

Effect of Lorazepam in Reducing Psychological Distress and Anticipatory Nausea and Vomiting in Patients Undergoing Chemotherapy

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Abstract

Objectives: To evaluate the efficacy and safety of lorazepam in reducing psychological distress and chemotherapy-induced nausea and vomiting. **Methodology:** It was a prospective interventional study with seventy patients for a period of 1 year. In which, patients' anxiety, distress and status of nausea, and vomiting were assessed in the first four chemotherapy cycles before drug intervention. During the subsequent chemotherapy cycles, the outcomes of the intervention were reassessed along with patient's quality of life (QOL). **Results:** Out of seventy patients, 62 showed improvement in their distress level after the drug intervention and patient counseling. Lorazepam along with other antiemetic drugs reduced chemotherapy-induced delayed nausea and vomiting. During the course of the study, 15 patients experienced drowsiness as an adverse reaction to lorazepam. The overall QOL of the population was also improved with lorazepam. **Conclusion:** Lorazepam along with patient counseling can improve patient's psychological distress and thus their QOL. The off-labeled use of lorazepam can be utilized for controlling chemotherapy-induced nausea vomiting.

Keywords: Anticipatory emesis, benzodiazepines, cytotoxic agents

INTRODUCTION

Cancer is a disease which occurs as a result of changes in the group of normal cells that results in uncontrolled growth called as tumor. There is growing recognition that psychosocial care is an important part of the comprehensive care of people diagnosed with cancer.^[1] Many cytotoxic agents used for the treatment of cancer can cause nausea and vomiting. Chemotherapy-induced nausea and vomiting (CINV) is associated with a significant deterioration in the quality of life (QOL) and is perceived by patients as a major adverse effect of the treatment.^[2]

Benzodiazepines such as lorazepam are prescribed for short periods of time to ease symptoms of anxiety or sleeping difficulties caused by anxiety. Lorazepam works by affecting the way some chemicals in the brain (neurotransmitters) pass messages to brain cells – this has a calming effect. We choose lorazepam as our study drug because it has an off-labeled use of reducing CINV.^[3,4] The purpose of the study was to find out how many patients starting chemotherapy have anxiety and psychological problems and to assess whether lorazepam

along with patient counseling by clinical pharmacist given to oncology patients will give a positive outlook toward their treatment and improve their QOL.

Ethics approval

Ethical approval was obtained from Human Research and Ethical Committee, Amrita Institute of Medical Sciences, Kochi, Amrita University, India.

METHODOLOGY

A prospective, interventional study was conducted in the Oncology Department, Amrita Institute of Medical Sciences

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Table 1: Baseline characteristics of the patients

Characteristics	n (%)
Female	64 (91.4)
Dose of T Lorazepam	1 mg OD
ADR developed	15 (21.7)
Age years (range)	
54-66	30 (42.8)
42-54	19 (27.1)
30-42	11 (15.7)
Comorbid condition	
Hypertension	29 (41.4)
Diabetes mellitus	20 (28.6)
Nil	25 (35.7)
Diagnosis of sample population	
Breast cancer	17 (24.3)
Ovarian cancer	11 (15.7)
Lung cancer	9 (12.9)
Rectal cancer	8 (11.4)
Other cancers	25 (35.7)
Reason for anxiety of sample population	
Appearance	42 (60)
Emotional problems	35 (50)
Physical problems	28 (40)
Family problems	20 (28.6)

ADR=Adverse drug reaction, OD=Once daily

Table 2: Pre- and post-comparison of Common Terminology Criteria for Adverse Events 4.0 V grade for nausea

Prenausea		Postnausea			P
Category	Number of patients	Nil, n (%)	Mild, n (%)	Moderate, n (%)	
Nil	17	17 (100)	0	0	0.030
Mild	34	1 (2.9)	33 (97.1)	0	
Moderate	19	0	6 (31.6)	13 (68.4)	

Table 3: Pre- and post-comparison of Common Terminology Criteria for Adverse Events 4.0 V grade for vomiting

Prevomiting		Postvomiting			P
Category	Number of patients	Nil, n (%)	Mild, n (%)	Moderate, n (%)	
Nil	18	18 (100)	0	0	0.012
Mild	34	2 (5.9)	32 (94.1)	0	
Moderate	18	1 (5.6)	8 (44.4)	9 (50.0)	

for 1 year. Study was initiated with 135 new chemotherapy patients, from which seventy patients with psychological distress who satisfied the inclusion criteria (patients >18 years, patients with no previous psychiatric issues, patients newly diagnosed with solid cancers and lymphomas, patients planning to start on chemotherapy, patients with average score >4 of in Distress Thermometer (DT) and >16 in Hamilton Anxiety Assessment Scale (HAMA) scale in distress thermometer (DT)

were enrolled in the study after signing their informed consent and exclusion criteria include patients already on lorazepam, patients contraindicated to benzodiazepines, and patients with brain tumors and leukemias. In the first cycle of chemotherapy, pertinent data regarding the patients were collected by direct interview of the patient or their caregiver. Anxiety level of the patient was measured consecutively in the first second and third cycles using HAM-A questionnaire and also asked them to fill the DT scale. The response to the counseling was also assessed. If the average score is above 4 in DT and above 18 in HAM A scale were referred to the oncologist for drug therapy. At the end of the third cycle, QOL of the patient was also measured using SF-12.

Patients were given lorazepam 1 mg OD from the fourth cycle to the sixth cycle. Using Common Terminology Criteria for Adverse Events (CTCAE) scale, nausea and vomiting of patients were also assessed before and after lorazepam, and additive effect was measured. During the follow-up visit (5th and 6th cycle), all the above parameters were reassessed and compared. Hence in this study, the sample population itself was used as control group and study group, i.e., pre- and post-intervention is compared in the same study population. All the patients received chemotherapy regimen according to their disease condition, and its effect on anxiety was also noticed. The drug-drug interactions were checked using up-to-date- lexicomb drug interaction checker. Adverse drug reactions (ADRs) were assessed using Naranjo ADR probability scale.

Statistical analysis

All analyses were conducted using SPSS version 20 statistical software. To obtain the characteristic of categorical variables, frequency and percentage were applied. To obtain the characteristic of numerical variables, mean and standard deviation were used. Categorical variables were compared using the Chi-square test. To compare pre- and post-categorical variables, McNemar's test and kappa methods were applied.

RESULTS

In this study from table 1, out of seventy patients the majority of the sample population were female 91.4%, and most of the patients were between the age group of 54–66 years. Most of the patients were diagnosed to have breast cancer (24.3%), and hypertension was the major comorbid condition (41.4%). Most of the study population were anxious about their appearance than other emotional problems.

Among the sample population, the mean HAM-A score before drug intervention and patient counseling was 19.54 ± 1.390 and after lorazepam and patient counseling was 17.06 ± 2.239 . The mean DT score before and after drug intervention and patient counseling was 5.94 ± 1.1 and 4.69 ± 1.2 , respectively. This shows that lorazepam and patient counseling significantly reduced patients' psychological distress.

While utilizing the additive effect of lorazepam, from table 2 and 3 we observed that along with other antiemetics,

lorazepam significantly reduced CINV. From the pre- and post-comparison of nausea, out of 34 patients from the mild category, one patient moved to nil, and also out of 19 patients from moderate, six patients moved to mild category.

While considering vomiting, initially 34 patients were in mild category before lorazepam of which two moved to nil category. 8 patients moved to mild from moderate category and 1 patient got complete recovery from vomiting after drug intervention. The results were statistically significant.

Most emetogenic chemotherapeutic agents were found to be platinum compounds. Carboplatin were prescribed to 21 patients of which 15 patients had mild vomiting; followed by cyclophosphamide (15 patients), in which nine patients had mild and one patient had moderate vomiting. Other less emetogenic chemotherapy regimens including adriamycin (14 patients), cisplatin (ten patients), paclitaxel, capecitabine, gemcitabine (nine patients each). Lorazepam along with domperidone caused 94% decrease in nausea and 82% decrease in vomiting, and with ondansetron, 86% and 79% decrease in nausea and vomiting, respectively. For aprepitant, there was 85% decrease in both nausea and vomiting as per Figures 1 and 2.

While analyzing the QOL, as per Figure 3 we found that there was a decrease in patient's physical component status (PCS), i.e., from 43.29 to 42.72, but the mental component status (MCS) shows a significant improvement, i.e., from 33.38 to 43.87.

DISCUSSION

Female patients (64, 91.4%) were more predominant than male patients (6, 8.6%) in this study. It may be due to more common diagnosis of breast cancer and ovarian cancer, also males were reserved to express their anxiety and fears. Most of our study populations were anxious about their appearance (60%), this might be because the majority of our sample population were females, and generally, they were concerned about alopecia and other physical changes occurring due to chemotherapy which makes them reluctant to face the society. Next, we observed emotional problems as a major issue (35 patients, 50%) since the majority of our sample population were women; they tend to express their emotional problems much comfortably than men.^[5]

Out of 70 patients, 62 showed improvement in their distress level after the drug intervention and counseling session which was similar to the results obtained from the study conducted by Bishop *et al.* This shows that lorazepam and patient counseling can significantly reduce patient's psychological distress.^[6]

One of the objectives of the study was to evaluate the additive effect of lorazepam along with other antiemetics in controlling CINV.^[7] For this, nausea and vomiting episodes before and after the administration of lorazepam was evaluated using CTCAE ver. 4.0, and we found out that lorazepam along

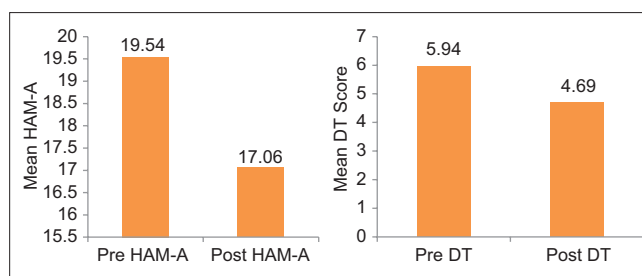


Figure 1: Comparison of HAM-A and DT before and after drug intervention. HAM-A: Hamilton Anxiety, DT: Distress thermometer

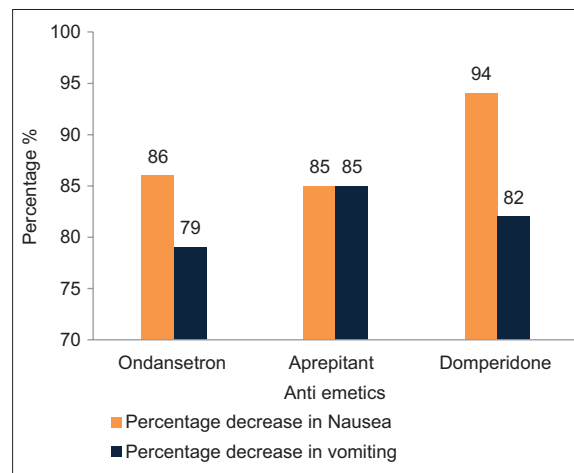


Figure 2: Overall percentage decrease in delayed nausea and vomiting

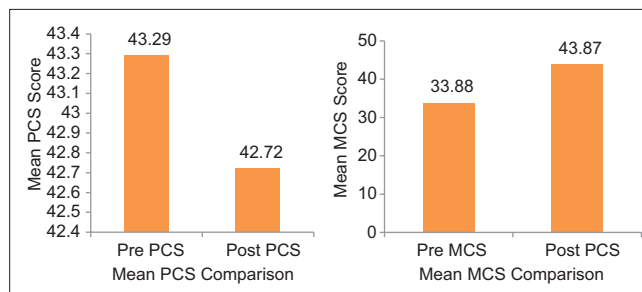


Figure 3: Pre- and post-comparison of PCS and MCS. PCS: Physical component status, MCS: Mental component status

with other antiemetic drugs reduced chemotherapy-induced delayed nausea and vomiting. This was statistically proven using McNemar's test ($P < 0.05$). These results were consistent with the results obtained by Bishop *et al.*^[6]

During the study period, we observed that the patients were mostly prescribed with platinum compounds (carboplatin 30%, cisplatin 14.3%, and oxaliplatin 11.4%) of which carboplatin showed more emetogenicity than other chemotherapy drugs.^[7] The patients in the study were given oral dosage form of lorazepam, as intravenous route was inconvenient for an outpatient and observed a decrease in the nausea and vomiting. However, Maher in a study observed that intravenous route of lorazepam had more effect in controlling vomiting due to chemotherapy.^[8]

While assessing the safety of lorazepam, 15 patients (21.4%) experienced drowsiness as an adverse reaction to lorazepam therapy, which was confirmed with Naranjo ADR probability scale as probable (score 5–8). Roscoe *et al.* also in their study found that lorazepam will cause drowsiness.^[9] Drowsiness was in turn beneficial for those patients who experienced sleeplessness due to anxiety. However, in some patients, this caused a hindrance in their daily activities which leads to noncompliance in drug therapy. Only three patients discontinued drug therapy due to noncompliance; those patients were excluded from the study.

The QOL of the sample population was assessed using SF-12 questionnaire which is a minor version of SF-36 questionnaire (used for large studies). Here, limitations in behavioral performance of everyday physical activity are calculated using PCS, and limitations in social activities from physical or emotional problems are calculated using MCS.^[10] In this study, PCS and MCS were analyzed before and after lorazepam administration. We observed that the mean pre-PCS (43.23 ± 3.48) had no significant difference with the mean post-PCS (42.72 ± 4.97) which was statistically proven with $P > 0.05$. This might be due to the physical ailments as part of their disease and chemotherapy. Whereas significant difference was observed between mean of pre-MCS (33.88 ± 3.77) and mean of post-MCS (43.8700 ± 5.92468). This was statistically proven with $P < 0.05$. Thus, we could observe that the overall QOL of the sample population was improved with lorazepam.

CONCLUSION

Patients diagnosed with cancer may experience psychological problems which may remain unnoticed. Medical expertise like clinical pharmacists can interview patients by using proper questionnaires and may alert the physicians for providing appropriate treatment. Lorazepam along with patient counseling significantly lowers patients' anxiety level. The additive effect of lorazepam in reducing CINV can also be utilized for a better outcome. This may change patients' outlook toward treatment, and their overall QOL will be improved.

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Conflicts of interest

There are no conflicts of interest.

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