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The Role of Clinical Guidelines for the Management of Chemotherapy-Induced Nausea and Vomiting in Children with Cancer

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Abstract
Background: Nausea and vomiting are among the most important side-effects associated with chemotherapy in children with cancer, affecting the quality of their lives. Clinical guidelines for selecting antiemetics are effective in reducing acute chemotherapy-induced nausea and vomiting (CINV).
Materials and Methods: The present quasi-experimental study compared the effectiveness of the Pediatric Oncology Group of Ontario (POGO) CINV guideline with that of conventional arbitrary therapies for CINV in 82 children aged 6 months to 16 years old. Out of 177 cycles of chemotherapy, in 101 cycles patients were treated according to POGO-CINV Guideline; in the other 76 cycles, patients were treated with arbitrary types and doses of antiemetics. Then, vomiting in the first 24 hours after chemotherapy in both groups was measured and compared.
Results: In this study, 82 patients hospitalized in the Hematology Department of Dr. Sheikh Children's Hospital were enrolled, of whom 48 patients (58.7%) were boys and 34 (41.3%) were girls. The mean age of patients was 6.24±4.47 years (6 months to 16 years). The results of the current study showed that using a protocol for the prevention of vomiting based on the patient's age and the type of chemotherapy is superior to conventional management of CINV. Findings showed that the frequency of nausea and vomiting in the protocol group was significantly reduced in comparison with the control group ($p<0.005$). Moreover, a reduction in the frequency of nausea and vomiting was quite significant in the sub-categories of the protocol group who had received high-risk or moderate-risk emetogenic drugs ($p<0.005$).
Conclusion: The results of the current study showed that using the POGO guideline, which takes into account the patient's age and the type of chemotherapy, is more effective than arbitrary management of CINV, particularly in children.
Keywords: Drug therapy, Nausea, Neoplasms, Practice guideline, Vomiting

Introduction

Chemotherapy-induced nausea and vomiting (CINV) is one of the most serious side-effects and a major concern in children with cancer, occurring in 70% of children under chemotherapy (1-7). Clinical evidence has shown that common chemotherapy regimens, even when complemented with the best antiemetic drugs, may still cause vomiting (8, 9). CINV disrupts the daily activities of children undergoing chemotherapy, and negatively affects the quality of their lives. It may also cause depression and anxiety in children. Vomiting can cause electrolyte disturbances and dehydration, and in severe cases can lead to death. In addition, emotional distress due to these side-effects can affect treatment protocols, and may even discourage children from continuing the treatment (4). Classification of chemotherapeutic agents based on their degree of emetogenicity can (5, 7, 10-12) facilitate the management of CINV (13). Accordingly, chemotherapy agents are divided into four categories based on their emetogenicity (14, 15): 1) Highly emetic: > 90 % risk of emesis, 2) Moderately emetic:

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30 -90%, 3) Low risk of emesis: 10-30%, and 4) Minimally emetic: <10% risk of emesis. Prescribing antiemetic drugs is a standard treatment for controlling nausea and vomiting caused by chemotherapy. However, despite using the latest anti-nausea medications, 47% and 29% of patients still experience delayed and acute nausea, respectively, after receiving chemotherapy (16). Studies showed that applying clinical guidelines for selecting chemotherapy-induced antiemetic drugs reduces acute nausea in adults, but there is still no comprehensive study investigating the use of advanced clinical guidelines for CINV in children (3, 5). In the guidelines for children, antiemetic drugs are selected according to the patient's age and the severity of vomiting caused by chemotherapy drugs. The effectiveness of a standard treatment protocol has been previously described. The Pediatric Oncology Group of Ontario (POGO) CINV guideline provides a standardized, evidence-based approach to the prevention of CINV in children aged 1 month to 18 years old who receive antineoplastic agents. The purpose of this guideline is to provide health care providers, who care for children receiving antineoplastic medication aged 1 month to 18 years, with an approach for the prevention of acute CINV; however, its application is limited to the prevention of CINV in the acute phase (i.e., within 24 hours of administration of an antineoplastic agent), and does not include anticipatory, breakthrough or delayed phases of CINV (3). The main aim of this study is to propose the guideline as a standard protocol in the management of vomiting and nausea in child patients undergoing chemotherapy. This paper argued that following this guideline can prevent arbitrary prescriptions, which may be either inadequate or excessive in CINV control. To this end, this study compared the degree of vomiting in two groups of child patients undergoing chemotherapy. In one group, CINV was treated according to the POGO guideline; and in the other group, arbitrary types and doses of antiemetics were prescribed. The degree of vomiting was then compared between the two groups, and the effectiveness of each approach was evaluated.

Materials and Methods

Sample Size Calculation and Inclusion Criteria

This is a quasi-experimental study. Based on previous studies, the reported sample size for controlling nausea and vomiting in children under chemotherapy using clinical guidelines was P1 = 0.78 (7), and the sample size for prevention of CINV without protocol was determined as P2 = 0.35 (10). Considering the power of 80% and the significance level of 95%, the calculated sample size using the following formula is 17 for each group and a total of 136 for all eight groups. In this study, patients were excluded in case of death, unwillingness to use the drugs to prevent CINV, and disinclination to participate at any stage of the study. Therefore, the inclusion criteria were children aged ≤18 years old undergoing chemotherapy with informed parental consent, and the use of medications, according to the protocol, to prevent nausea and vomiting after chemotherapy.

Patients' Enrollment and Research Method

This experimental study was conducted on all children under the age of 18, who were hospitalized for chemotherapy from July 2014 to June 2015 in Dr. Sheikh Hospital, the only chemotherapy center for children in Mashhad, Iran. Informed consent was obtained from children's parents and data including patients' age, sex, height, weight, body mass index (BMI), and type of disease were recorded. Then, CINV treatment protocols were selected, based on previous studies, by considering the age and possible severity of vomiting (Table I). Emetogenicity was graded according to the first POGO CINV guideline, which defines high, moderate, low, and minimal emetogenicity respectively as a >90%, 30 to

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<90%, 10 to <30%, and <10% chance of causing emesis when antiemetic prophylaxis was not provided (3, 8). The severity of vomiting was then measured in the first 24 hours after chemotherapy and graded as shown below (17):

Grade 1: Vomiting once every 24 hours,
Grade 2: Vomiting 2-3 times in 24 hours,
Grade 3: Vomiting 3-5 times in 24 hours.
The same data were collected from patients who were not treated based on the protocol.

Table I: Protocol and clinical guideline for prevention of vomiting in patients undergoing chemotherapy.

No.	Severity of vomiting	Age (years)	Drugs
Protocol 1	High	>12	1- Ondansetron or granisetron 2- Dexamethasone 3- Aprepitant
Protocol 2 (Chemotherapy interact with Aprepitant)	High	>12	1- Ondansetron or granisetron 2- Dexamethasone
Protocol 3	High	<12	1- Ondansetron or granisetron 2- Dexamethasone
Protocol 4 (corticosteroids contraindicated)	High	-	1- Ondansetron or granisetron 2- Chlorpromazine
Protocol 5	Moderate	-	1- Ondansetron or granisetron 2- Dexamethasone
Protocol 6 (corticosteroids contraindicated)	Moderate	-	1- Ondansetron or granisetron 2- Chlorpromazine or metoclopramide
Protocol 7	Low	-	1- Ondansetron or granisetron
Protocol 8	Minimal emetogenic risk	-	No routine prophylaxis

There are different kinds of anti-emetics in use for children. Aprepitant (Darou Darman Pars, Kish Medipharm, Kish Island, IRAN) is available as oral capsules of 125 mg and 80 mg strengths. The standard dose is 3 mg/kg on day 1 maximum of 125 mg 1 hour prior to chemotherapy administration on day 1, and followed by 2 mg/kg maximum of 80 mg once daily on the morning of days 2 and 3 in children aged <12 years. Dexamethasone (Caspian Tamin Pharmaceutical Co. Rasht-Iran) is recommended at a dose of 6 mg/m2 every 6 hours, administered orally or intravenously (dose halved if Aprepitant is being used concomitantly). Ondansetron (Tehran Chemie) is administered at a dose of 0.15 mg/kg intravenously (IV) 30 minutes prior to chemotherapy, followed by 8 hourly doses. Alternatively, granisetron (Aburaihan Co. IRAN) can replace it with a once-daily IV dose of 40 mg/kg. Chlorpromazine (Tehran Chemie) is recommended at a starting dose of 0.5 mg/kg (may be increased up to 1 mg/kg) IV every 6 hours. The recommended dose for metoclopramide (Alborz Darou) is 1 mg/kg IV pre-chemotherapy followed by 0.0375 mg/kg PO every 6 hours (Table II).

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Table II: Dosing of commonly-used anti-emetic drugs

Ondansetron	**5 mg/m2/dose IV/PO q 8-12 hours (max. 8 mg/dose) in HEC1/MEC2** **10 mg/m2 IV/PO stat dose in LEC3**
Granisetron	40 mcg/kg PO q 12 hours (or) 40 mcg/kg IV q 24 hours in HEC/MEC/LEC (max. 3 mg/dose)
Aprepitant	125 mg PO on day1, 80 mg on days 2 & 3, q 24 hours in HEC
Dexamethasone	6 mg/m2/dose IV/PO q 6 hours in HEC, 2 mg (BSA < 0.6) or 4 mg (BSA ≥ 0.6) IV/PO q 12 hours in MEC
Metoclopramide	1-2 mg/kg IV/PO q 8 hours in settings where steroids are not permitted

1: high emetogenic chemotherapy, 2: moderate emetogenic chemotherapy, 3: low emetogenic chemotherapy

Statistical Analysis

The data were collected, categorized and then analyzed by the SPSS 19.0 software. The Chi-Square test was used to determine the relationship between qualitative variables. T-test was used to investigate the relationship between quantitative variables when the data distribution was normal, and a non-parametric test was used when the data were not normally distributed. In all calculations, the significance level was considered at $P \leq 0.05$.

Ethical Consideration

This study was approved by the ethical committee of Mashhad University of Medical Sciences (IR.MUMS.fm.REC.1394.115).

Results

Demographic Information

In this study, 82 patients hospitalized in the Hematology Department of Dr. Sheikh Children's Hospital were enrolled, of whom 48 patients (58.7%) were boys and 34 (41.3%) were girls. The mean age of patients was 6.24±4.47 years (6 months to 16 years). The disease with the highest frequency was acute lymphoblastic leukemia (ALL) with 39 (47.6%) cases, and the least frequent disease was histiocytosis with only one case (1.2%) (**Table III**). Of the 82 patients undergoing chemotherapy, clinical guideline for the prevention of vomiting was used for 45 patients (55%), and no protocol was used for the other 37 patients (45%). Of the 45 patients treated according to the protocol, 17 (37.8%) were girls and 28 (62.2%) were boys. In the non-protocol group, 17 (45.9%) patients were girls and 20 (54.1%) were boys.

Treatment Outcomes

During the 101 chemotherapy cycles of patients in the protocol group, high-risk drugs were used in 50 cases (49.5%), and drugs with moderate, low, and minimal risk were used in 17 cases (16.8%). However, during the 76 chemotherapy cycles of patients in the non-protocol group, high-risk drugs were used in 20 (26.3%) cases, moderate-risk drugs in 19 (25%) cases, low-risk drugs in 17 (22.4%) cases, and minimal-risk drugs in 20 (26.3%) cases. In the non-protocol group, 68 cases (89.5%) experienced grade 1 vomiting severity with less than once a day incidence, and 8 cases (7%) were categorized in grades 2 and 3, with 4 cases in each grade. In the protocol group, however, the severity of vomiting was grade 1 in 96 cases (95%), and in 5 cases (5%) was grade 2 with the vomiting rate of 2 to 3 times a day. Treatment plan followed protocol No. 1 in 23 (22.8%) cases, No. 3 in 36 (35.6%) cases, No. 5 in 10 (9.9%) cases, No. 7 in 18 (17.8%) cases, and protocol No. 8 in 14 (13.9%) cases. In the non-protocol group, no medication was

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used in 7 cases (18.9%); Kytril was used in 28 (75.7%) cases, and Ondansetron was administered for 2 (5.4%) cases, to control vomiting and nausea.

The results of statistical analysis showed that in the protocol group, there was a significant relationship between the severity of vomiting and the type of protocol used (P = 0.01); also, the relationship between the type of drug used for chemotherapy and the severity of vomiting was significant (P = 0.05). In the non-protocol group, the results showed that there was a significant relationship between vomiting rate and the age of the patient (P = 0.05), indicating that the vomiting rate increases with the patient's age. Moreover, there was a significant relationship between the severity of vomiting and the medication used to prevent CINV (P = 0.01).

The comparison of the results showed that in the protocol group, the rate of vomiting was less than once a day in all 50 cases treated with high-risk drugs, and also in the other 17 cases treated with moderate and minimal-risk drugs. In the patients treated with low-risk drugs, the rate of vomiting was less than once a day in 12 (70%) cases, while 5 cases (30%) experienced vomiting 2 to 3 times per day (**Table IV**). The results of the Chi-Square and Fisher's Exact tests showed that there was a significant relationship between the use of clinical guidelines according to the type of chemotherapy drug to prevent vomiting, and the rate of vomiting (P < 0.005), indicating that the clinical protocol was effective for the prevention of CINV.

Table III: Frequency of diseases among the study population

No	Disease	Protocol		Non-protocol	
		Frequency	Percentage	Frequency	Percentage
1	Lymphoma	2	4.4	2	5.4
2	Retinoblastoma	3	6.7	-	-
3	Osteosarcoma	6	13.3	-	-
4	AML	4	8.9	4	10.8
5	ALL	16	35.6	23	62.2
6	Neuroblastoma	4	8.9	3	8.1
7	Germ cell tumor	1	2.2	-	-
8	Ewing Sarcoma	3	6.7	4	10.8
9	Wilms tumor	2	4.4	1	2.7
10	Hepatoblastoma	3	6.7	-	-
11	Histiocytosis	1	2.2	-	-
AML: Acute myeloid leukemia, ALL: Acute lymphoblastic leukemia.					

Table IV: The rate of vomiting according to the type of chemotherapy drugs in protocol and non-protocol groups

Groups	Type of chemotherapy drugs	Rate of vomiting			Total	P-value
		Grade 1	Grade 2	Grade 3		
Protocol group	High risk	50	0	0	50	0.005
	Moderate risk	17	0	0	17	
	Low risk	12	5	0	17	
	Minimal risk	17	0	0	17	
Non-protocol group	High risk	17	1	2	20	0.439
	Moderate risk	16	1	2	19	
	Low risk	17	0	0	17	
	Minimal risk	18	2	0	20	
P-value (comparing 2 groups)	< 0.005					

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Discussion

Nausea and vomiting are among the most important side-effects of chemotherapy in children with malignancy, which severely affect the quality of life in these children (2, 5). Besides, it is very difficult to treat CINV even with the best available antiemetic therapeutic strategies. Therefore, using a clinical guideline for the management of CINV would improve the quality of life in these patients (9). Clinical data indicated that using a guideline to control CINV can significantly reduce the rate of vomiting compared to other common CINV controlling methods (8). The present study, investigating 177 chemotherapy cycles in 82 children (101 in the protocol group and 76 in the non-protocol group), indicated that there is a significant relationship between the use of therapeutic protocols and the rate of vomiting ($P < 0.005$). In the high-risk drugs group, following the protocol, 50 chemotherapy treatments were performed, all of which resulted in the vomiting rate of less than once a day. In the non-protocol group, 20 cases were treated with high-risk drugs. The vomiting rate was less than once a day in 17 cases, 2-3 times a day in 1 case, and 3-5 times in 2 cases. These findings indicated that using a protocol for the management of CINV can significantly reduce the rate of vomiting in these patients. In the protocol used for high-risk groups, several treatment methods were employed according to the patient's age and the type of chemotherapy drug. If the patient was over 12 years of age, and the chemotherapy drugs were not contraindicated for the use of dexamethasone (Dexa) and did not interfere with aprepitant (App), a combination of 5-hydroxytryptamine receptors antagonist (5HT3 RA) + App + Dexa is used (2, 5, 16, 18, 19). In a study, 32 children aged 32 months to 18 years old, undergoing 146 chemotherapy cycles, were tested for high- and moderate-risk drugs. It was found that a combination of dexamethasone, 5HT3 RA, and aprepitant reduced vomiting rate, although further studies are still required to confirm the efficiency of aprepitant in children (10). Consistent with these findings, the results of a randomized double-blind study in 2003 on 12 children with malignancy aged 12 to 18 years old, treated with high emetogenic drugs, showed that treatment with aprepitant in combination with ondansetron and dexamethasone resulted in 60% and 100% of nausea control respectively (1, 11). The combination of 5HT3 RA and dexamethasone can be used if the child is under 12 years old or the chemotherapy drug used interferes with aprepitant. White and colleagues in a randomized controlled trial of 428 children receiving high-risk or moderate-risk medication showed that the oral or intravenous administration of dexamethasone and ondansetron can control CINV in 70% to 73% of children (20). For low-risk drugs, 5HT3 RA alone was used in this study. This was in agreement with findings of a meta-analysis that showed 5HT3 RA is more effective and less dangerous than metoclopramide, phenothiazines and cannabinoids and has fewer side effects (1). It has been suggested that chemotherapy agents that can cross the blood-brain barrier (BBB) directly affect the center of vomiting and cause nausea and vomiting, but the drugs that do not cross the BBB may stimulate the serotonin (5HT) and dopamine receptors in the chemoreceptor trigger zone (CTZ) center by their metabolites (21). Chemotherapy drugs also induce the release of serotonin by destroying enterochromaffin cells in the gastrointestinal system, and serotonin stimulates the vagus nerve, and subsequently CTZ and leads to vomiting (22). Therefore, based on clinical results, the combination of 5HT3 RA and corticosteroids is the mainstay of prevention of acute vomiting in CINV in children treated with high- and moderate-emetogenic medications (2). In recent years, the use of 5HT3 RA, including palonosetron, ondansetron, and granisetron, as an antiemetic has been recommended to control vomiting because

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the clinical findings showed that the rate of vomiting decreased by 15.6% using these drugs (23, 24). In 2013, Dupius et al. developed a guideline, based on the patient's age and the type of chemotherapy drug, used to control the rate of vomiting in children undergoing chemotherapy and reported that following the guideline can reduce the vomiting rate by 78% in patients (3). According to the results of the present study, unlike the non-protocol group (P = 0.439), in the protocol group, there was a significant relationship between the type of chemotherapy drug used and the severity of vomiting (P < 0.005). Therefore, the results of this study confirmed the superiority of the clinical guideline compared to common treatments for the management of CINV. The present study is particularly important as it is the first research conducted in Iran that investigates the effects of applying a standard protocol for controlling CINV in children. The result of the study demonstrated the advantages of Aprepitant capsules, and other hybrid/combinational treatments, for controlling CINV in children. Among the limitations of this study was the relatively small number of patients in some subgroups undergoing protocol treatment. Moreover, in this study, no method for measuring nausea data was devised; and it was not possible to administer all the recommended medications in the CINV treatment protocol.

Conclusion

Chemotherapy-induced nausea and vomiting is an important adverse effect of chemotherapy agents that negatively affects daily activities and the quality of life, especially in children. Clinical guidelines and the classical arbitrary treatments are the two main approaches for the management of CINV. The results of the current study, in consistency with other findings showed that using clinical CINV guidelines—the POGO guideline in this case—which took into account the patient's age and the type of chemotherapy, was more effective than arbitrary management of CINV, particularly in children.

Conflict of interest

The authors declare no conflict of interest.

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