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The effect of Vitamin B6 on chemotherapy induced nausea and vomiting in pediatric cancer

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Abstract

Background: Nausea and vomiting are the common side-effects of chemotherapy in children with malignancy. In this study, the effectiveness of vitamin B6 in reducing the chemo-induced nausea and vomiting (CINV) in children was tested.

Material and methods: A triple-blind clinical trials was performed on 100 children with malignancy referring to the pediatric clinic of Amir Kabir Hospital, Arak, Iran. Besides the infusion of granisetron (3mg/3ml) half an hour before each chemotherapy cycle, an intravenous dose of vitamin B6 (100 mg for children from 2 to 5 years old, 200 mg for children from 5 to 10 years old, and 300 mg for children older than 10) was given 6 hours before the first chemotherapy cycle and placebo was injected (2-5 years old: 100 mg, 5-10 years old: 200 mg, age≥ 10 years old: 300mg) 6 hours before the second cycle. Then the severity of nausea and the frequency of vomiting episodes in each cycle were recorded to be compared.

Results: The mean age of children was 7.98 ± 3.133 years old. The most common and rare malignancy were acute lymphocytic leukemia (ALL) (46%) and ependymoma (0.5%), respectively. Vincristin was the most commonly used chemotherapy agent (28%). A positive correlation between the severity of nausea(R=0.313, P-value=0.0016) and frequency of vomiting with age was found (R=0.319, P-value=0.0012). However, no noticeable association was observed between N/V and gender (P-value.0.05). There was a considerable correlation between the frequency of vomiting and different tumor types in this study (P-value=0.0006).In comparison with placebo, Vitamin B6 significantly reduced the severity of nausea (P = 0.0001) as well as the frequency of vomiting (P-value = 0.0005). It was also more effective in ALL compared to rhabdomyosarcoma (P-value=0.001).

Conclusion: This study suggested that vitamin B6 can be considered as an appropriate alternative to treat CINV in children with malignancy.

Keywords: Chemotherapy, Children, Vitamin B6, Vomiting

Introduction

Today, cancer is one of the most important challenges in medicine. Based on the World Health Organization (WHO) reports, the rate of cancer will have grown from 11.3 million individuals in 2007 to 15.5 million cases in 2030 In addition; the mortality rate is estimated to be nearly 7.9 million deaths throughout this period (1). The incidence of cancer in children living in the developed countries is approximately 105-150 new cases per one million children population. Malignancy is also the second cause of childhood death in these first-world countries (2). Although chemotherapy is usually used to relieve, control, and treat cancers, it causes certain complications, including nausea and vomiting, diarrhea, and constipation (3). Besides the patients' fear of chemotherapy, some of them refuse to continue the treatment and chemotherapy due to the severe and frequent chemo-induced vomiting. Furthermore, it might cause

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malnutrition, electrolyte imbalance, dehydration, esophageal perforation, functional disorders, noticeable reduction in their life quality, aspiration pneumonia, and intracranial hypertension (4).

Generally, nausea and vomiting are the most common complications of chemotherapy which make the patients speed up the process and end the treatment sooner than the expected time (5). In the last 25 years, doing clinical trials has brought improvements to the treatment of chemo-induced nausea and vomiting (CINV) (6). CINV includes 3 categories:

1) Acute nausea and vomiting within the first 24 hours after chemotherapy that would be the result of serotonin secretion from enterochromaffin cells.

2) Delayed nausea and vomiting, which happen more than 24 hours up to 5 days after chemotherapy, can be usually because of substance P, blood-brain barrier disruption, gastrointestinal motility disorders, and adrenal disorders.

3) Anticipatory nausea and vomiting which are learned or conditioned responses from previous chemotherapy experiences. It seems that emotion and memory regions of the brain are responsible for this type (7).

Prescribing anti-vomit medications is a prevalent method to reduce CINV. These days, new medications are available, such as granisetron; however, it has particular side-effects, namely headache, bradycardia, diarrhea, insomnia, fever, and anaphylactic reactions which can make more problems for the patients (8, 9). What is important in these patients is providing non-invasive, safe, inexpensive, and less complicated methods to control CINV. Even though different studies have verified the positive role of vitamin B6 in the restriction of CINV (10), there is lack of accurate information about its role of in reducing children's CINV. Therefore, the present study was undertaken to investigate therapeutic efficacy of this agent, as an alternative treatment, in reducing CINV in children.

Materials and Methods

This triple-blind clinical trial was performed in accordance with the regulations of the Ethics Committee standards of Arak University (Arak University of Medical Sciences, Research Ethics Committee, ethical approval #1395.443). The trial code was IRCT20141209020258N67. A triple double-blind clinical trial was performed on 100 children with malignancy referring to the pediatric clinic of Amir Kabir Hospital, Arak, Iran, 2016. The patients participated voluntarily, and their parents or legal guardians signed the relative consent forms. The patients were given the right to withdraw from the clinical trial at any moment.

Through a self-control method, in addition to infusion of granisetron (3mg/3ml) half an hour before each chemotherapy cycle, an intravenous dose of vitamin B6 (100 mg for children from 2 to 5 years old, 200 mg for children from 5 to 10 years old, and 300 mg for children older than 10) was given 6 hours before the first cycle. In the next chemotherapy session, the patients, who took the same chemo agents, received granisetron half an hour before the cycle and distilled water (100 mg for children from 2 to 5 years old, 200 mg for children from 5 to 10 years old, and 300 mg for children older than 10) , as placebo, 6 hours before the cycle. Vitamin B6 (as Drug A) and distilled water (as Drug B) were prepared by the head nurse of hemato-oncology ward who was blinded to the study. The practical nurse, the analyzer, and the correspondent were not aware of drugs' types. The severity of nausea and the frequency of vomiting in both cycles were recorded to be compared. Having applied SPSS

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(version 18), student's t-test and one-way ANOVA were used for data analysis. P value<0.05 was pondered to show statistical significance. It is required to be mentioned that the data were reported using Mean SD (based on the significant level of P value<0.05).

The severity of nausea was classified based on the common toxicity criteria (CTC):

Grade 0. No change

Grade 1. Loss of appetite with no change in eating habits

Grade 2. Disordered eating with no weight loss, dehydration, and malnutrition

Grade 3. Poor calorie or liquid intake, intravenous fluid therapy, nasogastric (NG) feeding or total parenteral nutrition (TPN)

Grade 4. Life-threatening consequences

The frequency of vomiting was categorized as below:

Grade 0. No vomiting

Grade 1. Once within 24 hours

Grade 2. 2-5 episodes within 24 hours

Grade 3. More than 6 episodes within 24 hours, or intravenous fluid therapy, or TPN

Grade 4. Life-threatening consequences

Results

In the present study, 100 children with malignancy were enrolled from the pediatric clinic of Amir Kabir hospital. The mean ± SD age of the patients in case and controle groups were 7.98 ± 3.133 and 8.2±2.88 years old respectively, and the minimum and maximum ages of the patients were 3 and 15, respectively. In terms of gender, 61% of children were boy and 39% were girl. Based on the results, 46% of the patients suffered from Acute lymphocytic leukemia (ALL), 11% from Acute myeloid leukemia (AML), 8% from rhabdomyosarcoma, 6% from Wilms' tumor and neuroblastoma, 5% from osteosarcoma, 4% from Ewing Sarcoma and lymphoma, 2% from primitive neuroectodermal tumor(PINET) and Non-Hodgkin lymphoma, 1% from central nervous system (CNS) tumors, Synovial Sarcoma, optic glioma, germ cell tumors and Hodgkin's lymphoma, and 0.5% from ependymoma and Langerhans cell histiocytosis(LCH)(Table I).

Furthermore, the severity of nausea after receiving vitamin B6 and placebo were 1.60± 0.84 and 1.91±0.80 (mean ±SEM), respectively. Based on the Wilcoxon matched-pairs signed-rank test, the comparison of severity of nausea after the infusion of vitamin B6 and placebo indicated that it significantly decreased among the patients after vitamin B6 administration (P-value<0.0001, Figure 1).

According to the results, the frequency of vomiting episodes after receiving vitamin B6 and placebo were and (mean ±SD), respectively. Based on the Wilcoxon matched-pairs signed-ranked test, vitamin B6 was more effective than placebo in alleviating the frequency of vomiting (P-value<0.0059, Figure 1).

Moreover, using Pearson Correlation Coefficient, the following result obtained. There was a positive correlation between the severity of nausea and age (R=0.313, P-value=0.0016), that is to say nausea was more sever in the older ages (Figure 2). There was also a positive correlation between the frequency of vomiting episodes and age (R=0.319, P-value=0.0012); In other words, more vomiting episodes were reported in the older patients (Figure 2). Unlike the age, which had a significant relation with the severity of nausea and vomiting episodes, there was no noticeable association between N/V and gender (P-value.0.05), (Table II).

On the other hand, according to Kruskal-Wallis test, there was a considerable correlation between the frequency of

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vomiting and different tumor types in the patients (P-value=0.0006). Besides, the frequency of vomiting episodes in the patients with ALL was significantly lesser than that in patients with rhabdomyosarcoma (P-value=0.001, Figure 3).

Of all the patients, 28% received Vincristin, 10% Adriamycin, 6% Cytozar, 5% Cyclophosphamide+ Adriamycin, 4% MTX, 4% Intra spinal chemotherapy, 3% Cyclophosphamide+ Adriamycin+ Vincristin, 3%Adriamycin+Ifex, 3%Vincristin+Actinomycin, 3%Cyclophosphamide+Vincristin,2% Cyclophosphamide+ Carboplatin, 2%Actinomycin, 2% Adriamycin+ Vincristin, 2% Daunomycin + Cytozarof , 2% Ifex+ Carboplatin, and 2% Carboplatin+ Vincristin. According to Spearman Correlation Coefficient, no statistical correlation was found between the type of chemotherapy agents and CIVN after the infusion of vitamin B6 and placebo (P-value<0.05, Table III).

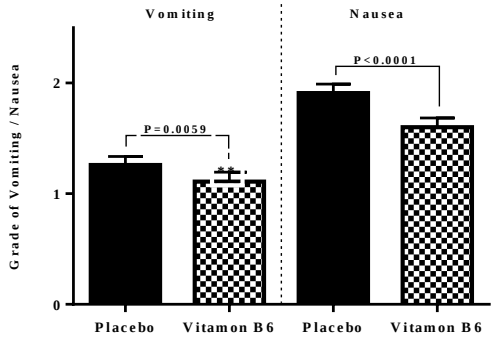

Figure1. Comparison of CINV grades after receiving Vitamin B6 and the placebo.

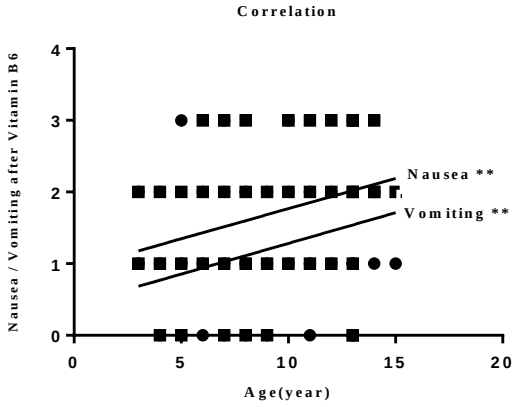

Figure2. Evaluation of the correlation between the grade of CINV and age in patients after receiving Vitamin.

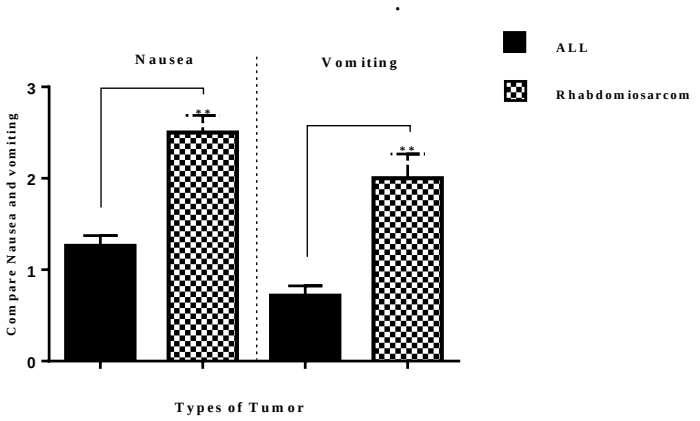

Figure3. Comparison of CINV grades in patients with different types of tumors after receiving Vitamin B6

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TableI: The frequency of different tumor types in the patients

Number (%)	Types of tumor
46%	ALL
11%	AML
8%	Rhabdomyosarcoma
6%	Wilms
6%	Neuroblastoma
5%	Osteosarcoma
4%	Ewing's sarcoma
4%	Lymphoma
2%	Non-Hodgkin lymphoma
2%	PINET
1%	CNS tumor
1%	synovial sarcoma
1%	optic glioma
1%	Hodgkin's lymphoma
1%	Germ cell tumor
0.5%	LCH
0.5%	Ependymoma

ALL : Acute lymphocytic leukemia, AML : Acute myeloid leukemia, PINET : Primitive neuroectodermal tumor, LCH : Langerhans cell histiocytosis

TableII: The frequency-correlation of CINV and gender after receiving Vitamin B6

P value	Correlation	Gender (%)	Variable	Patients(Received)
P=0.98	R=0.002	**Male = 61%**	**Nausea**	
P=0.70	R=0.038	**Female= 39%**	**Vomiting**	**Vitamin B6**

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Table III: The frequency of different chemotherapy agents in patients

Percentage	Number	Chemothrapy
28%	28	*Vincristin*
10%	10	*Adriamycin*
6%	6	Cytozar
5%	5	*Cyclophosphamide+ Adriamycin*
4%	4	MTX (Methoteroxate)
4%	4	Intra spinal chemotherapy
3%	3	*Cyclophosphamide+ Adriamycin+ Vincristin*
3%	3	*Adriamycin+Ifex*
3%	3	*Vincristin+ Actinomycin*
3%	3	*Cyclophosphamide+ Vincristin*
2%	2	*Cyclophosphamide+ Carboplatin*
2%	2	*Actinomycin*
2%	2	*Adriamycin+ Vincristin*
2%	2	*Daunomycin+* Cytozar
2%	2	*Ifex+ Carboplatin*
2%	2	*Carboplatin+ Vincristin*
2%	2	*Mitoxantrone*
1%	1	*Adriamycin+desefix.*
1%	1	*Adriamycin+desefix+VP16.*
1%	1	*Carboplatin+VP16*
1%	1	*Daunomycin*
1%	1	*Vinblastine*
1%	1	*Carboplatin*
1%	1	*Cyclophosphamide*
1%	1	*Carboplatin+ Adriamycin*
1%	1	*Adriamycin+ Cyclophosphamide+VP16*
1%	1	*Adriamycin+ \ifex+VP16*
1%	1	*Daunomycin* + Cytozar
1%	1	*Carboplatin+ Bleomycin+VP16*
1%	1	*Carboplatin+ Ifex+VP16*
1%	1	*Ifosophamide+ Carboplatin+ VP16*
1%	1	*Irinotecan+* Temozolomide
1%	1	*Vincristin+* Cytozar
1%	1	*Ifex+Carboplatin+VP16*
100%	100	*Total*

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Discussion

According to the findings, vitamin B6 administration before each chemotherapy cycle was reduced nausea and vomiting as it caused a drastic reduction in CINV. It should be noted that the statistical correlation of CINV and age showed that the severity of nausea and the frequency of vomiting episodes were higher in older patients; however, CINV was not linking to gender and the chemotherapy agent types. The comparison of CINV in patients with different tumor types indicated that the patients suffering from rhabdomyosarcoma experienced more severe nausea and vomiting in comparison with those with ALL.

An earlier study on the role of vitamin B6 in pregnancy-related nausea and vomiting by Haji Seid Javadi et al. showed that receiving vitamin B6 could reduce the severity of nausea and the frequency of vomiting (11). In the current study, vitamin B6 significantly reduced CINV in chemotherapy cycles; however, it affected the frequency of vomiting more than the severity of nausea.

Consistent with the present study, vitamin B6 significantly reduced the vomiting episodes in a study by Jarolmasjed et al., on the effects of vitamin B6 intra-muscular and normal saline injection on animals after administration of vomiting induced drugs (12).

In a double-blind study, Jenabi et al., compared the effects of vitamin B6 and ginger on pregnancy-related nausea and vomiting (13). Despite that receiving ginger had more effects than vitamin B6 on reducing the severity of nausea, they were equally effective in decreasing the number of vomiting episodes, which was in accordance with the results of current study. In the present study, vitamin B6 could decrease CINV in the patients and the difference between the results of these two studies might be due to the different tumor types in children with malignancy which could affect their responses to vitamin B6.

In a study by LI Yu-qi et al. (14), the efficacy of vitamin B6 in combination with Ondansetron for controlling CINV in children suffering from solid tumors was evaluated. According to the results, the combination of both vitamin B6 and granisetron (the main anti-nausea and vomiting agent) was more effective than granisetron itself in preventing chemo-induced vomiting. The present study reported that the combination of vitamin B6 and granisetron was influential on the restriction of both nausea and vomiting due to chemotherapy in children.

In another study, derakhshanfar.,(15) argued that the effect of vitamin B6, as the only treatment, on restricting nausea and vomiting in 96 children suffering from acute gastroenteritis was negligible. Whereas, our findings noted that using vitamin B6 as an additional agent to the main anti-vomit agent (granisetron) intensely controlled CINV in children with malignancy.

Notable findings also were reported from the study by Qi You et al., on the effectiveness of vitamin B6 combined with acupuncture medicine in CINV on 142 women with ovarian cancer (16). Since the suggested treatment was successful in their study and according to the previous mentioned studies, it seems that vitamin B6 can effectively modify the effects of other medications (ondansetron or gransetron) and other therapies such as acupuncture therapy in controlling CINV, especially in children who are more susceptible. Additionally, in a study by Sanaati et al., vitamin B6 played an effective role in the control of CINV in women with breast cancer (17).

However, vitamin B6 appeared as a helpful medication in the prevention of CINV in different patients' groups (18, 19) and our research revealed the positive role of vitamin B6 in CINV in children as an adjuvant therapy, further studies are required due toe limited number of research on this subject.

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A research by Ikuo Sekine et al. on the risk factors for CINV in adults illustrated that age (<55) and gender (female) were two risk factors of acute CINV, while delayed CINV was just related to gender. In contrast, in the current study, CINV was related to age but not to gender. There are two justifications behind the discrepancies between the two studies. Firstly, the cases in the present study were children from 3 to 15 years old, but the cases in their study were adults older than 20 years old. Thus, age could be a risk factor for children, not for adults. Secondly, the tumor types in children and adults and consequently, their effects on CINV can be various. Therefore, the severity and frequency of CINV might be different in these two case groups, such as the difference between children with ALL and children with rhabdomyosarcoma in the current study.

In a systematic review study by Mocellin S et al., (21) on the association of vitamin B6 and cancer risk, a negative correlation was found between them which supported the potency of vitamin B6 as a cancer risk reduction agent. Based on the current results, besides the role of tumor type in the severity of CINV, vitamin B6 reduced CINV in patients with ALL more significantly compared to patients with rhabdomyosarcoma.

Conclusion

Having provided deeper understanding of the vitamin B6 effects, this study indicated that vitamin B6 administration significantly reduced the severity of nausea and the frequency of vomiting in children with malignancy undergoing chemotherapy. Hence, it can be considered as an appropriate alternative to treat CINV in these children. Moreover, it was more effective in children with ALL in comparison with those suffering from rhabdomyosarcoma. Owing to the different results of the studies in this regard and small sample size in the current study, more studies with larger sample size in various clinics or hospitals on this subject are recommended to gain more valuable results.

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Conflict of interest

Authors declared no conflict of interest.

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