

## The relationship between serum serotonin levels and cytotoxic drugs' adverse effects in cancer patients

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### ABSTRACT

**Background:** nausea and vomiting induced by cytotoxic drugs cause a considerable distress to many cancer patients and may reduce food intake and affect patient's compliance with therapy. It is proposed that cytotoxic drugs evoke serotonin release from enterochromaffin cells in intestinal mucosa and this lead to stimulation of vomiting center in the brain. **Objective:** To investigate relationship between serotonin levels, liver functions and hematological parameters and various adverse effects of cytotoxic drugs especially nausea and vomiting in cancer patients. **Method:** This is an observational study in cancer patients receiving cytotoxic drugs in Basrah Oncology Unit extend up to 72 hours after treatment in which we took patients information by a special questionnaire form and blood samples were collected for the estimation of serum serotonin levels by ELISA method and measurement of other laboratory tests including liver enzymes and hematological parameters. **Results:** A total of 100 cancer patients were included in this study. Nausea occurred in 9%, 31% and 40% patients before, 24 and 72 hours after cytotoxic drugs respectively, while vomiting occurred in 6%, 19% and 50% patients in the same order. The severity and frequency of nausea and vomiting increased significantly at 24 and 72 hours. There was a significant ( $P<0.001$ ) correlation between serum serotonin levels and platelets count before and after treatment. Serum serotonin levels were positively correlated with both lymphomas and colorectal cancer and negatively correlated with leukemias, also serum serotonin levels was positively correlated with the emetogenic potential of cytotoxic drugs. There was no direct relationship between serum serotonin levels and nausea and vomiting. **Conclusions:** Cytotoxic drugs induced nausea and vomiting in a considerable number of cancer patients despite all antiemetic drugs at 24 and 72 hours. The level of serotonin was affected by both cancer type and emetogenic potential of cytotoxic drugs and there was no direct relationship between the changes of serotonin and nausea and vomiting. (MJBU,30,2: 2012, Page 122-131)

العلاقة بين مستوى السيروتونين في مصل الدم والآثار الجانبية للأدوية السامة للخلايا لمرضى السرطان

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الخلاصة: إن الغثيان والتقيء الناتجان عن الأدوية السامة للخلايا يسببان إجهاداً على مرضى السرطان، مما يؤدي الى فقدان الشهية و يسبب في عدم مطاوعة المرضى للعلاج. هناك افتراضية بان الأدوية السامة للخلايا تحفز خلايا (enterochromaffin) الموجودة في الغشاء المعوي على إفراز مادة السيروتونين مما يؤدي الى تحفيز مركز التقيء في الدماغ. الأهداف: لبحث وجود علاقة بين مستوى السيروتونين في مصل الدم مع وظائف الكبد ومعامل الدم والآثار الجانبية لهذه الأدوية خصوصاً الغثيان والتقيء عند هؤلاء المرضى. الطريقة: أنها دراسة متعلقة بمراقبة مرضى السرطان في وحدة الأورام في البصرة قبل وبعد العلاج الكيميائي استمرت لمدة 72 ساعة حيث تم جمع المعلومات عن المرضى عن طريق قائمة خاصة بالدراسة وكذلك اخذ عينات الدم من المرضى لقياس مستوى السيروتونين بطريقة ELISA وأجراء التحاليل المختبرية الأخرى. النتائج: ظهر ان من مجموع 100 مريض في دراستنا ان من يعانون من الغثيان كانوا بنسبة 9%، 31% و 40% قبل وعند 24 و 72 ساعة على التوالي، اما اللذين يعانون من التقيء كانوا بنسبة 6%، 19% و 50% و بنفس الترتيب. ان شدة حصول الغثيان والتقيء ازدادت بوضوح خلال 24 و 72 ساعة. لقد وجدت العلاقة معتدة إحصائياً ( $P < 0.01$ ) بين مستوى السيروتونين وتعداد الصفائح الدموية قبل وبعد العلاج أيضاً هناك علاقة ايجابية بين مستوى السيروتونين مع سرطان الغدد اللمفاوية وسرطان القولون. بينما كانت هذه العلاقة سلبية مع سرطان ابيضاض الدم. بالإضافة الى ذلك كانت هناك علاقة ايجابية بين مستوى السيروتونين مع قدرة الأدوية السامة للخلايا على تحفيز التقيء عند مرضى السرطان. الاستنتاج: إن الأدوية السامة للخلايا تسبب الغثيان والتقيء عند عدد لا بأس به من مرضى السرطان على الرغم من إعطائهم للأدوية المختلفة المضادة للتقيء خلال 24 و 72 ساعة بعد العلاج. وظهر إن مستوى السيروتونين يتأثر بنوع السرطان وكذلك قدرة الأدوية على تحفيز التقيء عند المرضى. لم تظهر علاقة مباشرة بين تغير مستوى السيروتونين وظهور الأعراض الجانبية للأدوية السامة للخلايا كالغثيان والتقيء.

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## INTRODUCTION

Chemotherapy-induced nausea and vomiting are significant side effects of cancer therapy for many years and are two of the greatest fear of patients with cancer.<sup>[1]</sup> Chemotherapy-induced nausea and vomiting can be classified as acute within 24 hrs, delayed 24 hours or more after chemotherapy which may last up to several days, and anticipatory before chemotherapy.<sup>[2,3]</sup> The susceptibility to nausea and vomiting increased in the young, female and those with a history of motion or morning sickness.<sup>[2,4]</sup> The risk of developing chemotherapy-induced nausea and vomiting was highly related to having the reaction in the previous treatment cycle<sup>[5]</sup> and the emetogenic potential of the drugs.<sup>[6]</sup> The distressing symptoms of nausea and vomiting have a considerable impact on all aspects of patient's quality of life, as well as those of their families and caregivers. The distress resulting from these symptoms can escalate over time<sup>[7]</sup> and can potentially lead to a patient's refusal to continue with the most effective antitumor therapy.<sup>[8,9]</sup> Unrelieved nausea and vomiting can result in physical complications, such as poor nutrition, aspiration pneumonia, dehydration, fluid and electrolyte imbalance, and mucosal tears.<sup>[10]</sup> Approximately 90 percent of the human body's total serotonin is located in the enterochromaffin cells (EC) in the gut, where it is used to regulate intestinal movements. The remainder is synthesized in serotonergic neurons in the CNS where it has various functions, including the regulation of mood, appetite, sleep, muscle contraction, and some cognitive functions including memory and learning.<sup>[11]</sup> The mechanism of cytotoxic drugs induced nausea and vomiting is not clear. However it was proposed that cytotoxic drugs induced free radicals generation leading to the release of 5-hydroxytryptamine (5-HT) from EC which acts on vagal afferent terminals in the wall of the bowel leading to stimulation of the chemoreceptor trigger zone (CTZ) or acting

directly on the vomiting center (VC) in the brain stem and eventually induces a vomiting reflex.<sup>[12]</sup> It was observed that strongly emetogenic regimens induce greater increases in serotonin release than moderately emetogenic regimens.<sup>[13]</sup> The aim of our study is to investigate the serotonin related adverse effects of cytotoxic drugs in cancer patients such as gastrointestinal tract, appetite and sleep pattern, by using a special questionnaire form and measuring serum serotonin levels, liver function tests and hematological parameters, also to find out any relationship between serotonin levels and various clinical and changes induced by cytotoxic drugs.

## MATERIALS AND METHOD

Adult cancer patients admitted to the Oncology Unit of AL-Sadir Teaching Hospital in Basrah for chemotherapy during the period from September, 2010 to July, 2011 were included in this study. The patients were divided into different groups according to the type of cancer and the type of treatment given. The patients in our study had lymphoma, leukemia, multiple myeloma and colorectal cancer types. All the patients (100) were evaluated before and 24 hours after treatment. Thirty patients were followed up for 72 hours after treatment to detect both early and late adverse effect of cytotoxic drugs. Patients parameters were recorded by a special questionnaire form which include age, gender, type of cancer, treatment given and the cycles of therapy, different cytotoxic drugs given, adjuvant therapies as antiemetics, analgesics, antibiotics, antifungal, antiviral, laxatives or any other treatment given. In addition, various adverse effects and patient's activity were evaluated by special scales as follow:<sup>[14]</sup>

- i. Nausea: was evaluated according to severity by three points verbal numerical scale as mild (1), moderate (2) and severe (3)

- ii. **Vomiting:** the incidence and frequency of vomiting occurrence per day
- iii. **Frequency of bowel motion per day**
- iv. **Sleep quality:** was recorded by three points verbal numerical scale as normal (1), bad (2) and no sleep (3)
- v. **Loss of appetite:** was assayed by four points verbal numerical scale as normal (1), reduced (2), bad (3) and very bad (4)
- vi. Patient's activity was measured by Eastern Cooperative Oncology Group (ECOG) grade as fully active (0), restricted in physically strenuous activity but ambulatory (1), ambulatory and capable of all self care but unable to carry out any work activities (2), capable of only limited self care (3) and completely disabled (4).<sup>[15]</sup>
- vii. **Other adverse effects:** any other adverse effects or symptoms were also reported by patients like dizziness, headache, diarrhea, itching, bleeding, fever and edema.

Five milliliters blood samples were collected from each patients for measurement of serum serotonin by ELISA method,<sup>[16]</sup> liver enzymes (alanine aminotransferase ALT and aspartate aminotransferase AST)<sup>[17]</sup> and WBC and platelets count by autohematology analyzer (BC-5300, China).

**Statistical analysis**

Analysis was carried out by using SPSS computer package version 15. Data were analyzed by Wilcoxon Signed Ranks test, *t*-test and *chi-square* test and linear regression analysis for correlation of different parameters. Ethical approval was obtained from the ethical committee of the college of Medicine University Basrah.

**RESULTS**

**characteristic of patients**

One hundred patients (53% males and 47% females) were included in the present study. Their mean ages was 41.94 ± 18.7 years, their

clinical diagnosis was presented in (Table-1). The cases included patients with hemopoietic tumors and gastro- intestinal tract tumors with majority of cases having leukemias (40%).

**Table 1. Characteristics of cancer patients.**

Characteristics of patients	No. of patients
Male	53
Female	47
Mean ages (years)	41.94 ± 18.7
<b>Type of cancer</b>	
Non Hodgkin's Lymphoma (NHL)	29
Colorectal Cancer (CRC)	18
Acute Lymphoblastic Leukemia (ALL)	15
Acute Myeloblastic leukemia (AML)	14
Hodgkin's Lymphoma (HL)	9
Chronic Lymphocytic Leukemia (CLL)	9
Multiple myeloma (MM)	4
Chronic Myelocytic leukemia (CML)	2
<b>Total</b>	<b>100</b>

**Clinical adverse effects**

**Nausea**

Out of the 100 patients that were observed before treatment seven patients (7%) had mild nausea and two patients (2%) had moderate nausea before treatment (Table-2). At 24 hours following cytotoxic drugs treatment there was a significant increased in the incidence and severity of nausea (P<0.001). Thirty one patients (31%) complained from nausea, which was mild in 18 patients (18%), moderate in 8 patients (8%) and severe in 5 patients (5%). At 72 hours 12 out of 30 patients (40%) complained from nausea, which was significant from base value (p<0.01), of those 4 patients (13.3%) had mild, 4 patients (13.3%) had moderate and 4 patients (13.3%) had severe nausea.

**Vomiting**

Six patients (6%) had vomiting before starting treatment and of those 1 patient had vomiting

once/day, 1 patient had vomiting twice/day and 4 patients had vomiting three times/day (Table-2). At 24 hours there was a significant increase ( $p < 0.05$ ) to 19 patients (19%) in the total number of patients complaining of vomiting. The vomiting occurred once daily in 5 patients (5%), twice daily in 8 patients (8%), three times daily in 4 patients (4%) and four times daily in 2 patients (2%). At 72 hours 15 out of 30 patients (50%) had increased in vomiting incidence and severity which was a significant ( $P < 0.05$ ) The vomiting occurred once daily in 2 patients (6.7%), twice daily in 3 patients (10%), three times daily in 8 patients (26.7%) and four times daily in 2 patients (6.7%).

**Bowel motion**

The frequency of bowel motion was normal in 87 patients (87%) before treatment as reported by patients. There was reduction in frequency of

bowel motion in 13 patients (13%), that occurred once daily in 2 patients (2%), once every other day in 5 patients (5%) and once every 3 days in 6 patients (6%). No significant changes occurred at 24 hours. At 72 hours 13 out of 30 patients (43.3%) had reduction in frequency of bowel motion which was also statistically significant.

**Loss of appetite**

Loss of appetite occurs in about 30% of patients before and after treatment and there was no statistically significant changes.

**Quality of sleep**

Before treatment 20 patients (20%) already had disturbed sleep pattern and at 24 hours after treatment also disturbance in sleep pattern occurred in 21 patients (21%). At 72 hours 8 out of 30 patients (26.7%) had disturbed in sleep pattern and there was statistically significant.

**Table 2. Nausea and vomiting incidence severity score for 100 cancer patients.**

Nausea severity	Number of patients		
	Before treatment n=100	24 hrs after treatment n=100	72hrs after treatment n=30
No nausea	91 (91%)	69 (69%)	18 (60%)
Total no. of patients with nausea	9 (9%)	31 (31%)	12 (40%)
Mild	7 (7%)	18 (18%)	4 (13.3%)
Moderate	2 (2%)	8 (8%)	4 (13.3%)
Severe	0 (0%)	5 (5%)	4 (13.3%)
Vomiting incidence and frequency	Before treatment n=100	24 hrs after treatment n=100	72hrs after treatment n=30
No vomiting	94 (94%)	81 (81%)	15 (50%)
Total no. of patients with vomiting	6 (6%)	19 (19%)	15 (50%)
Once/day	1 (1%)	5 (5%)	2 (6.7%)
Twice/day	1 (1%)	8 (8%)	3 (10%)
Three times/day	4 (4%)	4 (4%)	8 (26.7%)
Four times/day	0 (0%)	2 (2%)	2 (6.7%)

**Activity limitation grade**

Before treatment 58 patients (58%) had normal activity grade and 42 patients (42%) had various decrease of restriction of motor activity (Table-3). At 24 hours following treatment the number of fully active patients were reduced to 40 patients (40%) and those with restriction of

activity increased to 60 patients (60%) this difference was highly statistically significant from base line value (P<0.001). At 72 hours after treatment 19 out of 30 patients (63.3%) had restricted activity which was statistically significant from base line value (P< 0.001).

**Table 3. Activity limitation grade (ECOG) for 100 cancer patients.**

Activity limitation grade	Number of patients		
	Before treatment n=100	24 hrs after treatment n=100	72hrs after treatment n=30
Fully active	58 (58%)	40 (40%)	11 (36.7%)
Restriction of activity	34 (34%)	31 (31%)	9 (30%)
Ambulatory but unable to carry out any work	7 (7%)	25 (25%)	7 (23.3%)
Capable of only limited self care	1 (1%)	4 (4%)	3 (10%)
Completely disabled	0 (0%)	0 (0%)	0 (0%)

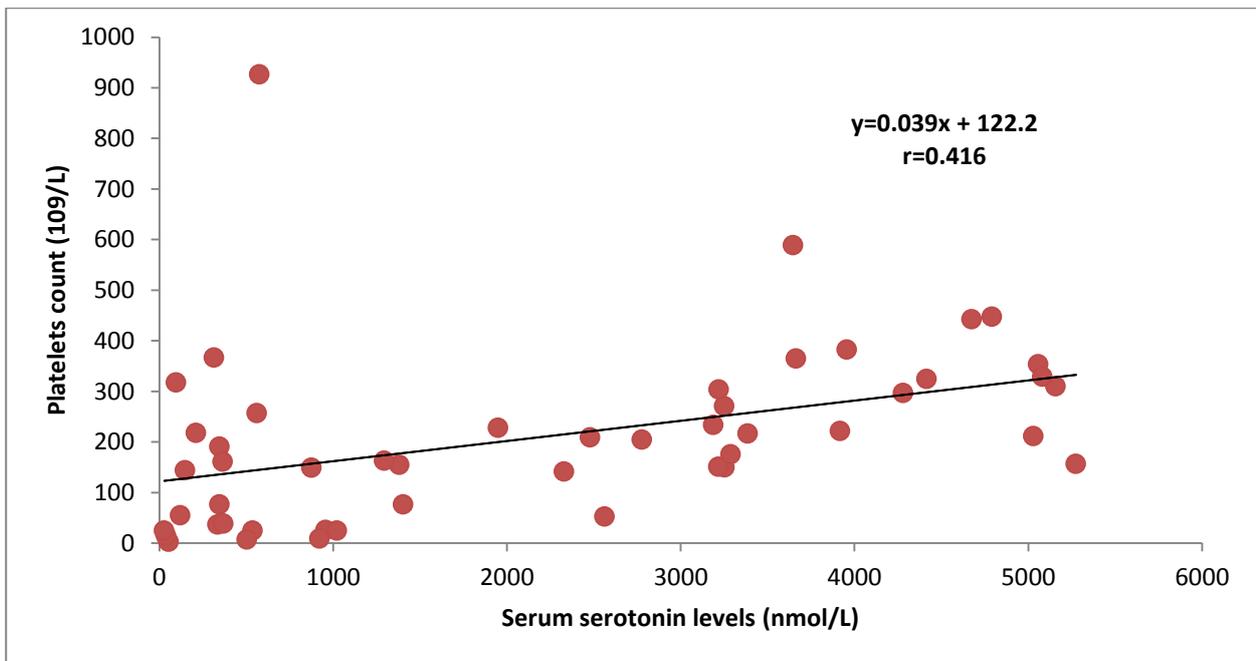
**Serum serotonin levels and other laboratory parameters**

There were a significant increased in serum serotonin levels in 30 patients at 24 hours (p< 0.05) following treatment from 960.8 to 1336.4 nmol/L, on other hand serotonin levels significantly decreased in 25 patients at 24 hours (p< 0.05) following treatment from 2882 to 1948 nmol/L. The liver aminotransferase enzymes (ALT, AST) showed that there was no difference between before and after treatment. The normal range for ALT (7-56 IU/L) and AST (5-40 IU/L). The total WBC count tend to decrease at both 24 and 72 hours following treatment but this reduction was not statistically significant. On the other hand the platelets count

was slightly decreased at 24 hours while slightly increased at 72 hours. The normal range for WBC count ( $4.3 \times 10^9$  to  $10.8 \times 10^9$  /L) and platelets count ( $150 \times 10^9$  /L - $400 \times 10^9$  /L).

**Correlation between serum serotonin levels with various laboratory parameters**

Among the different laboratory parameters there was a statistically significant correlation between serum serotonin levels and platelets count which occurred both before and 24 hours after treatment (Figure-1). Also the AST levels were significantly correlated with serum serotonin levels at 72 hours after treatment only. The WBC count and ALT levels were not significantly correlated with serum serotonin levels.



**Fig 1. Correlation between serum serotonin levels and platelets count (24 hrs after treatment)**

\*t= 0.417, p<0.01, n=49 (significant)

**The relationship between serum serotonin levels and clinical diagnosis (before and after treatment)**

The serum serotonin levels tend to increase significantly (P<0.001) among patients with lymphomas from 9 out of 29 patients (31%) to 20 out of 29 patients (69%) and also colorectal cancer from 0 out of 9 patients (0%) to 9 out of

9 patients (100%). In leukemias on other hand patients with high serum serotonin levels decreased significantly (p< 0.001) from 11 out of 17 patients(64.7%) to 6 out of 17 patients (35.3%) (Table-4).

**Table 4. Relation of serum serotonin levels to the clinical diagnosis and cytotoxic emetogenic effect.**

Diagnosis (No. of patients)	Serum serotonin levels (nmol/l)*		Chi-square tests
	<1000 No. of patients (%)	>1000 No. of patients (%)	
Lymphomas (29)	9 (31%)	20 (69%)	Significant P< 0.001
Leukemias (17)	11 (64.7%)	6 (35.3%)	Significant P< 0.001
Colorectal cancer (9)	0 (0%)	9 (100%)	Significant P<0.001
Total number of patients	20	35	
Emetogenic potential of cytotoxic drugs	<1000 no. of patients(%)	>1000 no. of patients(%)	Chi-Square tests
Mild and moderate	16 (72.7%)	12 (36.4%)	Significant P< 0.01
Severe	6 (27.3%)	21 (63.6%)	Significant P< 0.01
Total number of patients	22	33	

\* The reported range for normal serotonin levels from (284-1135 nmol/L)

### **The relationship between serum serotonin levels and the emetogenic potential of cytotoxic drugs and different treatment sequence**

In patients taking cytotoxic drugs with mild or moderate emetogenic potential, the serum serotonin levels was < 1000 nmol/L in 16 out of 22 patients (72.7%) and > 1000 nmol/L in 12 out of 33 patients (36.4%). While patients taking cytotoxic drugs with high emetogenic potential, the serum serotonin levels was < 1000 nmol/L in 6 out of 22 patients (27.3%) and > 1000nmol/L in 21 out of 33 patients (63.6%). The difference between the two groups were statistically significant ( $p<0.01$ ) (Table-4). There was no significant difference between serum serotonin levels at various of sequence cytotoxic drug treatment.

### **The relationship between serum serotonin levels with various clinical parameters**

Patients were divided into two groups according to the change in serum serotonin levels following treatment with cytotoxic drugs treatment (Table-5). In 30 patients (21 males and 9 females) serum serotonin levels increased following treatment as compared to base line

value and in 25 patients (12 males and 13 females) serum serotonin levels decreased following treatment from base line value. There were more male than female in the increased serotonin levels group, while the ratio was nearly equal in the decreased serotonin levels group. The nausea score significantly increased from 3.3% to 30% in increased serotonin group (Wilcoxon Signed Ranks test,  $P<0.05$ ) and from 12% to 40% in decreased serotonin group. The total incidence and frequency of vomiting had increased from 0% to 13.3% and 4% to 16% in both groups, but these was not statistically significant. The total delayed in frequency of bowel motion changed from 16.7% to 20% and from 12% to 20% in both groups, but these was not statistically significant. The loss of appetite was not different in the two studied groups as well as the sleep score. There was a significant activity limitation as measured by ECOG grade in both groups ( $P<0.01$ ) from 40% to 46.7% in the increased serotonin levels group and 44% to 64% in the decreased serotonin levels group.

**Table 5. Comparison between clinical parameters in patients with increased and decreased in serum serotonin levels from the base line value.**

Serum serotonin levels	Male	Female	Measurements	Nausea score and incidence		Vomiting frequency and incidence		Total delay in bowel motion/day		Loss of appetite score		Reduce of sleep score		Activity limitation by ecog grade	
				Before treatment	After treatment (24 hrs)	Before treatment	After treatment (24 hrs)	Before treatment	After treatment (24 hrs)	Before treatment	After treatment (24 hrs)	Before treatment	After treatment (24 hrs)	Before treatment	After treatment
increased serum serotonin levels group (n= 30)	21 70%	9 30%	Number of patients	1	9*	0	4	5	6	10	11	9	7	12	14**
			Percentage	3.3%	30%	0%	13.3%	16.7%	20%	33.3%	36.7%	30%	23.3%	40%	46.7%
decreased serum serotonin levels group (n= 25)	12 48%	13 52%	Number of patients	3	10*	1	4	3	5	5	9	5	5	11	16**
			Percentage	12%	40%	4%	16%	12%	20%	20%	36%	20%	20%	44%	64%

\*  $P < 0.05$  (Wilcoxon Signed Ranks test, significant from base line)

\*\* $P < 0.01$  (Wilcoxon Signed Ranks test, significant from base line)

## DISCUSSION

The incidence and severity of nausea and vomiting in the present study increased at both 24 hours and 72 hours following treatment with cytotoxic drugs. This is an expected effect which is supported by different studies.<sup>[18,19]</sup> Before treatment nausea occurred in 9% and vomiting in 6% in our cancer patients and these percents agreed with other studies,<sup>[18]</sup> they can be attributed to different causes as secondary bowel obstruction, psychological (anticipatory) response to the admission to the Oncology Unit and the anxiety precipitated by previous cycle of chemotherapy.<sup>[20,21]</sup> Thirty one percent of our patients developed acute nausea and 19% acute vomiting, and 40% developed delayed nausea and 50% delayed vomiting and these percent comparable with other studies.<sup>[22]</sup> Vomiting that occurred in the first 24 hours is the acute reaction to the cytotoxic drugs while during 72 hours it is considered as delay reaction.<sup>[3,12]</sup> The nausea and vomiting occurred in our patients despite various antiemetic drugs given before cytotoxic drugs administration and afterword. This is in agreement with other studies which showed that antiemetic drugs were not fully effective in preventing nausea and vomiting in all patients.<sup>[20]</sup> Many factors could be contributed to the incomplete response to the antiemetics, as the genetic variations in serotonin receptors which make patients resistant to serotonin modifying antiemetics.<sup>[23,24]</sup> The involvement of other type of mediators in vomiting as substance P which binds to neurokinin1 receptors in the gut and selectively blocked by the newly discovered antiemetic Aprepitaint (neurokinin receptor blocker).<sup>[20,25]</sup> Patients in our study complained of various reduction in frequency of bowel motion which was increased in incidence at 24 and 72 hours, this effect could be due to the direct effect of cytotoxic and adjuvant drugs on gastrointestinal tract,<sup>[26]</sup> which was greatest at 72 hours, or could be due to reduction in food intake as a result of nausea and vomiting that

occurred in those patients. The loss of appetite occurred in a considerable number of patients even before the administration of cytotoxic drugs, there was increased at both observation periods following drug administration, with a trend of increasing severity. The loss of appetite could be due to the cancer itself <sup>[27]</sup> which is further aggravated by the cytotoxic drugs.<sup>[28,29]</sup> Chemotherapy may interfere with appetite secondary to nausea and vomiting,<sup>[10]</sup> in addition to psychological state may reduce food intake.<sup>[30]</sup> Changes in serotonin levels might be another factor causing loss of appetite.<sup>[31]</sup> About quarter of the patients in our study rated their sleep as abnormal even before cytotoxic drug treatment with little deterioration during hospital admission.<sup>[32]</sup> Cytotoxic drugs can affect sleep quality, in addition to the presence of pain, other adjuvant drugs used and the associated psychological impact and depression which may disrupt the sleeping patterns of cancer patients.<sup>[33,34]</sup> The ECOG is a measure of the patient activity and it is useful in the evaluation of activity limitation in cancer patients.<sup>[15]</sup> Patients in our study already had activity limitation before treatment which was increased to a significant level after treatment. This could be due to the effect of cytotoxic drugs (type-and dose-dependent), acute reduction of hemoglobin level, appetite loss, pain, insomnia, depression, anxiety, diarrhea, adjuvant drugs (as opioids and steroids) and/or to the disease itself.<sup>[35-37]</sup> The wide variability in levels of serotonin in our patients could be attributed to many factors; the type of diet,<sup>[38]</sup> as it is suggested that eating a diet rich in carbohydrates and low in protein can increase serotonin,<sup>[39]</sup> The platelets count which was variable in our patients as the majority of them had hemopoietic cancer that directly affect platelets count, which can further be affected by cytotoxic drugs.<sup>[40]</sup> The presence of tumor of gastrointestinal tract specially colorectal cancer which can directly affect serotonin storing

enterochromaffin cells.<sup>[41]</sup> Other factors that may affect serotonin levels are the psychological state of the patients, the administration of other drugs like antiemetics, antipsychotics, anxiolytics and analgesics and gender of patients.<sup>[42,43]</sup> The cytotoxic drugs are known to cause hepatotoxicity by direct hepatocellular injury, inflammation and/or cholestasis.<sup>[44]</sup> The failure to detect such adverse effect in our study is probably due to early sampling time. In our study the majority of patients with lymphomas and colorectal cancer had high serum serotonin levels before the administration of cytotoxic drugs, while patients with leukemias had significantly low serum serotonin levels. This could be explained as the colorectal cancer can increase the secretion of serotonin from enterochromaffin cells by raising the intraluminal pressure and secondary to the mechanical obstruction,<sup>[41]</sup> while in lymphomas the cause of higher serotonin levels need further investigation. In leukemias we found in our study a reverse effect in which the majority of patients had lower serum serotonin levels which could be due to suppression of platelet in the leukemic patients.<sup>[45]</sup> The emetogenic potential of cytotoxic drugs significantly affected the serotonin levels as we found higher levels in patients receiving highly emetogenic drugs as compared to those taken mild and moderate emetogenic drugs. This is agreement with other studies.<sup>[23]</sup> The total nausea score significantly increased following cytotoxic drugs treatment and this increase was not directly correlated with change in serum serotonin levels. In our study we found no significant correlation between the two parameters which could be explained by various factors that directly affect serotonin levels and complicated the relation. There are some limitations in present study which include control of patients diet, The selection of identical patient groups as regarded to age, gender, type of cancer and treatment regimen. It was also unethical to withhold any adjuvant drugs given to the patients during study period and this might have many effects

on our results. In conclusion cytotoxic drugs induced nausea and vomiting in a considerable number of patients despite all antiemetic drugs given, which occurs significantly at both 24 and 72 hours after treatment. No direct relationship was found between serotonin levels and nausea and vomiting scores. We recommended future studies to select larger number, homogenous group of cancer patients as regarded to type of cancer, type of cytotoxic drugs and uniform adjuvant therapy.

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