The combination of hydration and antiemetics in controlling chemotherapy induced delayed nausea and vomiting

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Abstract

Background and objectives. Delayed emesis during chemotherapy is a significant problem, especially with drugs like cisplatin, which is often poorly controlled with conventional anti-emetics. There is a relative paucity of data on the control of delayed emesis and rather inconsistent results have been reported. The present study is to check the efficacy of hydration in reducing the incidence and severity of chemotherapy induced nausea and vomiting. This study also compares the efficacy and tolerability of tropisetrone versus metoclopramide in a permissive environment of good hydration. *Methods*. The in-patients since June 2005, who received cisplatin 75 mg/m^2 to 100 mg/m^2 intravenously (*i.v.*) over two consecutive daily single dose in Grade 4 to 5 emetogenic potential regimens were observed in the study. A total number of 35 patients receiving 54 cycles of cisplatin based chemotherapy were observed for 5 days from the beginning of chemotherapy cycle for the first two cycles. In the test group, for 20 cycles, tropisetrone (a 5-HT3 blocker) was used and for another 20 cycles metoclopramide was used as antiemetic for delayed emesis in presence of good hydration. In the control group, 14 cycles were studied using tropisetrone (7 cycles) and metoclopramide (7 cycles) for controlling delayed emesis in presence of restricted hydration. *Results.* The control of nausea was significantly greater in the hydration group as compared to the control group ($P < 0.01$). 11 of the 20 patients receivd tropisetrone had nausea (55%) and 6 patients in the same group developed vomiting (30%). In the metoclopramide group consisting 20 patients, 9 patients suffered from nausea (45%) and 4 had vomiting (20%). The difference was statistically insignificant. *Conclusion.* Hydrating the patient with the use of metoclopramide is a cheap method with good efficacy to control the delayed phase of nausea and vomiting in patients undergoing emetogenic chemotherapy. The use of 5-HT3 blockers in the control of delayed nausea and vomiting is not better than using metoclopramide and it also enhances the cost of the therapy.[Life Science Journal. 2007; 4(2): 46 – 49] (ISSN: 1097 – 8135).

Keywords: delayed nausea and vomiting; hydration; cisplatin

1 Introduction

Nausea and vomiting are two of the greatest fears of patients with cancer[1]. If these are not controlled adequately it may precipitate a number of medical complications like dehydration, electrolyte imbalances or cause physical damages like Mallory Weiss tears in esophagus. The complications may be severe enough to prolong the stay in the hospital, increasing the burden on medical resources and having considerable cost implications for the patient. These symptoms may be so distressing for the patients that it may lead to refusal of the effective chemotherapy.

The chemotherapy induced nausea and vomiting (CINV) is classified as – acute, delayed and anticipatory. Acute nausea is defined as nausea occurring within 24 hours of the therapy. Delayed nausea and vomiting is defined as the one occurring after 24 hours of therapy, which may last for variable period as per chemotherapy. Delayed emesis has also been reported as early as 16 hours after the chemotherapy. Anticipatory emesis can occur before, during or after the beginning of chemotherapy. It occurs commonly if the emesis control in previous cycle was inadequate.

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Various therapies have been proposed for the control of the above disorders. The cause of acute emesis is the release of serotonin from the GI tract which acts on the chemotherapy trigger zone (CTZ) to induce nausea and vomiting[2]. This has been well established and therefore the therapy (the use of 5-HT3 blockers with dexamethason) is well defined for it. Since the patho-physiology of delayed emesis is still unclear, a number of regimen protocols have been proposed for its control, but which is the best is unknown.

This study focuses on control of delayed nausea and vomiting, which commonly occurs after the administration of cisplatin, carboplatin, cyclophosphamide, doxorubicin[3]. Since cisplatin has already been proved that it induces delayed nausea and vomiting substantially, we use cisplatin as the drug for our study[4].

As hydration is already proven to improve the outcome in post operative nausea and vomiting[5], here, we study about the effectiveness of hydration in association of the antiemetic drugs to control delayed nausea and vomiting. We also compare the efficacy of metoclopramide and tropisetrone in controlling delayed CINV.

2 Materials and Methods

2.1 Patients

From June 2005, consecutive adult patients scheduled to use moderate to high cisplatin based chemotherapy were enrolled in the study. The cisplatin was administered in a dose of 75 mg/sqm to 100 mg/sqm alone or in combination in two divided doses on the first day and the second day.

The criteria for exclusion were the presence of nausea and vomiting or the use of antiemetics during the preceding 24 hours of the chemotherapy, a concurrent treatment with dexamethasone, severe concurrent illnesses leading to emesis, or radiotherapy. Also the patients were excluded with Karnofsky Performance Score (KPS) below 60, pregnant women and patients unwilling or unable to comply.

35 patients who received 54 cycles of cisplatin based chemotherapy were observed for a period 5 days from the beginning of chemotherapy cycle for the first two cycles.

The patients varied from 37 years old to 79 years old with median age 56 years. There were 7 females and 28 male patients in the study.

2.2 Design of therapy

A comparative study with a randomized design was conducted, at the oncology department of the First Affiliated Hospital of Zhengzhou University (Zhengzhou, Henan, China).

The patients receiving cisplatin 75 mg/m^2 – 100 mg/m^2 were divided into two groups, test group and control group. In the test group, daily hydration of more than 3,000 ml on the first day and the second day with cisplatin and more than 2,000 ml from the third day to the fifth day was maintained. The control group was given fluids equivalent to 2,000 – 2,500 ml on the first day and the second day and then limited to 2,000 ml or less from the third day to the fifth day comprising of I/V fluids < 500 ml per day.

In both groups, patients were given both schedule I antiemetic therapy (tropisetrone for delayed vomiting) and schedule II antiemetic therapy (metoclopramide for delayed vomiting).

Schedule I, 5-HT3 antagonist Tropisterone 5 mg intravenously was administered daily for a period of 5 days, given 30 minutes before the chemotherapy of cisplatin on the first day and the second day. Schedule II, 5-HT3 antagonist granisterone 3 mg was given only 30 minutes before the administration of cisplatin on the first day and the second day. And on rest of the days metoclopramide (20 mg qid) was administered.

In both groups, dexamethasone with 5-HT3 blocker was used to prevent acute CINV but not delayed CINV. Dexamethasone was used to control breakthrough nausea or vomiting of grade 3 or higher severity. A total number of 14 cycles were observed for the control (limited intake of fluids). 20 cycles of schedule I and 20 cycles of schedule II in presence of hydration were observed.

2.3 Clinical assessment

Episodes of nausea and vomiting were recorded for the first 24 hours (acute) and from the second day to the fifth day for the delayed effects.

An episode of vomiting was defined as single instance of vomiting, single instance of retching, continuous vomiting or continuous retching. A vomiting episode was considered to have ended when retching or vomiting had ceased for at least one minute. Complete protection was defined as the absence of vomiting episodes, major protection as episodes of grade one or grade two (CINV) and failure of treatment as episodes of grade three or more. Complete or major protection was considered to indicate successful treatment.

Nausea and vomiting was graded according to the NCI grading for gastrointestinal toxicities[6] (Table 1). A patient who had breakthrough vomiting or nausea equivalent of grade 3 or more was administered metocloperamide (during schedule I) or 5-HT3 blocker (during schedule II or dexamethasone for control. These patients were considered failure cases.

Table 1. Criteria for grading severity of nausea and vomiting

	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated < 24 hours	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or TPN indicated ≥ 24 hours	Life-threatening consequences	Death
Vomiting	1 episode in 24 hours	2 – 5 episodes in 24 hours; IV fluids indicated < 24 hours	≥ 6 episodes in 24 hours; IV fluids, or TPN indicated ≥ 24 hours	Life-threatening consequences	Death

Adapted from Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS

2.4 Statistical analysis

Analysis of nausea and vomiting were performed separately by using Chi square test.

3 Results

Results were summarized in Table 2. Of the 20 patients receiving tropisetrone, 11 patients (55%) suffered from nausea. Only one case reported a grade 3 nausea and the rest cases were grade 1 or 2. The vomiting of grade 1 or 2 severities was observed in 5 patients and there was 1 failure case because of grade 3 vomiting (30%).

As compared to tropisetrone group only 9 patients had nausea (45%) of grade 1 or 2 and 4 patients had vomiting (20%) in the metoclopramide group. There was no grade 3 nausea or vomiting.

In the control group for hydration we observed 14 patients of which 13 patients (93%) developed nausea and 8 patients (57%) developed vomiting. Grade 3 or more nausea was observed in 8 patients and grade 3 or more vomiting in 2 patients.

The use of hydration positively affected nausea ($P < 0.01$). The patients who were supported with better hydration were having significantly less nausea and there was only 1/40 case of grade 3 nausea as compared to control group having 8/14 cases of grade 3 nausea.

The control of vomiting was better in the patients who had been supported with higher fluid intake, though it was not analytically significant. There was no significant difference between the use of metoclopramide or tropisetrone in controlling nausea or vomiting ($P > 0.05$).

Table 2. The incidence of nausea and vomiting in test group and control group

	n	Nausea				Vomiting				*P*	
Grade		0	1	2	3	0	1	2	3	T *vs.* M	Test *vs.* Control
Test group	40	20	13	6	1	40	4	5	1		
Tropisetrone	20	9	6	4	1	14	2	3	1		Nausea: $P < 0.05$
Metoclopramide	20	11	7	2	0	4	2	2	0	$P > 0.05$	
Control group	14	1	3	1	9	6	-	6	2		
Tropisetrone	7	1	1	-	5	2	-	4	1		Vomiting: $P > 0.05$
Metoclopramide	7	-	2	1	4	4	-	2	1		

T = tropisetrone, M = metoclopramide

4 Discussion

Prevention of nausea and vomiting induced by cytotoxic agents is critical in the management of the patient with cancer. The control of acute emesis using a 5-HT3 inhibitor alone or with dexamethasone has given gratifying results clinically[7].

At present this is the only phase of vomiting where the guidelines for control are very clear, as the pathophysiological cause of acute emesis has been well emphasized. But as the nausea and vomiting enter the delayed phase a number of drugs are advised, which may be from classical antiemetic group or the newer 5-HT3 antagonists. Both these have been studied and most authors are of conclusion that neither of them is superior to the other and either can be used in combination with dexamethasone for the prevention of delayed nausea and vomiting [7,8,9].

All the drugs used in management mainly act to sup-

press the vomiting and secondarily control the nausea. Therefore, vomiting is not as distressing presently as nausea is turning out to be. The pathophysiology of nausea does not follow exactly the pathophysiology of vomiting, e.g. anti-diuretic hormone (ADH) has a role in pathogenesis of nausea[10].

This study emphasizes on the role of hydration, from the beginning of chemotherapy to the perceived period for delayed emesis, in controlling the CINV. Anti-emetic regimen for the control of delayed emesis has a better prevention when it is compared to that of a poorly hydrated patient. Hydration has been proved to be effective in prevention of emesis in post operative nausea and vomiting (PONV)[5].

In this study we see that a good hydration is helpful in controlling the nausea and it is a cheap and viable addition to the armature of a clinical oncologist in controlling CINV. Although metoclopramide seems to be a little more effective than tropisetrone, there is no significant difference on the efficacy between the two drugs. The good control of acute nausea and emesis is important as it is emphasized by one failure case in which the patient had nausea since the first day and vomited by the second day. In this study since the cisplatin was used on day one and two this patient seems to have a combination of delayed and acute emesis. It has already been proved that the most important factor in controlling delayed nausea and vomiting is the control of acute emetic effects of the chemotherapy[11]. In all other patients, the control had been satisfied.

The side effects for 5-HT3 blocker tropisetrone were not severe, with only one patient headache and 6 patients constipation. In the group of patients taking metoclopramide, somnolence was the most common side effect. It was observed in 8 out of the 20 patients receiving this drug. Although, we did not observe any extra-pyramidal system toxicity, it is one of the main side effects for metoclopramide and many of the drugs from this classical group acting on dopaminergic pathways. This side effect is more common in young people below 30 years of age, so we have to be careful of administration in this age group of patients.

The age group of cancer is relatively older and with the high incidence of diabetes mellitus around the globe it is easy to find significant number of cancer patients suffering from diabetes, undergoing highly emetogenic chemotherapy. Addition of dexamethasone during the period of chemotherapy makes the control of this metabolic disorder a little more difficult. Similarly, a number of patients may be having gastritis and dexamethasone may enhance the suffering. These all and other similar effects may enhance the hospital stay and cost of the patients.

The onset of nausea is usually associated with decreased oral intake. At this time supervised uptake of oral fluids can easily help in preventing and reducing the severity of CINV.

5 Conclusion

Hydrating the patient with the use of metoclopramide is a cheap method with good efficacy to control the delayed phase of nausea and vomiting in patients undergoing emetogenic chemotherapy.

The use of 5-HT3 blockers in the control of delayed nausea and vomiting is not better than using metoclopramide and it also enhances the cost of the therapy. The use of newer 5-HT3 blocker increases the cost of the therapy and fails to enhance any significant control of CINV.

The use of hydration therapy may circumvent the side effects of dexamethasone and it can be used to prevent CINV. Also, it is an economical treatment.

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