Clinical Observation of Comparing the Efficacy of Three-drug Regimens Containing Olanzapine/Dexamethasone in Preventing Hyperemetic Chemotherapy-induced Nausea and Vomiting (CINV)

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Research Article

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Abstract

A randomized, open-label, parallel-controlled study was conducted to compare the efficacy of two kind of three-drug Regimens containing olanzapine/dexamethasone for the prevention of CINV induced by hyperemetic chemotherapy. The results showed that there was no significant difference in the complete response rates of nausea and vomiting between the two groups. However, the anxiety, depression and sleep quality of the patients in the olanzapine group were improved. It was concluded that the three-drug antiemetic regimen of "olanzapine +palonosetron+fosaprepitant" could effectively prevent CINV caused by hyperemetic chemotherapy, and its effect was similar to that of the antiemetic regimen containing dexamethasone. In addition, the anxiety, depression and sleep disorders of patients in the olanzapine group were all improved to different degrees.Our study has provided a theoretical basis for the clinical application of the three-drug regimen of "dexamethasone removal".

Introduction

According to the latest worldwide cancer burden data released by the World Health Organization's International Agency for Research on Cancer (IARC)[1], there were 19.29 million new cancer cases worldwide in 2020, while in China there were 4.57 million new cancer cases in 2020, representing an increase of nearly 300,000 people compared with the latest national cancer report released by China's National Cancer Center in 2018. China is the hardest hit by diabetes and the incidence of cancer in people with type 2 diabetes is more than twice that of the general population[2]. It is well known that the treatment methods for cancer include surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy, while chemotherapy is the main treatment method for advanced cancer. In the treatment process, chemotherapy is one of the indispensable treatments for malignant tumors, and chemotherapy-related nausea and vomiting (CINV) is one of the most common adverse reactions in the anti-tumor treatment process[3], which not only result in decreased quality of life of cancer patients, but also affects the treatment effect[4]. Prevention is much more important than treatment for CINV, the 2018 National Comprehensive Cancer Network (NCCN) guidelines for emesis recommended the use of three different drugs combination regimens to prevent CINV for highly emetic chemotherapy regimens[5], and the 2020 NCCN guidelines recommended the use of the quadruple antiemetic regimen[6] (based on the addition of olanzapine to the traditional triple antiemetic), but no matter which antiemetic regimen contains dexamethasone[7]. Dexamethasone is the main antiemetic drug for the prevention of nausea and vomiting. However, studies have shown that the use of dexamethasone during the prevention of CINV increases the risk rate of diabetes[8]. Studies have shown that about 20% of non-diabetic cancer patients develop steroid-induced diabetes during the use of dexamethasone to prevent CINV[9], which is particularly important for patients receiving high doses of dexamethasone. In addition, for tumor patients with diabetic, the application of dexamethasone will cause stress hyperglycemia, aggravating blood glucose fluctuation and making blood glucose more difficult to control, thus aggravating the disease and even causing serious consequences[10]. Therefore, although dexamethasone is administered as a base in

an antiemetic regimen of medium to high antiemetic risk chemotherapy regimens, its side effects cannot be ignored.

The 2018 edition of NCCN Guidelines recommends the new drug for the prevention and treatment of CINV: olanzapine, which has affinity for multiple receptors and can not only improve schizophrenia and other mental diseases with positive symptoms, but also achieve the curative effect of checking vomiting[5]. Various institutions in China and abroad have reported that in the clinical application studies, the anti-vomiting regimen containing olanzapine significantly improved the prevention of CINV[11], and the prevention rate of nausea and complete remission rate of vomiting in the olanzapine group during the acute phase, the delayed phase and the whole process were significantly increased[12]. NCCN guidelines clearly state that a three-drug regimens containing olanzapine—a 5-HT3 receptor antagonist in combination with dexamethasone and olanzapine, is effective in preventing CINV[5]. In recent years, more and more attention has been paid to the study of physical and mental health of patients with malignant tumor[13]. Some studies on cancer patients in China and abroad have found that this population is usually accompanied by the occurrence of emotional disorders, and the most common emotional disorders are anxiety and depression[14]. As the most common emotional disorder in patients with malignant tumors, it can directly affect the treatment and prognosis, the development of tumors, and the quality of life of patients, thus gradually attracting the attention of medical staff[15]. In summary, whether a scheme can be designed to effectively prevent CINV without affecting the blood glucose level of cancer patients is a current problem to be solved.

Materials And Methods

1.1 clinical data

Our study was scheduled to enroll 80 patients (40 in the experimental group and 40 in the control group) according to random number table. 7 patients were excluded from the study due to noncompliance with clinical trial scale assessment or noncompliance with clinical trial protocol. From April 2020 to November 2021, a total of 73 patients who met the inclusion criteria and completed the clinical trial and completed the follow-up were included in the First Affiliated Hospital of Xinxiang Medical University, including 38 patients in the test group (olanzapine group) and 35 patients in the control group (dexamethasone group). The percentages of male patients were 38%(n=28), female patients were 62%(n=45), stage II cancer patients were 64%(n=47), stage III cancer patients and above were 29%(n=21), 24 patients (33%) received platinum-containing hyperemesis chemotherapy, and 49 patients (67%) received cyclophosphamide /ifosfamide-containing hyperemesis chemotherapy (Supplementary table 1). This study was reviewed by the Ethics Committee of the First Affiliated Hospital of Xinxiang Medical University and has been registered in China Clinical Trial Registration Center (Registration Number : ChiCTR2100042829), all patients signed informed consent forms.

1.2 Research method

1.2.1 Test group

This was a randomized, open-label, parallel-control clinical trial of positive drugs. The random number table was used for simple randomization, and the subjects were randomly assigned to the test group or the control group in a 1: 1 ratio.

1.2.2 Antiemetic regimen and dosing time

(1) On the first day, fosaprepitant for injection and palonosetron hydrochloride injection were given 30 minutes before chemotherapy; Dexamethasone injection 12mg in tablets was administered 30 minutes before chemotherapy (control group), or olanzapine tablets was administered 5mg po 30 minutes before chemotherapy and before bedtime (test group).

(2) On the second day, 8mg of dexamethasone injection (control group) or 5 mg of olanzapine tablets BID po (test group) was administered in the morning.

(3) On the third day, 8mg of dexamethasone injection was given in the morning (control group), or palonosetron hydrochloride injection was given in the morning and olanzapine tablets 5mg bid po was given (test group).

(4) On the fourth day, 8mg of dexamethasone injection (control group) or 5 mg of olanzapine tablets BID po (test group) was given in the morning.

1.3 Observation index

1.3.1 Nausea assessment

Subjects on the 100mm horizontal visual analogue scale (VAS) were self-evaluated for nausea severity, which was assessed within the last 24 hours with the left boundary (0mm) of the scale being "no nausea" and the "most severe nausea" being marked at the right boundary (100mm) of the scale. Subjects will be marked on the scale based on an assessment of the degree of nausea they have experienced in the last 24 hours. No nausea occurred and was defined as Grade 0 without drug rescue; Mild nausea without affecting food intake (VAS < 3mm) was defined as Grade I; Moderate nausea and affecting food intake is defined as Grade II; Frequent nausea and inability to eat were defined as Grade III. Level 0 was considered complete response (CR), while Levels II and III were considered invalid controls.

1.3.2 Blood glucose level test

Blood glucose was measured daily for patients with no previous history of diabetes on d0-d4 and d21 , and at least 4 times a day for patients with previous history of diabetes (including fasting blood glucose and 2-hour blood glucose after three meals). If blood glucose increased during the observation period, ask the patient to test fasting blood glucose every day outside the hospital until the blood glucose returns to normal without the need of hypoglycemic drugs (non-diabetic)/without the need of adjusting hypoglycemic drug intervention (diabetic); During the observation period, if there was any increase in

blood glucose, the fasting blood glucose was measured at least once a week, and the patient was admitted to hospital for treatment next cycle. Evaluation records: During the 21-day follow-up period, the proportions of increased blood glucose and non-increased blood glucose in each group were calculated according to whether the blood glucose was increased or not; The proportion of the treatment intervention group and the treatment non-intervention group in the hyperglycemia group was calculated respectively.

1.5 Statistical methods

Statistical analysis was performed using SPSS 26.0 statistical software. Measurement data were statistically described with mean, median, standard deviation, maximum and minimum values. The count data or grade data are expressed with frequency. All statistical tests were performed using two-sided tests. The test level α=0.05 (one-sided test α=0.025), and the significance of $P \leq 0.05$ indicated that the difference tested was statistically significant.

Result

2.1 Effect of preventing nausea

Analysis of 73 patients nausea showed:

The complete response rate (CR) of nausea in the 35 patients of the control group during the overall observation period was 57% (20/35), and the CR of nausea in the 38 patients of the test group during the overall observation period was 66% (25/38). The CR levels in the acute phase and the delayed phase of the 35 patients in the control group were 86% (30/35) and 74% (26/35). The CR levels in the acute phase and the delayed phase of the 38 patients in the test group were 84% (32/38) and 81% (31/38). There was no significant difference in the complete response rates of nausea between the control group and the test group in the overall observation period, the acute period, and the delayed period (P > 0.05) (Table 1).

Table 1
Comparison of effects of preventing nausea

		Control group	Experimental group	χ^2	*P*
Total observation period	CR(%)	20(57)	25(66)	0.576	0.448
Acute stage	CR(%)	30(86)	32(84)	0.032	0.858
Delay period	CR(%)	26(74)	31(81)	0.566	0.452

2.2 Effect of preventing vomiting

Analysis of 73 subjects vomiting showed:

The complete response rate (CR) of vomiting during the overall observation period in 35 patients of the control group was 91% (32/35), and the CR of vomiting during the overall observation period in 38 patients of the test group was 89% (34/38). The CR of vomiting in the acute phase and in the delayed phase of 35 patients in the control group were 100% (35/35) and 94% (33/35) respectively. The CR of vomiting in the acute phase and in the delayed phase in the total observation of 38 patients in the test group were 95% (36/38) and 92% (35/38) respectively. There was no significant difference in the complete response rates of vomiting between the control group and the test group in the overall observation period, the acute period, and the delayed period ($P > 0.05$) (Table 2).

Table 2
Comparison of effects of preventing voting

		Control group	Test group	χ^2	*P*
Total observation period	CR(%)	32(91)	34(89)	0.080	0.777
Acute stage	CR(%)	35(100)	36(95)	1.894	0.169
Delay period	CR(%)	33(94)	35(92)	0.136	0.713

2.3 Anxiety (SAS) and depression (SDS) scores before and after chemotherapy

The observation results of 35 cases of patients showed that in the control group, the average values of SAS d1 and SAS d4 were 27.71 and 29.17 (Table 3) respectively. When the two pairs of samples were tested, the corresponding p-value was 0.001($P < 0.05$) (Table 4), which indicated that the differences of SAS scores before and after chemotherapy in 35 control subjects were statistically significant. Similarly, SDS scores of 35 subjects in the control group showed significant difference before and after chemotherapy. The SAS and SDS scores of the 38 subjects in the test group before and after chemotherapy showed significant differences ($P < 0.05$) (Table 4).

Table 3
SAS and SDS scores before and after chemotherapy

□□		$\bar{x} \pm S$	σ			$\bar{x} \pm S$	σ
Control group	SAS d0	27.71 ± 5.05	0.853	Experimental group	SAS d0	31.26 ± 6.17	1.000
	SAS d4	29.17 ± 5.45	0.920		SAS d4	29.45 ± 5.69	0.923
Control group	SAS d0	29.86 ± 7.86	1.328	Experimental group	SAS d0	34.45 ± 10.61	1.720
	SAS d4	31.29 ± 8.45	1.428		SAS d4	33.18 ± 10.09	1.637

Table 4
Comparison of SAS and SDS scores before and after chemotherapy

	□□	$\bar{x} \pm S$	σ	95%CI	t	P
Control group	SAS d0-d4	-1.457 ± 2.318	0.392	(-2.253 -0.661)	-3.719	0.001
	SDS d0-d4	-1.428 ± 3.247	0.549	(-2.544 0.313)	-2.602	0.014
Test group	SAS d0-d4	1.816 ± 2.204	0.358	(1.091 2.540)	5.079	0.001
	SDS d0-d4	1.263 ± 1.968	0.319	(0.616 1.910)	3.956	0.001

2.4 Comparison of sleep quality before and aft chemotherapy

The results of sleep observation in 73 cases of patients showed that 49% (17/35) of the patients in the control group were at risk for sleep disorders and 66% (25/38) of the patients in the test group were at risk for sleep disorders. At the end of the study, we conducted independent sample test on the GSDS scores of patients with sleep disorder in the control group and the test group respectively. The results showed that the sleep quality of patients with sleep disorder risk in the control group was not significantly improved ($P > 0.05$), and the sleep quality of patients with sleep disorder risk in the test group was improved 100% ($P < 0.01$) (Table 5).

Table 5
Comparison of sleep quality score before and after chemotherapy

Group	Time	$\bar{x} \pm S$	t	P
Control group	GSDS d0	3.83 ± 0.63	-0.239	0.813
	GSDS d6	3.89 ± 0.67		
Test group	GSDS d0	3.60 ± 0.51	5.130	0.000
	GSDS d6	2.82 ± 0.56		

2.5 Summary of adverse reactions

Adverse reactions related to antiemetic drugs are mainly concerned when adverse reactions are recorded, and factors such as obvious adverse reactions related to chemotherapeutic drugs are excluded. We therefore report the case described by our patient, but we are not sure that all adverse events were caused by antiemetic therapy or chemotherapy. Olanzapine-related adverse reaction events during the study were all below Grade 2. The most common adverse reactions were Hypersomnia(28%) (21/73), hypodynamia(22%) (16/73), abdominal distension (19%) (14/73) and dry mouth (18%) (11/73). Almost

all of the adverse reaction events were in the patients who used olanzapine, but most of them were Grade 1 adverse reaction events (Table 6). In actual clinical investigation, patients are more willing to accept the adverse reactions of hypersomnia and increased appetite.

Table 6

Summary of adverse reactions

Symptom	Grade1	Grade2	Grade3	Total
	Control/ Test group（%）	Control/ Test group（%）	Control/ Test group（%）	
Hypersomnia	5/16（23.8/76.2）	0/0（0/0）	0/0（0/0）	21（28）
hypodynamia	8/8（50/50）	0/0（0/0）	0/0（0/0）	16（22）
Abdominal distension	9/5（64.2/35.7）	1/0（0/100）	0/0（0/0）	14（19）
Increased appetite	1/9（10/90）	0/0（0/0）	0/0（0/0）	10（14）
Constipation	3/6（30/60）	0/1（0/10）	0/0（0/0）	10（14）
Dry mouth	3/8（27.3/72.7）	0/0（0/0）	0/0（0/0）	11（15）
Hyperglycemia	5/1（83.3/16.7）	0/0（0/0）	0/0（0/0）	6（8）
Edema	2/0（100/0）	0/0（0/0）	0/0（0/0）	2（3）
Flushed face	3/0（100/0）	0/0（0/0）	0/0（0/0）	3（4）

Further analysis showed whether there was a difference in the incidence of the above adverse reactions between the test group and the control group. There were significant differences in the incidence of the three adverse reactions including Hypersomnia, Hyperglycemia, Increased appetite and Dry mouth

between the control group and the test group (P < 0.05). Among them, the incidence of Hypersomnia was higher in the test group, while the incidence of Hyperglycemia and Dry mouth were higher in the control group. There was no significant difference in the incidence of Fatigue, Abdominal distension, Constipation, Edema and Flushing between the two groups (P > 0.05).(Supplementary table 2)

Discussion

For the prevention and treatment of CINV, clinical practices were mostly in compliance with the requirements of the national comprehensive cancer network (NCCN), the American Society of Clinical Oncology (ASCO)[16]. In order to further improve the effective control rate of nausea and vomiting in the delayed phase, authoritative international guidelines such as the Multi-National Association Supporting Care Cancer (MASCC) and the European Society for Medical Oncology (ESMO) have been issued. Based on data from various clinical studies, the guidelines have been continuously adjusted. The application of multiple drugs in combination for the prevention and treatment of CINV is recommended in the relevant clinical application guidelines[17]. Based on the traditional three-drugs antiemetic regimen, olanzapine is introduced into the guidelines as a class of anti-psychotic drugs, and its efficacy has been recognized through clinical application both in China and abroad[18]. However, looking back at the current clinical studies on CINV, both the traditional triple antiemetic regimen and the quadruple antiemetic regimen recommended by NCCN in 2020 (based on the addition of olanzapine to the traditional triple antiemetic drug) contain dexamethasone[6].

However, studies have shown that about 20% of non-diabetic cancer patients develop steroid-induced diabetes when using dexamethasone to prevent CINV[8]. For diabetic tumor patients, the use of dexamethasone will aggravate blood glucose fluctuation and make blood glucose more difficult to control, thus aggravating the disease and even causing serious consequences[19]. In addition to affecting the level of blood glucose, studies have also revealed that the glucocorticoid can inhibit T-cells activity by inhibiting interleukin-2-mediated T-cells proliferation and activation, and inducing T-cells apoptosis, thereby affecting the efficacy of immune checkpoint inhibitors[20]. A retrospective analysis study examined the effect of dexamethasone on the efficacy of PD-1/PD-L1 inhibitors. This study included 640 patients with NSCLC, and the results showed that the baseline use of glucocorticoid for patients from two cancer centers significantly reduced the ORR, PFS, and OS of PD-1/PD-L1 inhibitors[21]. Glucocorticoids may be an independent risk factor for poor prognosis in patients after treatment with immune checkpoint inhibitors.

The reduced use of dexamethasone and the recommended use of antipsychotic drugs have become a trend in the development of antiemetic guidelines in the new era. Most clinical studies on the prevention and treatment of CINV in China and abroad focus on the addition of olanzapine in the traditional three-drug antiemetic regimen, or the replacement of olanzapine only when dexamethasone cannot be tolerated[17]. As for the nausea and vomiting caused by hyperemesis chemotherapy, there is currently no complete scheme of "desamethasone removal" in China and abroad. In our study, 50 chemotherapy-

induced hyperemesis patients were randomly divided into the control group (dexamethasone group) and the test group (olanzapine group) according to random number table. The CR of nausea in the control group receiving dexamethasone combined with fosaprepitant and palonosetron in the overall observation, acute and delayed phases were 57%, 86% and 74% respectively. While the CR of vomiting during the overall observation, acute and delayed phases were 91%, 100% and 94% respectively in the control group. The patients in the test group who received the three-way antiemetic regimen of olanzapine combined with fosaprepitant and palonosetron orally achieved the complete remission rates of 66%, 84% and 81% of nausea in the overall observation period, acute period and delayed period respectively, and the complete remission rates of vomiting reached 89%, 95% and 92% respectively. Therefore, the antiemetic effect of the three-drug regimen containing olanzapine was not only not inferior to that of the traditional three-drug regimen in the control group. And is not lower than the olanzapine-containing quadruple antiemetic regimen recommended by the guidelines[22]. Meanwhile, compared with similar studies at home and abroad, the olanzapine-containing quadruple antiemetic regimen also has good efficacy. In general, the efficacy of replacing traditional dexamethasone with 5-HT3 receptor antagonist and NK-1 receptor antagonist with olanzapine in controlling the nausea and vomiting in the acute phase caused by hyperemesis chemotherapy has reached the expectation.

With the transformation of modern medical model, the mental and psychological factors of patients with malignant tumor have been paid more and more attention. Patients with malignant tumor often suffer from different degrees of anxiety and depression. However, studies have shown that anxiety and depression are often related to chemotherapy-induced nausea and vomiting. Throughout the previous clinical studies on chemotherapy-related antiemesis containing olanzapine, mental, psychological, emotional, and sleep factors were not included in the clinical studies as observation indexes for clinical efficacy[12]. Therefore, based on the development trend of clinical antiemesis guidelines in China and abroad, we made further exploration in this study and added observation indexes, so as to provide safe and alternative antiemesis regimens for patients with malignant tumors, especially for patients with glycosuria history, when receiving high-emesis chemotherapy regimens, which had certain guiding significance. Many studies have shown that olanzapine can significantly improve the symptoms such as pain, nausea, vomiting, insomnia, anxiety and depression in cancer patients and improve the quality of life of patients with advanced cancer[7]. In this study, we assessed the anxiety and depression scores of patients before and after chemotherapy, and analyzed the correlation between the presence of anxiety and depression in patients and the occurrence of CINV. The results showed that the nausea and depression scores in the control group were significantly and positively correlated. Vomiting had no significant correlation with the anxiety and depression scores before and after chemotherapy, while nausea and vomiting were not significantly correlated with the anxiety and depression scores in the test group. Considering that the olanzapine application cycle in this study was only four days, and the observation cycle was short, it was not enough to have a positive effect on the anxiety and depression symptoms of the patient. In this study, 19 of 50 patients (38%) had sleep disorders, which deserves our attention. Analysis of the results of the General Sleep Disturbance Scale (GSDS) found that the sleep quality of patients in the test group at risk of sleep disorders was 100% improved after the observation

period. We know that drowsiness and increased appetite are adverse reactions of olanzapine. Some patients suffer from daytime drowsiness, but in general, drowsiness and increased appetite are conditions that cancer patients are willing to accept.

On the whole, with the gradual change of medical model from "Biomedical Model" to "Bio-Psychological-Social Medical Model" in the new era, which also guides the change of guidelines and the new development direction of anti-vomiting in recent years. The decrement application of dexamethasone and the recommendation application of antipsychotic drugs have become the development trend of anti-vomiting guidelines at present. Most clinical studies on the prevention and treatment of CINV in China and abroad focus on the addition of olanzapine to the traditional antiemetic regimen, or the replacement of olanzapine only when dexamethasone cannot be tolerated. Whether olanzapine can completely replace dexamethasone in the antiemetic regimen will need more clinical research data to verify.

Declarations

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Consent to participate: (include appropriate statements)

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