


Letter to Editor

Effectiveness of intravenous promethazine and diazepam in the treatment of peripheral vertigo in emergency department visits

Seyed Mohsen Fayyazi¹, Mehrdad Taghizadeh², Zohreh Nabizadeh-Gharghozar³, Hamidreza Javadzadeh¹, Sadrollah Mahmudi¹, Kamran Heidari^{2*} 

1. Department of Emergency Medicine, Baqiyatallah University of Medical Sciences, Tehran, Iran

2. Skull Base Research Center, Loghman Hakim Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran

3. Student Research Committee, School of Nursing and Midwifery, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Abstract

Introduction: To improve our understanding of dizziness, its assessment, as well as its management to identify the appropriate treatment in order to reduce the costs and to increase the patients' quality of life.

Methods: A single blind parallel group randomized controlled trial was conducted on 164 participants with dizziness. One group received 25mg/ml promethazine and another received 5mg/ml diazepam. To assess the severity of dizziness, Visual Analog Scale was used prior to and two hours after treatment.

Results: Both promethazine and diazepam had significant effects on decreasing the severity of dizziness, i.e. the severity score decreased from 9.31 to 1.81 in promethazine versus 9.33 to 4.50 in diazepam ($P < 0.001$).

Conclusion: A single IV dose of promethazine is more effective in reducing vertigo as compared with diazepam.

Keywords:

Diazepam;
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*Correspondence to:

K. Heidari

Tel: +98-2151025582

Fax: +98-2155416130

Email:

heidari-k@sbm.ac.ir

Dear Editor

Dizziness is a frequent complaint. Current or chronic symptoms of dizziness are reported by 10% (Aggarwal et al., 2000; Stevens et al., 2008) to 30% (Colledge et al., 1994) of community-dwelling adults with an increasing prevalence as people age (Colledge et al., 1994; Aggarwal et al., 2000; Maarsingh et al., 2010). Dizziness markedly impairs quality of life (Neuhauser et al., 2005), and is associated with a two-fold increase in the prevalence of self-reported functional disability (Aggarwal et al., 2000), worsening of depressive symptoms (Tinetti

et al., 2000b; Stevens et al., 2008), decrease of participation in social activities, poor self-reported health and reduction of falls self-efficacy (Tinetti et al., 2000b). There is also evidence of a relationship between acute dizziness and falls (Stevens et al., 2008; Delbaere et al., 2010) and the frequency of dizziness episodes is associated with disability (Aggarwal et al., 2000), falls and syncopal events (Delbaere et al., 2010).

Dizziness is a subjective sensation that is used to describe feelings such as light-headedness, feeling faint, head spinning, room spinning, unsteadiness and feeling woozy or giddy. Clinically, dizziness is described as a feeling of altered orientation in space

(Halmagyi and Baloh, 1996). Traditionally, it has been divided into four main subtypes (Drachman and Hart, 1972): (i) vertigo, where patients express illusory sensation of self-motion, which is often the result of a vestibular system disorder; (ii) pre-syncopal dizziness, a light-headed sensation associated with cerebral hypo perfusion; (iii) psychogenic dizziness, associated with a mental health issue, such as generalized anxiety and (iv) disequilibrium and non-specific dizziness, often associated with neuromuscular causes. In older people, dizziness may have a multifactorial etiology, with many dizzy older patients fulfilling criteria for two or more of the subtypes described above (Kroenke et al., 1992; Tinetti et al., 2000a; Sloane et al., 2001).

Treatment of peripheral vertigo is symptomatic and mainly includes anti-nausea and inhibitors of the ear balance system but there is no confirmed standard guideline to select the type and duration of treatment (Strickland et al., 2003; Roceanu et al., 2016). The benzodiazepines, anticholinergic and phenothiazine are some common medications used in the treatment of vertigo. The efficacy of corticosteroids has also previously been reported in some studies (Strupp et al., 2004; Amini et al., 2015; Roceanu et al., 2016; Shahrami et al., 2016).

Currently due to the variety of vertigo treatments, the lack of a single protocol in dealing with dizziness, complications of medical and surgical treatments as well as limitation of exercise and physical therapy to resolve dizziness, there are limitations on how to deal with vertigo. For this reason, we decided to compare the effectiveness of intravenous promethazine and diazepam, two drugs that have the least side effects and maximum effect on reducing dizziness, in the treatment of peripheral vertigo in patients referring to the emergency department.

The current randomized control trial was carried out to improve the understanding of dizziness, its assessment as well as its management to identify the appropriate treatment so as to reduce the costs and to increase patients' quality of life.

A single blind parallel group randomized controlled trial was conducted after receiving the ethics approval and patient informed consent from 164 participants randomly selected from among individuals with dizziness who had referred to Baqiyatallah Hospital, Tehran, in 2015. The Ethics Committee at Baqiyatallah University of Medical Sciences approved

the study. Also, the present study was reviewed and approved by Iranian Registry of Clinical Trials (IRCT 20171221037984N1).

Dizziness was diagnosed by a Emergency Medicine with more than 10 years of experience. Patients were randomized into two groups using a computer generated randomization list. One group received 25mg/ml promethazine intravenously and the other group received 5mg/ml diazepam intravenously. If the patients did not respond to the treatment initially, they would be assigned to the other group, and still if they did not respond to the other treatment protocol, they would undergo other more aggressive treatments. To assess the severity of dizziness, Visual Analog Scale (VAS) was used prior to and two hours after the treatment in setting position. This way, patients were asked to score the severity of their vertigo from 1 to 10. To evaluate the reliability, test-retest reliability proved to be good, but higher among literate ($r: 0.94$, $P < 0.001$) compared with illiterate patients ($r: 0.71$, $P < 0.001$) prior to and after their visit to the clinic.

The inclusion criteria were age over 18 and diagnosis of peripheral vertigo. Potential participants were excluded if they; (i) had a degenerative neurological condition, (ii) were currently (in the past 24 hours) receiving treatment for their dizziness, (iii) had a cognitive impairment (a General Practitioner Assessment of Cognition (GPCOG) of < 5) (Brodaty et al., 2002) and/or, (iv) were unable to walk 20m without difficulty using a walking aid, and had evidences of developing drug-induced vertigo and head trauma. Participants were asked to sign an informed consent form before answering the questionnaire. All personal information remained anonymous.

Data were analyzed using Statistical Package for Social Sciences (SPSS), version 19 (SPSS Inc. Chicago, IL). Sample size was calculated using sample size formula. We considered $\alpha = 0.05$ and power = 90%. Normal distribution variables (approved by one-sample Kolmogorov-Smirnov test) were compared using independent sample t-test between the groups and paired sample t-test within the groups. In addition, Chi square test was run to compare categorical variables between the two groups. Analysis of the simultaneous effect of variables was carried out running logistic regression. Furthermore, repeated measures two-way ANOVA was employed to compare dizziness score and

Table 1: Comparison of mean dizziness score in diazepam and promethazine groups prior and two hours after the treatments.

	Type of medication	Mean dizziness	Std. Deviation	Std. Error Mean	Sig. (2-tailed)
Before treatment	Promethazine	9.31	.704	.176	
After treatment	Promethazine	1.81	.655	.164	
Pair after before treatment	Promethazine	-7.500	.816	.204	.000
Before treatment	Diazepam	9.33	.651	.188	
After treatment	Diazepam	4.50	1.446	.417	
Pair after before treatment	Diazepam	-4.833	1.193	.345	.000

duration between groups during time. P -values <0.05 were considered as statistically significant.

The average ages of the patients who consumed diazepam and promethazine were 45 ± 11 and 47 ± 12 , respectively. Of the patients who were taking diazepam, 24.3% ($n=17$) were male and 75.5% ($n=53$) were female and 32.9% ($n=23$) reported a positive history of an underlying disease. In addition, among patients who took promethazine, 43.6% ($n=41$) were male and 56.4% ($n=53$) were female and 37.2% ($n=35$) were with a positive history of an underlying disease.

Both promethazine and diazepam had significant effects on decreasing severity of dizziness; the severity score decreased from 9.31 to 1.81 in promethazine group versus 9.33 to 4.50 in diazepam group ($P<0.001$), but comparison of the means showed that promethazine was more effective (Table 1). Furthermore, the influence of the drugs was not found to be significantly associated with any factor, including age, gender, duration of vertigo, etc. According to Table 2, there is no significant relationship between the mean age ($P=0.729$) as well as gender ($P=0.266$) and the effects of the drug; however, promethazine had better effects in males than in females.

The means of dizziness duration in patients who consumed diazepam and promethazine were 7 ± 2 hours and 8 ± 2 hours, respectively. According to the results of repeated measures two-way ANOVA, the statistical relationship between dizziness duration as well as scores and the effect of drugs were not observed to be significant after treatments ($P>0.05$).

Furthermore, no significant relationship was found between underlying disease and the drug effect ($P=0.833$) (Table 1).

In addition, no significant relationship was observed between cause of dizziness and effect of the drugs ($P=0.947$); however, the effects of promethazine was better in patients who had dizziness due to Meniere's disease (Table 2).

Vertigo is a common complaint in the emergency departments that influences daily activities and increases medical consultations (Irving et al., 2002). Although many pharmacological agents appear to be clinically useful, insufficient investigations have been carried out to find the most effective anti-vertigo medication with the least adverse effects. Therefore, we conducted the current randomized, double-blind trial to compare the effects of two common intravenously administered medications, i.e. promethazine and diazepam.

To treat vertigo, several medications from different pharmacologic groups have been employed, including antihistamines, anticholinergics, benzodiazepines, calcium channel blockers, diuretics, neuroleptics, psychotherapeutic agents and corticosteroids. It seems that these medications influence on the level of neurotransmitters involved in the transmission of impulses through vestibular neurons and in maintenance of tone in the vestibular nuclei (Kerber et al., 2008).

Promethazine and diazepam are among the drugs used in emergency departments to treat vertigo. Promethazine, a component of phenothiazine drugs, acts as an antiemetic agent with dopamine, histamine

Table 2: The effect of diazepam and promethazine on the severity of dizziness based on Visual Analog Scales prior and two hours after the treatments

		Diazepam		Promethazine	
		Before treatment (Mean score)	After treatment (Mean score)	Before treatment (Mean score)	After treatment (Mean score)
Gender					
Female	(75%)	9	5	(56.3%)	2
Male	(25%)	9	4	(43.7%)	2
Underlying disease					
Yes	(33.3%)	10	5	(37.5%)	2
No	(66.7%)	9	5	(62.5%)	2
The cause of dizziness					
BPV	(75%)	9	4	(75%)	2
Meniere	(8.3%)	10	7	(6.3%)	2
Vestibular	(16.7%)	10	5	(18.7%)	2
History of dizziness					
Yes	(100%)	9	5	(100%)	2
No	(0.0%)	-	-	(0.0%)	-

(H1) and muscarinic receptor antagonist activity (Hain and Uddin, 2003), whereas diazepam is a benzodiazepine producing gamma-aminobutyric acid modulation and central suppression of vestibular responses. Also, benzodiazepines are useful medications for the management of vertigo in small dosage administration (Hain and Uddin, 2003).

Both promethazine and diazepam had significant effects on decreasing the severity of dizziness; however, comparison of the means showed that promethazine had better effects on patients. The influence of drugs was not significantly associated with any of the factors studied, including age, gender, duration of vertigo, etc. To the best of our knowledge, no previous article had reported studying these patients after receiving promethazine to treat vertigo in Iran.

Kerber (2009) concluded that 86% of the dimenhydrinate-treated patients were with no symptom two hours after intervention, compared with 69% in the lorazepam group.

To relieve the nausea and vomiting correlated with vertigo, antihistamines are administered (Lopez-Escamez et al., 2005). When nausea and vomiting are prominent, using a vestibular suppressant with antiemetic effect, such as promethazine and diazepam, appeared useful to control the symptoms. The function of promethazine in the management of vertigo and nausea in emergency departments was inadequately studied in trials. Based on the 2005 National Hospital Ambulatory Survey, promethazine

is among the top generic medications prescribed in the emergency departments (McClure and Willett, 1980). This can be due to its many advantages, including low cost, slow intramuscular absorption and long elimination half-life (McClintock et al., 2010).

Previous studies have confirmed the effectiveness of promethazine in the treatment of nausea and vomiting in patients who had undergone ear operation. According to Morales-Luckie et al. (2005) study, promethazine 25mg administered intravenously was more effective than placebo for the treatment of postoperative nausea and vomiting after middle ear surgery. In the current study, both promethazine and diazepam had significant effects on decreasing the severity of dizziness (the severity score decreased from 9.31 to 1.81 in promethazine versus 9.33 to 4.50 in diazepam).

Moulin et al. (2003) showed that promethazine and ondansetron have similar efficacy in reducing nausea after surgery.

In the current investigation, drowsiness was the main side effect of promethazine. Also other adverse effects such as bradycardia, change in blood pressure, extrapyramidal symptoms, respiratory depression, nervousness, urinary retention and dry mouth are reported. On the other hand, increased lethargic condition was prominent in diazepam group.

Limitations

Like any other study, there are some limitations to the

present trial that should be considered when generalizing the findings. Data reporting may have been confounded by patients' subjective sensation of symptoms. Patients' symptoms may have been reported differently depending on the self-perception of discomfort. Another limitation of the study was evaluation of vertigo initially and after only a period of two hours. Several outcome measures during different time intervals could make our findings more comprehensive. In the present study, we employed the most common doses of drugs (25mg/ml promethazine vs 5mg/ml diazepam) which have been frequently used in clinical practice; however, various dosages may have different effects and the observed differences between two groups may be related to the use of different doses. We did not compare the efficacy and safety of several effective dosages of study medications. Thus, future studies to examine the effectiveness of alternative treatment options with different doses are warranted.

Conclusion

Based on the findings of the present study, it can be concluded that a single IV dose of promethazine has more efficacy at vertigo reduction as compared with diazepam. We also showed that promethazine plays a vital role in the treatment of peripheral vertigo. These findings can be generalizable to other patients presenting with vertigo symptoms similar to those of peripheral origin. Future trials may also consider the therapeutic efficacy of promethazine versus other medications, such as dimenhydrinate, in patients presenting to the emergency department with acute peripheral vertigo.

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Conflict of interest

The authors declare that they have no conflict of interest.

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