

A clinical trial study on the efficacy of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in children with cancer

Gholamreza Bahoush^{1✉}, Pourya Salajegheh², Ahmadsreza Shamshiri³, Masoumeh Jafari⁴

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Author Affiliation:

¹Associate Professor of Pediatric Hematology-Oncology, Ali-Asghar Children hospital, Pediatric Department, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.

²Neuroscience Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran

³Department of Epidemiology and Biostatistics, School of Public Health, Tehran University of Medical Sciences, Tehran, Iran.

⁴Fellow of Pediatric Hematology and Oncology, Ali-Asghar Children Hospital, School of Medicine, Iran University of Medical Sciences, Tehran, Iran.

✉Corresponding author

Associate Professor of Pediatric Hematology-Oncology, Ali-Asghar Children hospital, Pediatric Department, School of Medicine, Iran University of Medical Sciences, Tehran, Iran; Email: Bahoush.gh@iums.ac.ir

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ABSTRACT

Background: Preventing and controlling cancer-induced nausea and vomiting (CINV) in children undergoing chemotherapy is a great challenge because of more vulnerability and susceptibility of this age group. The present clinical trial study aimed to compare the antiemetic regimens including ondansetron and aprepitant in management of CINV among children. **Material and Methods:** In this, quazi-experimental double blind and self-control clinical trial study, 85 children ranged 1 to 15 years suffering cancer and scheduling for moderate or severe protocols for chemotherapy referred to Ali-Asghar children hospital in September to December 2020 were included. The patients in first course of chemotherapy received ondansetron at a single dose of 0.1 mg/kg before starting chemotherapy (as the comparison course) and also received aprepitant in the next course of chemotherapy exactly the same as the first course (as the intervention group). **Results:** The severity of CINV during the first 24 hours of chemotherapy as well as after the first 24 hours of chemotherapy up to 120 hours in the intervention period was significantly lower than the comparison period ($P < 0.001$), independent to gender and severity of chemotherapy. **Conclusion:** Aprepitant is very effective in preventing CINV in children higher than 6 months as compared to ondansetron as the control. Such effectiveness is independent to baseline variables including gender and severity of chemotherapy.

Keywords: Aprepitant, Vomiting, Children, Cancer.

1. INTRODUCTION

Applying recent chemotherapeutic regimens has contributed to successful management of different types of cancers within childhood increasing patients' survival, however almost all regimens have been accompanied with some annoying side effects such as cancer-induced nausea and vomiting (CINV) which appear in up to 70% of patients (Adel, 2017). Despite



development of efficient and safe antiemetic drugs for management of CINV within childhood, a notable number of patients continue to suffer from this complication and therefore face a decrease in quality of life, electrolyte imbalance, feeling frustrated by the treatment regimen, and helplessness from the healing process (Navari and Aapro, 2016; Shankar et al., 2015; Mansy et al., 2020). This issue has even affected patients' adherence to treatment (Gutstein, 2003). There are several mechanisms for this condition, but two of the most common include 1) the efferent emetic reflex created following the activation of the neurohormonal vagal pathway due to 5-hydroxytryptamine and 2) direct anti-neoplastic stimulation on Postrema area (Horn et al., 2014; Janelins et al., 2013). Because the occurrence of CINV is potentially influenced by multidimensional factors including, age, baseline metabolic condition, and even baseline psychological condition especially anxiety, the proper management of these chemotherapy side effects also serve as a therapeutic challenge (Watson et al., 1998). Besides, although there are several guidelines for controlling and resolving these complications in adult patients, there is still no consensus on providing similar guidelines in children (Gan et al., 2019).

Administrating ondansetron, a 5-HT₃ receptor antagonist, as an effective antiemetic medication has been well understood among adult patients (Patel et al., 2020). In some clinical trials on children with cancer and suffering CINV, the use of ondansetron was well tolerated and successful in abolishing emesis with infrequent side effects (Gupta et al., 2013). In this regard, many oncologists tend to add this drug in their treatment repertoire. As another protocol, aprepitant, neurokinin 1 (NK-1) receptor antagonist, was introduced in 2003 for preventing CINV in both oral and parenteral roots (Morita et al., 2017). This latter drug can target substance P and NK-1 receptors in the central nervous system leading prevention of CINV in adults (Bubalo et al., 2018); however its efficacy remained unclear in pediatric population. The present clinical trial study aimed to compare the antiemetic regimens including ondansetron and aprepitant in management of CINV among children.

2. MATERIALS AND METHODS

In this quazi-experimental double blind and self-control clinical trial study, children ranged 12 months to 15 years suffering cancer and scheduling for chemotherapy with moderate or high potency drugs referred to Ali-e-Asghar children hospital in September to December 2020 were included into the study. In this regard, those with nausea and vomiting for reasons other than chemotherapy, history of radiotherapy, history of other underlying disorders, history of cardiovascular disorders or any allergy to chemotherapy were all excluded from the study. Before any intervention, the written informed consent was taken from all parents. The study protocol was scientifically and ethically approved by Iran University of Medical Sciences. The IRCT (Iranian Registry of Clinical Trials) code is IRCT20200819048455N1.

As shown in Table 1, the patients in first course of chemotherapy received Ondansetrone at a single dose of 0.1 mg/kg before starting chemotherapy (as the comparison course) and also received aprepitant in the next course of chemotherapy exactly the same as the first course (as the intervention group).

Table 1 the intervention protocols by Aprepitant in our experimental study

Group	First day	Second day	Third day
Age: 12-17 years	125 mg, OR	80 mg, OR	80 mg, OR
Age: 6 months-11 years	Oral suspension powder 2 mg/kg up to 125 mg	Oral suspension powder 2 mg/kg up to 80 mg	Oral suspension powder 2 mg/kg up to 80 mg

Then, the occurrence of CINV, its frequency, as well as possible side effects of drugs were recorded by a person who was completely unaware of the groups and drugs. To describe qualitative variables such as vomiting severity, number and percentage were reported. Generalized Estimating Equations method was used for analytical assessment of data due to the correlation of data between the two courses. Since the range of variation of the vomiting intensity score ranged from 0 to 5, this variable was considered quantitatively and thus the linear regression model was use for analyzing with the Exchangeable Correlation Matrix. Subgroup analysis was performed to evaluate the interaction of variables in age subgroups, gender and intensity of chemotherapy. The statistical significance limit for Main effects analyzes was less than 0.05 and for subgroup analysis was 0.10.

3. RESULTS

In total 85 children (50.6% male and 49.4% female) ranged 12 months to 14 years were included into study. The most prevalent malignancy was ALL (44.7%) followed by NB (24.7%) and Wilm's tumor (12.9%) (Figure 1). In this study, 41 patients (48.2%) received moderate intensity chemotherapy and the rest (44 patients, 51.8%) received high intensity chemotherapy.

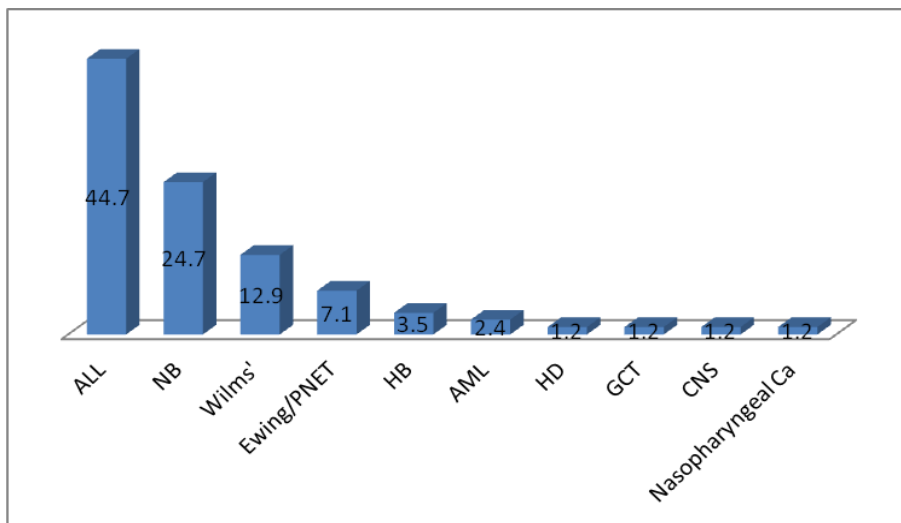


Figure 1 The types of cancers in children included

The severity of CINV during the first 24 hours of chemotherapy in the intervention period (Figure 2) was significantly lower than the comparison period (Mean difference = 2.17; SE = 0.13; p-Value <0.001). In the subgroup analysis, the effect of the intervention on reducing the severity of CINV during the first 24 hours after chemotherapy was not affected by gender variables and the severity of chemotherapy (p-value of interaction was 0.33 and 0.40, respectively). However, the effect of the intervention was not the same in different age groups (p-value of interaction was equal to 0.08) so that the effect of the intervention was greater in children under seven years.

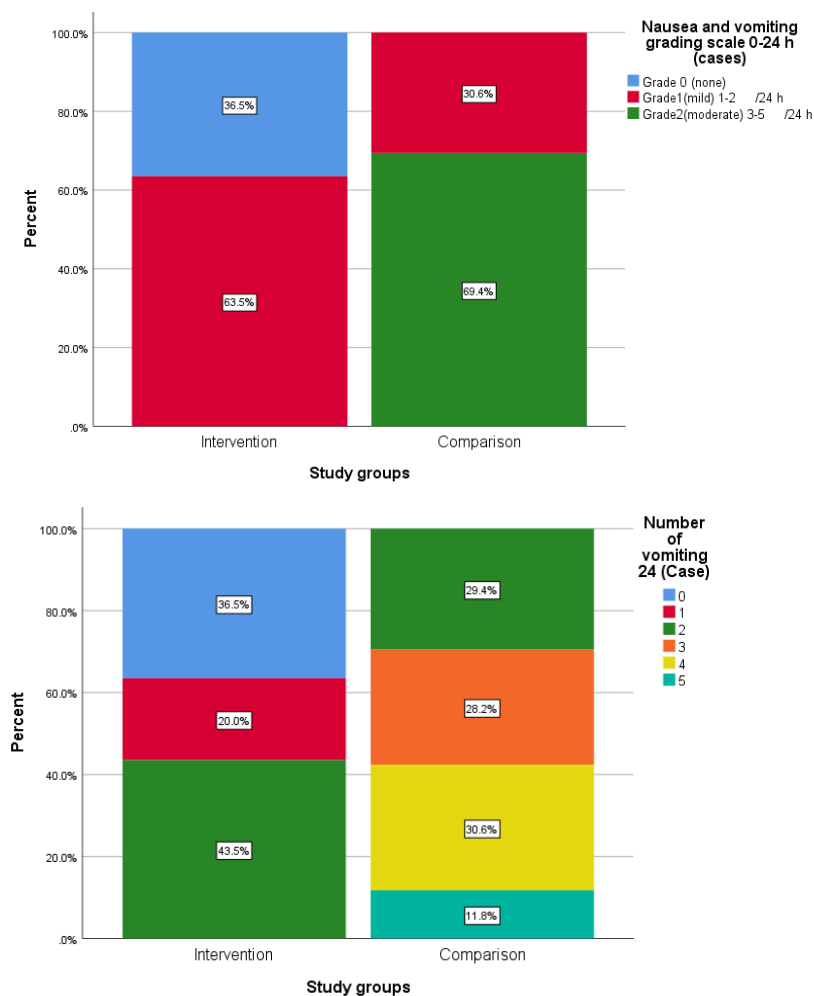


Figure 2 Distribution of CINV severity in two periods with and without intervention within 24 hours of chemotherapy

The intensity of CINV after the first 24 hours of chemotherapy up to 120 hours in the intervention period (Figure 3) was significantly lower than the comparison period (Mean difference=2.13; SE=0.12; p-Value<0.001). In the analysis of subgroups (Table 2), the effect of intervention in reducing the severity of vomiting from the first 24 hours of chemotherapy to 120 hours was not affected by gender variable (p-value of interaction equal to 0.62). But it was interacted with two variables of age group and intensity of chemotherapy (The p-value of the interaction was 0.048 and 0.053, respectively), so that the effect of the intervention was greater in children over 7 years of age (compared to children under 7 years of age) and children receiving moderate chemotherapy (than children receiving severe chemotherapy). None of all enrolled patients experienced any side effects after receiving aprepitant.

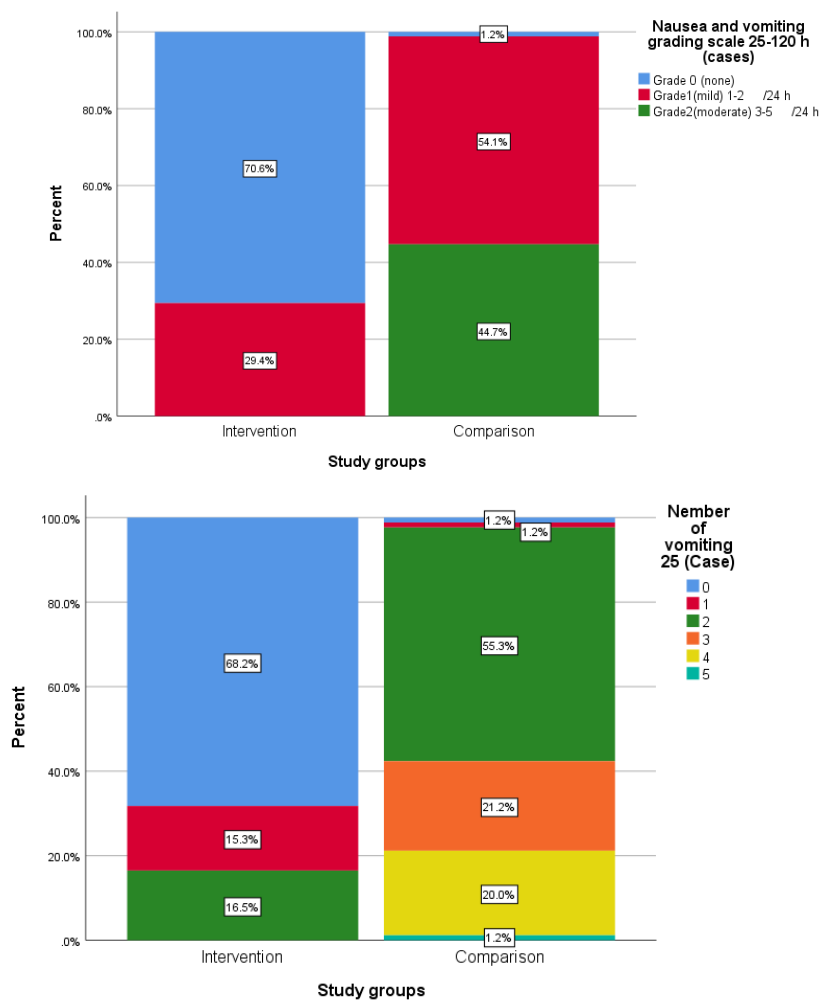


Figure 3 Distribution of CINV severity in two periods with and without intervention between 24 to 120 hours of chemotherapy

Table 2 Subgroup analysis of the effects of study interventions

Time	Subgroups	Mean difference in vomiting grade (intervention vs. comparison)	Standard error (SE)	p-Value
During first 24 hours of chemotherapy				
Age groups	≤7years (n=59)	2.32	0.16	<0.001
	>7years (n=26)	1.85	0.22	<0.001
After the first 24 hours of chemotherapy				
Age groups	≤7years (n=59)	1.98	0.15	<0.001
	>7years (n=26)	2.46	0.19	<0.001
Chemotherapy scale	Moderate (n=41)	2.37	0.16	<0.001
	High (n=44)	1.91	0.18	<0.001

4. DISCUSSION

Preventing and controlling CINV in children undergoing chemotherapy is a great challenge because of more vulnerability and susceptibility of this age group to drug reactions and side effects. Additionally, not only physical reactions, but also psychological disturbances are the results of chemotherapy protocols among affected children. A notable number of such children suffered from CINV, but it seems that the present protocols for preventing this side effect are efficient, however optimizing the dosages and route of drug administration to maximize its efficacy and minimize its side effects are necessary. According to the literatures, both regimens including ondansetron and aprepitant are effective regimens, but our study shows higher anti-emetic efficacy because of more lowering intensity of CINV in. More importantly, such drug efficacy was not affected by baseline parameters such as gender or severity of chemotherapy, but the patients' age has been an effective confounder on the effectiveness of the drug so that administering aprepitant within the first 24 hours of chemotherapy was significantly higher in older ages with lower factors-related interaction. Also, using the drug after the 24 hours of initiating chemotherapy led to greater effect in children over 7 years of age (compared to children under 7 years of age) and children receiving moderate chemotherapy (than children receiving severe chemotherapy). As shown by Kang et al. (2018) complete response rate was higher with the aprepitant than the placebo regimen across all age categories, and reached significance for subjects aged 12-17 years, similar to our study. However, they also indicated that using dexamethasone doubled the response rate of aprepitant.

Felix-Ukwu et al. (2018) also revealed enhancement of antiemetic regimen containing aprepitant leading a 54% reduction in the use of as-needed other anti-emetics. A study by Cristofori et al. (2014) on children suffering chemotherapy, there was a significant decrease in cyclical vomiting syndrome episodes/year, hospital admission number/year, cyclical vomiting syndrome episode length, number of vomits per hours, as well as an increase in symptom-free interval duration and school attendance percentage following administration of aprepitant. Bakhshi et al. (2015) also indicated that acute moderate and severe vomiting was reported in 72 % patients receiving placebo and 38% patients receiving aprepitant with higher complete response rate in the latter group (48% versus 12%) and also without major adverse effects by patients/guardians. In final, in a study by Duggin et al. (2014) on children suffering chemotherapy due to brain tumors, controls without aprepitant were more likely to have higher grades of vomiting than the aprepitant recipients after controlling for radiation-associated vomiting toxicity.

Based on the recent guidelines, first, in children aged high than 6 months who receiving highly emetogenic chemotherapy, interact with aprepitant is highly suspected and thus the best anti-emetic regimens include a combination of ondansetron or palonosetron with aprepitant and dexamethasone. However, in those who younger than 6 months, granisetron or ondansetron or palonosetron plus dexamethasone is highly recommended. Thus, a combination of ondansetron with aprepitant with the optimized dosages is recommended for the children aged higher than 6 months.

5. CONCLUSION

According to our findings, aprepitant is very effective in preventing CINV in children higher than 6 months as compared to ondansetron as the control without any significant side effects. Such effectiveness is independent to baseline variables including gender and severity of chemotherapy, however due to the interactive role of patients' age on drugs efficacy, optimizing the anti-emetic drugs in different age subgroups is essential.

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Conflict of Interest

The authors declare that there are no conflicts of interest

Authors' contributions

All authors contributed to the design of the study, as well as data collection and analysis, and the writing of the manuscript. All authors read and approved the final manuscript.

Informed consent

Written & Oral informed consent was obtained from all individual participants included in the study. Additional informed consent was obtained from all individual participants for whom identifying information is included in this manuscript.

Data and materials availability

All data associated with this study are present in the paper.

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