with randomly assigned patients who received at least one study treatment dose.

Results: twelve patients of the Abitant group (66/7%) and 11 patients of the placebo group (64/7%) showed complete response (P=0.186). There was no significant adverse effect observed in both groups. Complete response on day 5 was 83.3% in the Abitant group and 86/7% in the placebo group.

Conclusion: The efficacy of a combination of abitant along with ondansetron in controlling CINV was not inferior to the ondansetron alone in our pediatric population study group.

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Introduction

Chemotherapy-induced nausea and vomiting is a recurrent and treatment-limiting problem in cancer treatment in children. Excellent and robust recommendations regarding the best effective antiemetic protocols in children with cancer are scant. The "Multinational Association of Supportive Care in Cancer" and "American Society of Clinical Oncology" guidelines highly recommend a 5-HT3 antagonist along with dexamethasone to prevent acute chemotherapy-induced nausea and vomiting (CINV).[1]

The available standard of care (i.e., a 5-HT3 antagonist and dexamethasone) is associated with a high incidence of acute CINV.[2] The National Comprehensive Cancer Network (NCCN) guidelines lack age-appropriate references in this issue,[3] but the Children's Oncology Group (COG) guidelines recommend using serotonin receptor antagonists and dexamethasone in children on the first day of the chemotherapy administration.[4]

Explanations for diverse responses in children and adults might be intrinsic differences in the pathogenesis of chemotherapy-induced nausea and vomiting, differences in emetogenicity of chemotherapeutic drugs, and personal predisposition to nausea and vomiting in response to chemotherapy regimens.[5] Serotonin and substance P are the principal neurotransmitters involved in the vomiting process. Serotonin receptors mediate acute CINV through the peripheral pathway of the gastrointestinal tract.[2, 6, 7] Substance P is a regulatory peptide that binds to neurokinin-1 (NK1) receptors in the vomiting center. Delayed CINV, which usually occurs 24 hours after chemotherapy administration, is predominantly driven by substance P.[7]

Aprepitant, which targets the central pathway of vomiting, is approved to prevent CINV.[7, 8] Aprepitant (Emend) is a substance P/NK1 receptor antagonist in the central nervous system that is approved in the United States for treatment of chemotherapy-induced nausea and vomiting (CINV).[7] Oral Aprepitant was approved for pediatric patients aged six months to less than 12 years to treat CINV in December 2015.[6, 7]

Our study was designed to assess the efficacy and safety of oral Abitant in preventing acute and delayed nausea and vomiting according to moderately, highly, and very emetogenic chemotherapy regimens in pediatric patients aged six months to 15 years.

Materials and Methods

During a randomized, triple-blind trial, children with malignancy aged six months to 15 years were planned to receive chemotherapeutic agents with at least moderate to the very high-risk group of emetogenicity (very high risk: >90% emetogenicity: if this group of drugs is used, the probability of nausea and vomiting is more than 90%, high risk: 60-90%emetogenicity, moderate risk:30-60% emetogenicity).[2]

The exclusion criteria were: occurrence of vomiting 24 hours before the first day of chemotherapy, known history of QT prolongation, history of allergic reaction to any of the drugs of the study, irradiation to the abdomen or pelvis in the week before chemotherapy, any active infection or uncontrolled simultaneous disease except malignancy, abnormal laboratory tests at the initiation of the chemotherapy (absolute neutrophil count <1000 /μL, platelet count <100,000/μL, alanine aminotransferase or aspartate aminotransferase >five times of the upper limit of normal for age, bilirubin or serum creatinine >1.5 times the upper limit of normal for age), taking any antiemetics, benzodiazepine or opioids within 48 h before initiation chemotherapy.

This triple-blind prospective, crossover randomized permuted blocking study was conducted in Mofid children's Hospital, Tehran, Iran. The investigators and analysts were unaware of the treatment arms to prevent any bias in this study. We did the trial in line with good clinical practice standards and regulations. The ethics committee of Shahid Beheshti University of Medical Sciences approved the protocol, and the parent or legal guardian of each patient was provided with the written informed consent. The trial was registered on the Iranian Registry of Clinical Trials (IRCT) website with a registration number of IRCT20200204046377N1. Patients who met the inclusion criteria were randomly assigned (1:1); the case group received abitant orally, and the control group received placebo form by an allocation concealment randomized block design. The Pharmacist of the trial assigned identification numbers to the participants, then coded them privately to assign allocation concealment. The batches were encoded to A and B, hidden in an opaque sealed envelope, not disclosed until the end of the study.

Randomization was stratified based on the patients' age (6 months to <2 years, 2 to <6 years, 6 to <12 years, or 12-15 years). Patients in the abitant group received abitant 125 mg for ages 12-15 years; 3 mg/kg up to 125 mg for ages six months to 12 years) on day 1, followed by 80 mg for ages 12–15 years; 2 mg/kg up to 80 mg for ages six months to 12 years on days 2 and 3. Patients in the placebo group received a placebo on days 1-3. Abitant and the placebo were supplied in a masked manner as capsules for patients aged 4-12 years and as suspension formulation for less than four years. All patients simultaneously received Ondansetron 0.15 mg/kg 30 minutes before initiation of chemotherapy. Ondansetron was continued as prophylaxis on the other days of chemotherapy. None of the patients received corticosteroids.

Any episode of retching or vomiting, or need to use rescue medications, or both were recorded by the "Linkert scale tool" during the efficacy evaluation period (0–120 h after the start of chemotherapy). The investigator recorded the time and date of each vomiting episode at the time of the occurrence. In addition, vital signs and adverse reactions were recorded during the study. The patients and their parents or guardians were trained to inform the investigators of any adverse event, and the investigator kept searching for any adverse event daily. Patients could recede from the study at any time or be removed by the investigator if hazardous effects had occurred. Rescue treatments were any antiemetic drugs (except the study drugs) administered due to breakthrough vomiting.

The first rank efficacy endpoint was the proportion of patients who achieved a complete response (defined as no vomiting, no retching, and no use of rescue medication) during the 25–120 h (delayed phase) after starting emetogenic chemotherapy. The secondary endpoint was the proportion of children who attained the complete response in the acute phase (0-24 hours). The acute phase was defined as 0 to 24 hours after the start of chemotherapy. Complete response was defined as no vomiting or retching and no use of rescue medication in the acute phase.

Table 1: Intensity of nausea and vomiting in two groups of "placebo" and "Abitant"

Severity of nausea	Placebo group (n=17)	Abitant group (n=18)	Severity of vomiting	Placebo group (n=17)	Abitant' group (n=18)
With no sign	11(64.7%)	9(50.5%)	With no sign	11(64.7%)	12(66.7%)
Able to eat	3(17.6%)	5(27.8%)	Once in 24 hours	2(11.8%)	2(11.1%)
Decreased tolerance for edibles	3(17.6%)	0(0.0%)	2 to 5 times in 24 hours	4(23.5%)	1(5.6%)
Need for intravenous fluid therapy	0(0.0%)	4(22.2%)	Six times in 24 hours or need for intravenous fluid therapy	0(0.0%)	3(16.7%)
Mann-Whitney U	0.38			0.93	

The qualitative variables are reported as percentages and numbers. The quantitative variables other than age are reported as Mean±SD. We assessed data distribution with Kolmogorov-Smirnov (K-S) test. The standard level of statistical significance was considered to be P≤0.05. According to the small sample size, we used non-parametric tests for data analysis. Chi-square and Fisher's test were used for assessing Mean±SD.

Results

Out of 35 patients (18 patients in the abitant group and 17 patients in the placebo group), 13 were men, and 23 were women. The mean age of the patients in the group receiving Abitant and placebo was 7.56±4.19 and 5.74±3.69 years, respectively (Table 1). Among the patients, 11 patients had a history of CINV, of whom seven patients (38.9%) were in the Abitant, and four (23.5%) in the placebo group, respectively.

The proportion of patients who received high and very high emetogenic regimens was higher in the Abitant group (P=0.471). Twelve (66.7%) of eighteen patients in the Abitant group and eleven (64,7%) of 17 in the placebo group achieved a complete response and stated as no vomiting, no retching, and no need for rescue medication during the 0–24 h after starting chemotherapy (in the acute phase) with no statistically significant difference.

83.3% of patients in the Abitant group and 88% of the placebo group achieved a complete response in the delayed phase. Among them, six patients received rescue medication due to the severity of the symptoms, of whom five patients were in the Abitant group, and one patient was in the placebo group. There was no statistically significant difference between the two groups in terms of controlling CINV (P=0.93). None of the patients experienced any specific symptom or adverse effect attributed to the study medication (figures 1 and 2).

Discussion

To the best of our knowledge, this is the first triple-blind randomized trial on the efficacy and safety of the Iranian neurokinin receptor antagonist, Abitant, on the control of CINV in children with malignancy. According to the results of our study, there was no significant difference between Abitant and placebo in controlling CINV. Furthermore, results from this study showed that a three-day, age and weight-adjusted oral abitant regimen, in combination with ondansetron without dexamethasone, could not yield a notable advantage in terms of prevention of nausea and vomiting associated with emetogenic chemotherapy regimens in children and adolescents, compared with a control regimen of Ondansetron without Aprepitant.

Our study is a non-inferiority trial because it is designed not to reveal that treatments are equal, or not different, but that the new treatment is not unacceptably worse than, or non-inferior to the control arm.[9] Saito and colleagues reported a complete response rate in the Aprepitant group during 45 cycles in children under 18 years old from 0 to 120 hours after chemotherapy.[10]

Patients younger than 18 years who received Aprepitant or fosaprepitant (an intravenous form of Aprepitant) to control CINV during 2015-2018 at Tokyo hospital were enrolled in this study. The primary endpoint was complete response (defined as neither vomiting nor utilizing rescue medication between 0 and 120 h after the initiation of chemotherapy).[10] Of the 25 chemotherapy cycles that were assessed, no significant adverse events were detected in either group.[10]

In the present study, the complete response rate in the Abitant group at 24 and 120 hours after chemotherapy

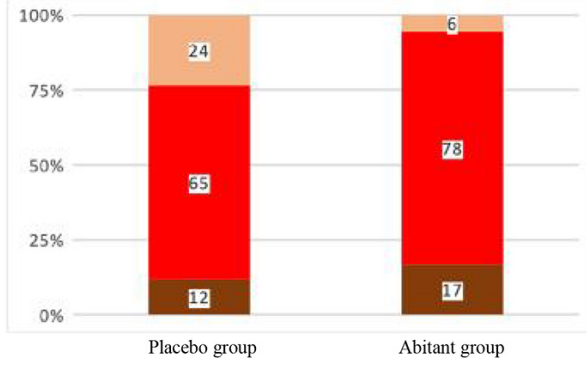

Figure 1: Intensity of nausea and vomiting in patients among two groups receiving Abitant and placebo.

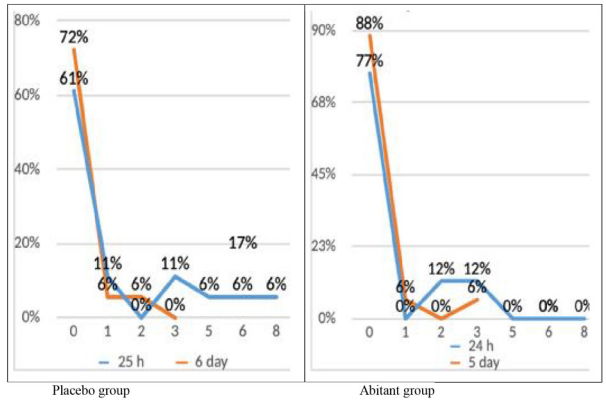

Figure 2: Trend of the severity of nausea and vomiting in patients in the two groups of Abitant and placebo.

was 66.7% and 88.3%, respectively, with no statistically significant difference detected in comparison to the placebo group. In the study of Kang and co-workers on children aged six months to 18 years undergoing chemotherapy, the rate of complete response in the delayed phase in the Aprepitant group was higher in all groups.[11] In our study, there was no significant difference between the Abitant group and the placebo. In Kang's study, dexamethasone was administrated with Aprepitant, which has a synergistic effect in controlling CINV. Kang and colleagues also found that the rate of complete response in the age range of 6 months-2 years in the Aprepitant group was twice that of the placebo group.[11] Iman and co-workers concluded that adding Aprepitant to the metoclopramide granisetron and dexamethasone effect significantly better than dexamethasone, granisetron, and metoclopramide in the controlling acute emesis, with no significant change in delayed emesis in the Arab population.[12] In another study, patients between the ages of 12 months and 17 years with a confirmed malignancy that were eligible enrolled in study they were scheduled to receive aprepitant as part of combination therapy antiemetic prophylaxis before administration of highly emetogenic chemotherapy. Eleven patients were evaluated for the incidence of nausea, episodes of emesis, interference with activities of daily living Aprepitant was well-tolerated and complete response rate was 38.9%. Additionally, complete response in the Aprepitant group was 33.3% in children >40 kg and 44.4% in children <40 kg.[13]

A considerable number of reported studies favored the safety of Aprepitant in children.[6, 8] Giagnuolu and colleagues report the efficacy and safety of Aprepitant as part of triple antiemetic prophylaxis in a cohort of thirty-two children and adolescents aged between 1 to 17 years with malignancy that treated with moderate/highly emetogenic chemotherapy regimens in a single Institution. Giagnuolu and colleagues have stated that Aprepitant's most expected adverse effect was neutropenia and transaminitis.[14] In our study, no adverse effect was found in the two groups.

In a systematic review, the Aprepitant triple regimen consisting of Aprepitant, ondansetron, and dexamethasone was advantageous for preventing CINV in patients treated with moderate to highly emetogenic chemotherapeutic regimens and was capable of decreasing the risk of constipation and increasing the incidence of hiccups.[15]

Conclusion

Oral Abitant in combination with ondansetron could not yield a dramatic advantage in the prevention of CINV in infants and children. Although in terms of safety, our study; did not reveal any adverse effect. We may conclude that our study is non-inferior to ondansetron administration alone.

Acknowledgments

This study was approved by the Research Ethics Council of Shahid Beheshti University of Medical Sciences (Ethics ID: IR.SBMU.RICH.REC.1398.008) and registered in the Clinical Trial Registration System (Code: IRCT20200204046377N1).

Conflict of Interest: None declared.

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