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Original Article

Randomized Double Blind Trial to Compare the Efficacy of Granisetron And Ondansetron in Controlling Emesis in Children with Acute Lymphoblastic Leukemia

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Abstract

Introduction: *Nausea and vomiting are the most important side effects of cytotoxic chemotherapy and it is reported by the patients who receive chemotherapy for malignancies. Ondansetron and granisetron(5 HT3 receptor antagonists) are effective compounds with relatively less toxicity to prevent nausea and vomiting induced by high and moderate emitogenic chemotherapy.*

Objective: *This study was carried out to evaluate the efficacy of granisetron and ondansetron preventing chemotherapy induced nausea and vomiting (CINV).*

Methods: *In this randomized double blind trial 60 children (4-11 years) with acute lymphoblastic leukemia (ALL) who received high dose methotrexate (HDMTX-2.5gm/$m^{2)}$. Each patients received either ondansetron 4 mg or granisetron 1mg (n=30) orally half an hour before HDMTX. Nausea and vomiting were assessed based on ''modified Morrow Assessment of Nausea and Emesis'' (MANE) scale for application to the children.*

Results: *Complete response of granisetron significantly differed from ondansetron from day 2-4 (delayed emesis) (p=0.028).Complete response to acute CINV were 90% in granisetron and 70% in ondansetron treated children (p=0.053), which was not statistically significant. No Child of granisetron group required additional dose but 16.7% children of ondanseton group required additional dose on the first day (p=0.05). Episodes of nausea found in ondansetron treated children 36.7% and in granisetron group 3.3% on day four (p=0.001). Maximum episodes of vomiting found in ondansetron treated children 33.3% and minimum episodes in granisetron group 3.3% on day 2 (p=0.003). In few cases adverse effects (headache, constipation, abdominal pain, loose motion and decreased appetite) were observed in both group of patients (p=0.999). Only in 3.3% cases anticipatory nausea and vomiting had observed.*

Conclusion: *In conclusion, single dose oral granisetron (1mg) is superior to oral ondansetron (4mg) preventing chemotherapy induced emesis in children with ALL receiving HDMTX therapy.*

Key words: *Granisetron, Control emesis, Ondansetron, Chemotherapy.*

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Introduction

Nausea and vomiting is one of the major adverse effects of cytotoxic drugs and it is most frequently reported by the patients those who are undergoing chemotherapy for hematological and oncological malignancies like, ALL, Hodgkin's lymphoma (HL) and Non-Hodgkin's lymphomas (NHL)[1].Without appropriate and effective prophylactic measurement severe nausea and protracted vomiting may results in severe dehydration, electrolyte abnormalities, malnutrition

and aspiration of food materials leading to aspiration pneumonia and increased frequency of hospital admission. So, a very effective, well tolerated and potent antiemetic drug is mandatory for those patients who are receiving intensive chemotherapeutic agents[2].

Nausea is the subjective feeling of unpleasantness that may signal an imminent vomiting of the patients following receiving of chemotherapeutic agents[3]. Chemotherapy related nausea and vomiting (CRNV) may be: a) acute onset-developing within 24 hours, b) anticipatory nausea and vomiting: occurring before getting chemotherapeutic agents and d) delayed onset:- vomiting developed from the second day to sixth day of chemotherapy. The prevention of acute CRNV decreases the risk of development of delayed and anticipatory emesis[4].The incidence and severities of CRNV are affected by the individual specific factors of patient and the specific factors related to treatment. The most important indicator of these factors is the intrinsic emetogenicity of the chemotherapeutic agents[5]. Based on the emitogenicity; chemotherapeutic agents are classified as high emitogenic, moderate emitogenic and low emitogenic[3].

Granisetron and ondansetron are selective antagonists of 5-hydroxytryptamine type 3 (5-HT_3) receptors. Granisetron is well tolerated and demonstrates substantial efficacy for the treatment of emesis in patients receiving cytotoxic drugs[6]. It is more potent and has longer acting antiemetic properties than ondansetron when used in connection with chemotherapy[7]. Intravenous granisetron is more expensive than other antiemetics used for this purpose, such as droperidol and metoclopramide[8]. An oral granisetron preparation is now available that is less expensive than the IV preparation but still effective in reducing emesis induced by cancer chemotherapy is now available[9].

During the last two decades several drugs like-metochlorpropamide, levosulpride, steroids, phenothiazine and other compounds were randomly used to combat CRNV without any satisfactory results[1].Moreover, the compounds had moderate efficacy and significant adverse effects, such as sedation and extra pyramidal symptoms[4]. Since mid-1980s a major advancement had found in the development of antiemetic drugs[4]. The 5-HT3 receptors antagonist (granisetron and ondansetron) represents a significant advancement in the control of acute onset nausea and vomiting due to high emetogenic chemotherapy[10]. 5-HT_3 receptors antagonists are regarded as the “Gold standard” in antiemetic therapy when a patient is schedule for chemotherapy. It is also the first line of treatment for moderate and high emetogenic chemotherapy and radiotherapy regimens in adult children[4]. 5-HT_3 receptors antagonist (granisetron and ondansetron) are considered as very effective and potent against moderate and high emetogenic chemotherapeutic agents[11].

The mode of action of serotonin receptor antagonists is by blocking the serotonin stimulation of vagal afferent receptors in the gut and it may also act centrally via inhibition of serotonin receptors in the chemoreceptor trigger zone[12]. Individual 5-HT_3 receptor antagonist exhibits a remarkable pharmacologic difference in their selectivity, dose response and their half life[4].

Granisetron and ondansetron exhibits high binding affinities for their 5-HT_3 receptor. Granisetron is specific for the receptor whereas, ondansetron has a weak affinity for 5-HT_{1B}, 5-HT_{1c}, á$_1$-adrenagic and µ-opid receptors[4]. The chemotherapy of patients with high or moderate emetogenic potential should receive a 5-HT_3 antagonist to prevent acute emesis[13].

Various data from extensive clinical trial and follow-up showed that granisetron is a very effective and well tolerated agent for the prevention of nausea and vomiting in the oncology patiens[14]. There were only a few studies carried out in children addressing the prevention of chemotherapy related nausea and emesis and they had reported that despite all other improvement in treating CRNV, no standard pediatric antiemetic drug had yet been established[15].

Inadequately controlled emesis impair the functional activity and quality of life of patients, increases the requirement of health care support and may compromises the compliance of treatment. New observation of pathophysiology of CRNV, has better understanding of the risk factors for these effects. The availability of new antiemetic agent has contributed to a marked improvement in the control of emesis[16]. The well control of delayed emesis decreases hospital stay and ancillary expenditure of the patients receiving chemotherapy.Several international studies have indicated that granisetron and ondansetron are equally effective to control CRNV. However there are variations the efficacy and potency depending upon their individual variation in their metabolism [17].

Nausea and vomiting were assessed based on ''modified Morrow Assessment of Nausea and Emesis'' (MANE) scale for application to the children. Initially the MANE scale was used to assess emesis in the adult patents. Later on, the MANE scale was changed and named as "modified MANE scale" applicable for the children to assess nausea and emesis on six points following 24 hours of chemotherapy[15].

However, till date there is no such published report regarding the comparative efficacy of oral granisetron and ondansetron in the prevention of CRNV in the children with acute lymphoblastic leukemia receiving HDMTX therapy in Bangladesh. So, the study was conducted to evaluate the efficacy and tolerance of oral granisetron and ondansetron in the prevention of CRNV in children with ALL who were scheduled for HDMTX therapy.

Materials and Methods

This prospective, randomized, double-blind study was carried out in the Department of Pediatric Hematology and Oncology, BSMMU, Shahbag, Dhaka, Bangladesh from January 2010 to December 2010 on sixty (60) diagnosed children with ALL of both sexes, age ranged from 4-11 years, who were scheduled to receive HDMTX (2.5gm/m^2) therapy and not exposed to receive any antiemetic drug 24 hours before the beginning of chemotherapy. Following taking written consent from the parents and permission from ethical committee the patients were stratified into an ondansetron (30) and granisetron (30) group based on the random sampling. Drugs (antiemetis) were then supplied to the patients following randomization with appropriate code (1-60).The patients and investigators were unaware of the drugs (antiemetic) which was supplied to the patients. Each of the samples (oral granisetron 1mg tablet and oral ondansetron 4mg tablet) was crushed and stored in an eppendorph with randomized code. Additional three samples of the same drug (antiemetic) with same code were prepared and reserved to supply if required for subsequent nausea and vomiting. Acute emesis was considered when vomiting occurred within the first 24 hours of chemotherapy and delayed emesis when it occurred from second to fourth day of therapy. Complete response was considered when there was no CRNV and no administration of additional antiemetics from day one today four of therapy. Partial response was considered when there was CRNV and required administration of additional antiemetics. The patients were followed up from first to fifth day of therapy. Each patient was evaluated every 24 hours of chemotherapy for nausea, vomiting, dry heaving or any adverse effects of antiemetic which was supplied to the patient to control of nausea and emesis. Antiemetic effect were assessed by modified MANE scale (nausea=1, dry heaving=2, vomiting=3).

Following proper counseling to the parents complete blood count (CBC), serum alanine transferase (ALT), serum creatinine and the base line assessment of nausea, dry heaving and vomiting were evaluated in every patient who had met the inclusion and exclusion criteria. The antiemetic (study drug) was given to the patients to take orally dissolved in 50 ml of drinking water one hour before chemotherapy. Additional (antiemetic) drug was given to the patient for moderate nausea (Interference with normal daily life) and/ or vomiting each two episodes within 24 hours of receiving therapy. It was planned to withdraw the patient from study if the paitient would vomit five times and/ or had severe nausea. Then, the patients were evaluated through physical and laboratory investigations. Following 24 hours of chemotherapy, blood sample was collected for CBC and it was estimated by automated hematology analyzer (Sysmex XS-800i) and checked it manually. Serum ALT and serum creatinine were estimated by biochemistry analyzer (RA-50).The response of the study sample were recorded using modified MANE scale- Complete response: 0, Partial response: 1-10, minimal response: 11-20, absence of response: >20.The potency of antiemetic drug was evaluated against acute and delayed emesis.

Collected raw data were organized into a statistical format and appropriate analyses were done using the statistical package for social science (SPSS), version 12.0. All continuous data were expressed as mean± SD and the categorical data of the test in percentage (%). The Chi square (â2) test was used to express the sex distribution, the response of antiemetic drugs following 24 hours of chemotherapy. The Fisher's exact test were done to measure the probability of relationship of patients for additional dose of antiemetic when required, effect of drugs on CRNV and the adverse effect of antiemetic drug between two groups. Paired't' test was done to compare serum ALT and serum creatinine within the group before and after 24 hours of chemotherapy. Unpaired't' test was done to compare the final score of nausea and vomiting every 24 hours in between two groups. Frequency of patients

considered when there was CRNV and required

24 hours in between two groups. Frequency of patients

with anticipatory nausea and vomiting were calculated in percentage. P value of less than 0.05 and confidence interval 95% were taken as the minimum level of statistically significant value.

Results

Baseline characteristics of 60 patients in our observation showed Male: Female=1.4:1. Mean ± SD of age in ondansetron (6.03±1.90) and in granisetron (5.76±2.16) years. Bodysurface area mean±SD of children in ondansetron group (0.78 ± 0.16) and granisetron group (0.76 ± 0.15) The different values showed no significant difference between two studied groups in relation to age, sex and body surface area. Table I.

Table I

Demographic distribution of patients

Parameters	Ondansetron (n=30)	Granisetron (n=30)	P value
Age(year)			
4-5	14(46.7)#	15(50.0)	
5-8	12(40.0)	11(36.7)	0.603**
8-11	4(13.3)	4(13.3)	
Mean±SD	6.03±1.90	5.76±2.16	
Sex			
Male	18(60.0)	17(56.7)	
Female	12(40.0)	13(43.3)	0.793*
Male : Female	1.5:1	1.31:1	

*Chi-square test was done to measure the level of significance
** Unpaired "t" test was done to measure the level of significance
# Figure within parenthesis indicated in column

To control acute emesis, the ondansetron group had 70% complete response and 30% partial response on the first day of chemotherapy but it was 90% and 10% in the granisetron treated patients respectively (p=0.053). Regarding the control of delayed emesis ondansetron group had 43.4% had complete response 50% had partial response,3.3% had minimal and 3.3% had absence of response. It was 80% had complete and 20% had partial respose in granisetron group of patients (p<0.05) (Table II).

Score for nausea and vomiting in ondansetron group 1.73±3.00 and in granisetron 0.23± 0.73 on the first day therapy and on the second day it was 3.07± 5.13 in ondansetron and (0.27±1.14) in granisetron group. Statistically it was significant between two group of patients (p<0.05) (Table III).

Among 60 children, 3.3% had anticipatory nausea and 3.3% anticipatory nausea and subsequent vomiting during the whole period of study (Figure I).

Adverse events were observed in both groups of patients. Although number of patients with headache was more in onadansetron group, no significant differences regarding headache, constipation, abdominal pain, loose motion, and decreased appetite were observed. Visual disturbance and sleep disorder were not found in any patient in both groups.

Table II

Antiemetic efficacy of ondansetron and granisetron based on response criteria (modified MANE scale)

Time	Response	Ondansetron (n=30)	Granisetron (n=30)	P value*
	Acute emesis			
Day-1	Complete response	21(70.0)#	27(90.0)	0.053
	Partial response	09(30.0)	03(10.0)	
Delayed emesis				
Control of delayed	Complete response	13(43.4)	24(80.0)	
emesis(D_{2-4})	Partial response	15(50.0)	06(20.0)	
	Minimal response	01(3.3)	00(0.0)	0.028
	Absence response	01(3.3)	00(0.0)	

* Chi-square test was done to measure the level of significance

Figure within the parenthesis indicated in column percentage

Table III

Assessment of antiemetic efficacy of ondansetron and granisetron in different days following chemotherapy (modified MANE scale)

Emesis	Days	Score (Mean ± SD) Ondansetron (n=30)	Granisetron (n=30)	P value*
Acute emesis	Day 1	1.73 ± 3.00	0.23 ± 0.73	0.012
Delayed emesis	Day 2	3.07 ± 5.13	0.27 ± 1.14	0.006
	Day-3	2.31 ± 3.64	0.57 ± 1.61	0.023
	Day 4	1.07 ± 2.17	0.07 ± 0.37	0.020

*Unpaired't' test was done to measure the level of significance

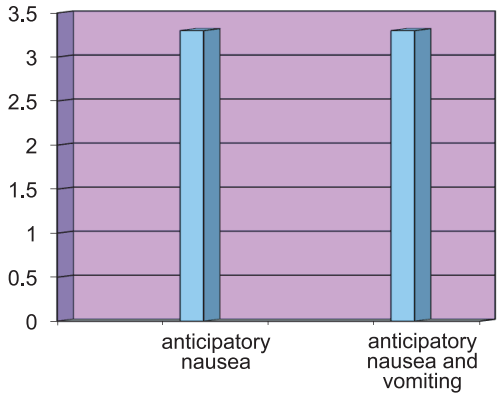

Fig.-1: *Distribution of patients based on anticipatory nausea and subsequent vomiting*

Table-IV

Adverseeffeects observed among

Adverse effects	Group A (n=30)	Group B (n=30)	P value
Headache	5 (16.7)	3 (10.0)	0.70
Consstipation	5 (16.7)	4 (13.3)	0.99
Abdominal Pain	2 (6.7)	2 (6.7)	0.99
Loose motion	2 (6.7)	1 (3.3)	0.99
Decreased appetite	3 (10.0)	1 (3.3)	0.99
Visual disturbance	0 (0.0)	0 (0.0)	
Sleep disorder	0 (0.0)	0 (0.0)	

Fisher Exact test was done to measure the level of significance

Figure within parenthesis indicated in column percentage

Discussion

Availability of new 5-HT_3 receptor antagonists, ondansetron had reduced the incidence and severity of CRNV in patients with cancer[18]. The different retrospective analysis of data reported in the medical literature suggests a difference of 20% between the two antiemetic drugs in favor of granisetron group of patients with cancer[18], our observations had also matched with their observation in controlling of emesis.

The pharmacokinetics and comparative clinical studies have supported the use of granisetron 3 mg/day as the standard antiemetic therapy for the patients with cancer[19]. Our observations are also consistent with their findings. A different randomized study on ondansetron in patients treated with high emetogenic chemotherapy had supported the superiority of higher doses of ondansetron over lower dose[20]. But our observation do not match with their findings, where it was found in our study that single oral dose of granisetron (1mg) is superior to oral ondansetron (4mg) in the prevention of CRNV in children with ALL receiving HDMTX therapy.

Chemical structure of all 5-HT_3 antagonists are similar, the individual 5-HT_3 receptor antagonists exhibit a notable pharmacologic difference in their selectivity, potency, dose response profile and their half life that affect their activity as antiemetic agents in certain individuals. Ondansetron has the affinities for receptors other than the targeted 5-HT_3 but granisetron do not possess the affinity for other receptors[4].

Two different studies conducted by Poon et al. in 1998 and Luis et al., 2006, observed the response to nausea and vomiting had achieved 70% in the patient who had received granisetron and the value was statistically significant[21,15]. Our observational findings are also consistent with their study.

A separate observation had showed by Gebbia et al.in 2000, that a complete protection from acute emesis was 69% in children treated with oral ondansetron and 67% in those treated with oral granisetron for moderate emetogenic chemotherapy. But in case of delayed emesis the antiemetic protection had achieved 43.3% in children receiving ondansetron and on the contrary, 80% in children treated with granisetron who had achieved complete response and their observation was very much statistically significant[1].Our observation had also matched with the study done by Friedman et al., where they had showed that at 48 hours of treatment, granisetron group of children had achieved

a significant emetic control of about 82.2% and at 72 hours it was about 90% [22].

A separate study was done by Perez et al., where they compared the single oral dose of granisetron versus IV ondansetron to prevent CRNV by moderate emetogenic chemotherapeutic agents and they observed no significant emetogenic control during 24 hours of chemotherapy[23],which are against our observations, where it was found that ondansetron group of children achieved 60% complete response at 48 hours, on the other hand, granisetron group had achieved 93.3% complete response following chemotherapy and the findings were statistically significant.

Spector et al. had compared the efficacy and safety of oral ondansetron versus IV granisetron as a single dose before high emetogenic chemotherapy and their observation was 58% complete response achieved with ondansetron treated children and 51% in granisetron treated children. Confident interval (CI) was 95% and their subjective assessment had revealed no difference. The investigators had concluded that single 24 mg oral ondansetron is safe and effective compared to single IV infusion of 10ìgm/kg of granisetron in the prevention of nausea vomiting in high emetogenic chemotherapy[11], which is in contrast to study done by Perez[23]. But our findings had proved that granisetron is more effective than ondansetron in the prevention of both acute (90% vs 70%) and delayed onset (80% vs 43.4%) nausea and emesis. Our observation is consistent with the findings of Stewart et al., where they had showed that granisetron was more effective in the prevention of both acute and delayed onset nausea and emesis following a very high emetogenic chemotherapy[24].

When the patients are treated with same drug there is an extensive individual variation in human drug metabolism that leads to a number of various outcome. This is mainly due to genetic polymorphism along with induction or inhibition of enzyme involved in the drug metabolism leading to increased or decreased enzymatic activity[25].

Regarding the additional dose requirement of antiemetic drugs on the first day, ondansetron treated children had required 16.7% and granisetron group required nothing and the findings were significant. On the second day, ondansetron group required 30% and granisetron group required only 3.3%, which was also very significant. Our observations were consistent with the findings of other observers.

In a separate study, therapeutic failure was found in 27% in ondansetron treated patients[11], but in our study the it was 3.3%. It might be due to the degradation of ondansetron by isoenzyme.

Considering the adverse effect of antiemetic drugs like headache, constipation and abdominal pain were common in both ondansetron and granisetron treated children. But headache and constipation were more common in ondansetron than granisetron treated children. Our findings are consistent with the observations of other investigaors[22, 26].

Conclusion

Though oral onadansetron and granisetron are well tolerated and both are effective in control of acute CINV (HDMTx) but oral granisetron 1 mg is more effective than ondansetron 4 mg to prevent delayed emesis (HDMTx induced) in children with ALL

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