



Comparison of the Effectiveness of Intravenous Promethazine and Intravenous Diazepam in the Treatment of Benign Paroxysmal Positional Vertigo in the Emergency Department

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Authors' contributions

This work was carried out in collaboration between all authors. Author MM designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors FR and MS managed the analyses of the study. Author MS managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Objective: The aim of researches was comparing the effectiveness of promethazine with that of diazepam in the treatment of Benign Paroxysmal Positional Vertigo (BPPV) in the emergency department.

Methods: This clinical trial was conducted on 100 patients with BPPV who were presented in the emergency department of Besat Hospital, Tehran, IR Iran, March 2013- March 2014. Patients were selected based on convenience sampling method, matched according to their age, sex, clinical symptoms and features, and then randomly divided into two groups. 50 patients received promethazine and 50 patients received diazepam.

Results: Both drugs had comparable effects (P value < 0.05). The clinically treatment of BPPV was seen in 76% of patients in the promethazine group and 82% of whom received diazepam. The

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median of the duration with a feel of heaviness in the head after the first injection was 37 minutes in the promethazine group and 33 minutes in the diazepam group. The time to discharge the patient in the promethazine group was 30 minutes longer than the diazepam group.

Conclusions: This study demonstrated no more effectiveness of study medications on each other in management of BPPV, but given the better performance of diazepam regarding the secondary outcomes compared to promethazine, it could be the preferred choice in patients with BPPV.

Keywords: Diazepam; Benign paroxysmal positional vertigo; Promethazine.

1. INTRODUCTION

Vertigo is common in the general population, observed in 5-10% of the society population [1]. The incidence of vertigo in people over 60 years old is also reported to be between 20% and 30% [2]. Peripheral vertigo occurs due to disturbances in balance organs such as the ear [3]. BPPV accounts for one third of vestibular diagnoses in the general population [4]. BPPV as the most common recognized peripheral vestibular disorder [5] is responsible for a remarkable volume of emergency department admissions [6]. BPPV is characterized by rotatory dizziness usually lasting less than 1 minute triggered when a patient stands up or lies down on bed or rolls over in that and also when changes occur in the head position such as tilting the head back, or bending it forward [7] and may be accompanied by nausea, vomiting, paleness and sweating [8]. The cause of BPPV attacks usually is unknown; however, problem may be associated with head trauma, inner ear diseases, a prolonged recumbent position (e.g., at a dentist's office or hair salon), osteopenia or osteoporosis, decreased serum levels of vitamin D [7], senility, prolonged rest hypertension, hyperlipidemia, stroke, and migraine [5].

The patient's health and quality of life is strongly affected by vertigo disorder. Immobilization, chronic invalidism [9], severe anxiety and depression are some of the reported adverse effects [10].

Treatment of BPPV is a therapeutic maneuver, drug therapy, or a combination of both. The first therapeutic maneuver was described by Epley in 1992, which is now used with some modifications as the most effective treatment [11]. Maneuver repetition is useful for shortening the duration of the recurrence form of BPPV, while in cases of BPPV persistence, additional treatment strategies such as vestibular rehabilitation exercises, vestibular function suppressive drugs and surgical procedures may be necessary [12]. Drug therapy is introduced as the appropriate

BPPV treatment [2]. Equilibrium system inhibitors are the major drugs effective in the treatment of peripheral vertigo [11]. Promethazine and diazepam are among the drugs used to treat BPPV in the emergency department [13]. Promethazine, a component of phenothiazine drugs [9], is the most widely used antiemetic agent used in the emergency department [14]. Diazepam is a benzodiazepine compound [15]. Rapid onset, considerable efficacy and negligible cases of life threatening side effects are some properties attributed to this drug [16].

There are a limited number of clinical trials focusing on emergency care of BPPV [9]. Given that a special treatment is not agreed in the treatment of peripheral vertigo, in the current study, the effectiveness of intravenous promethazine was compared versus intravenous diazepam for emergency treatment of BPPV.

2. METHODS

2.1 Study Design and Population

This study was a randomized clinical trial with control group and without blindness and was conducted to compare the effectiveness of promethazine and intravenous diazepam reducing dizziness in patients with diagnosed Benign Paroxysmal Positional Vertigo presented to the emergency department of Besat hospital of Tehran city, IR Iran between March 2013 and March 2014. The include criteria were the patients more than 18 years old that without history of smoking, Ischemic heart disease, Hypertension, Diabete Mellitus, Hyperlipidemia, Cerebrovascular Attact, Transiant Ischemic Attact The exclusion criteria were decreased consciousness, symptoms of central nervous system disorders, cardiovascular instability (systolic pressure less than 100 mmHg), physician preference for patient treatment with a particular drug, history of allergic reaction to any of drugs, and lack of patient consent to participate in the study.

2.2 Sample Size

In order to homogenize the two groups of study, the available and targeted sampling method was used. To calculate the sample size, an initial sample consisted of 10 patients was first examined. After assessing the mean and standard deviation of improvement rates in each of the studied groups, the sample size required for study was determined according to the following formula:

$$n = \frac{2 \times \left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta} \right)^2 \times (Sd_1^2 + Sd_2^2)}{(\mu_1 - \mu_2)^2}$$

Where $Z_{1-\frac{\alpha}{2}}=1.96$, $Z_{1-\beta}=0.84$, $\mu_1=8 \pm Sd_1(1.45)$, $\mu_2=7.2 \pm Sd_2(1.8)$, $\alpha = 0.05$, $\beta = 0.2$. Accordingly, a total of 50 patients were required in each of the treatment and control groups to demonstrate significant statistical differences.

2.3 Collecting Data

In the questionnaire prepared for patients, demographic data including age and gender were first determined. Then information on the clinical characteristics of vertigo and its duration, time of heaviness in the head after every attack, duration of the disappearance of vertigo symptoms, frequency of dizziness and the associated symptoms and finally the epidemiological data were recorded. Clinical characteristics including oscillopsia, nausea and vomiting, imbalance, ear pain and tinnitus, and hearing loss and clinical records of patients including history of BPPV attacks, history of depression and high blood pressure and diabetes, hyperlipidemia, history of coronary artery disease in the heart and stroke requiring drug follow-up, history of using a specific drug for the heart problem or blood pressure or blood lipids and diabetes, history of smoking even one cigarette per day, and history of head trauma due to accident or beating or falling due to imbalance were other variables included in the questionnaire.

2.4 Intervention

For the intervention, patients were randomly divided into two groups. As the first step in randomization, equivalent to the sample size, 100 envelopes were prepared. The half of envelopes contained the word promethazine and the word diazepam was included in the remains.

After selecting each of the envelopes by the main researcher depending on the content of the envelope, each patient was included in one of two groups. Promethazine 25 mg per 25 ml of normal saline solution was infused over 10 minutes to each of the patients in the first group. If treatment was not effective, after 15 minutes, the second dose of promethazine 25 mg per 25 ml of normal saline solution was infused over 10 minutes. For the patients in the second group, diazepam 5 mg was administered intravenously over 5 minutes. After 15 minutes, the second dose of diazepam 5 mg was injected intravenously over 5 minutes if the first dose was not effective. In both groups, if vomiting occurred, regardless of whether the second dose was given or not, after 15 minutes, 10 mg metoclopramide was injected intravenously over 4 minutes. To compare duration to recovery, number of vertigo attacks, and duration of feeling heaviness in the head after each attack between the groups these characteristics were recorded using a follow-up form (after treatment).

2.5 Outcomes

The primary endpoint was successful treatment of vertigo defined as the proportion of patients with complete improvement after the first injection, and duration of the vertigo disappearance after intervention. Secondary endpoints were frequency of vertigo attacks, and duration of heaviness in the head after the treatment and need for second dose of study medications.

2.6 Data Analysis

Data collected were categorized using descriptive statistical methods and analyzed using the Statistical Package for Social Sciences version 18. Qualitative variables were reported as ratio and frequency while quantitative variables were demonstrated using median. Median values were compared using Mann-Whitney test. The relationship between qualitative variables was evaluated using chi-square test. A p-value of 0.05 was considered statistically significant.

2.7 Statement of Ethical Approval

In this study, principles of the Helsinki Declaration strictly were considered. Study protocol was approved by Ethical Committee of AJA University of Medical Sciences. All patients who met the inclusion criteria of the study signed

informed consent form. Although the risks were so simple and innocuous in this research, the predictable risks were declared to the participants and appropriate information was given to the participants about the duration of the research, the method employed, and the potential benefits and harms of the plan. The researcher also gave a convincing answer to all the questions of the subjects. Participants were told that they could leave the study at any time.

3. RESULTS

3.1 Demographic and Baseline Characteristics

Considering the researcher's intention to match the research groups, same proportions of men and women were allocated to both promethazine and diazepam groups. Therefore, in each group, 50% of patients were male (n= 25). Table 1 shows the age classification of the studied samples. Clinical characteristics of patients based on diagnostic examinations were determined and reported in Fig. 1. Accordingly, imbalance, nausea, and vomiting were the most common clinical symptoms among patients with vertigo problem. Furthermore, subjects of two groups had similar baseline conditions in terms of all clinical symptoms.

3.2 Effectiveness

The effectiveness of the used drugs is expressed in the form of primary and secondary outcomes

in Table 2. The majority of patients in both groups achieved their overall improvement after receiving the first dose of drugs. Given the rates of improvement, greater proportion of promethazine treated-patients (12/50) needed the second dose compared with the diazepam treated-group (9/50).The median of the duration with a feel of heaviness in the head after the first injection was 37 minutes in the promethazine group and 33 minutes in the diazepam group. The time to discharge the patient in the promethazine group was 30 minutes longer than the diazepam group. Compared with the first intervention, the recovery rates decreased after the second intervention. Overall, no significant difference was found between the two groups regarding the incidence of primary and secondary outcomes.

Table 1. Frequency of patients in different age groups

Age groups (years)	Promethazine N=50	Diazepam N= 50
19-24	4(8%)	3(6%)
25-29	4(8%)	5(10%)
30-34	6(12%)	4(8%)
35-39	8(16%)	7(14%)
40-44	7(14%)	8(16%)
45-49	3(6%)	4(8%)
50-54	5(10%)	5(10%)
55-59	5(10%)	6(12%)
60-64	3(6%)	3(6%)
65 and older	5(10%)	5(10%)

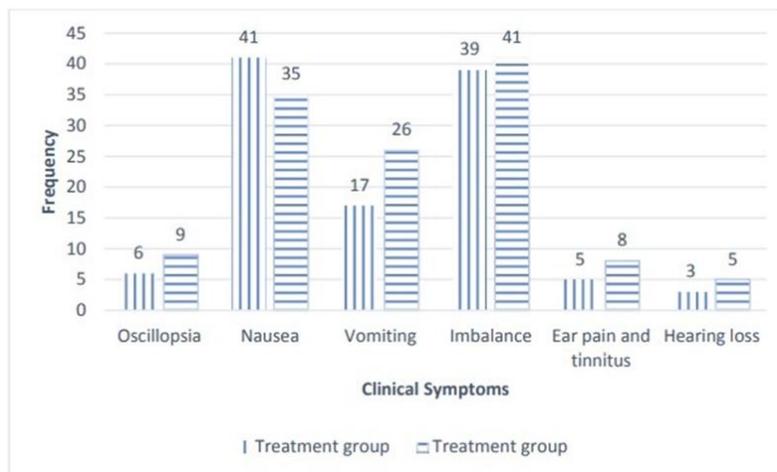


Fig. 1. Comparison of the frequency of clinical symptoms between the two groups before treatment

Table 2. Comparing the efficacy of treatment in patients receiving promethazine with patients receiving diazepam

Outcome		Promethazine (N=50)	Diazepam (N=50)	P-value
After the first dose	Duration of vertigo disappearance (min)	3	2.5	0.19
	Frequency of vertigo attacks per day	2	2	0.32
	Duration of heaviness in the head (min)	37	33	0.25
	The rate of improvement (%)	76	82	0.45
	Time to discharge the patient (hour/min)	5/30	5	0.378
After the second dose	Duration of vertigo disappearance (min)	2.9	3.1	0.389
	Duration of heaviness in the head (min)	40	38	0.285
	The rate of improvement (%)	45	50	0.19

4. DISCUSSION

In this study, an equal proportion of females were included in the groups of study. Literature review showed that the risk of BPPV in women was twice that of men [17]. In a number of reports, the frequency of vertigo in females was more than 60% [6,18]. In addition, researchers tried to match the study groups in terms of age variable. It was conducted to eliminate the interventional effect of age parameter because increased age is proportional to the incidence of BPPV [19], and some of the other neurotological disorders caused by deterioration in equilibrium and hearing function [20]. The drugs used in this clinical trial were effective in 76-82% of cases. Literature review showed that pharmacologic agents were successful in vertigo management in 60–80% of cases [9]. According to the results of this study, diazepam and promethazine both were remarkably effective in reducing the cases of BPPV and diazepam improved peripheral vertigo a little better than promethazine which dramatically contrasts with the results of the study conducted by Shafipour et al. [2] where excellent levels of improvement were observed in 94.7% patients receiving promethazine while only 17.3% patients receiving diazepam experienced a good level of improvement. In present research 76% of subjects receiving promethazine improved after administration of the first dose while in the study of Amini et al. [9] 90% of cases in the promethazine group achieved their overall improvement. The baseline clinical conditions that were assessed prior to the intervention showed that nausea and vomiting were prominent clinical symptoms among the study population. The use of promethazine as a vestibular suppressant is proposed to decrease these symptoms. The anticholinergic or antihistamine properties of vestibular suppressants create antiemetic qualities [9]. To control the nausea and vomiting caused by

vertigo antihistamines suppress the central emetic center [21]. The function of promethazine is Antihistaminergic [22]. Habib et al. [23] reported that promethazine was significantly effective for treating postoperative nausea and vomiting. The number of clinical studies regarding the usefulness of diazepam for treating ED patients with vertigo is not high [24]. Kariman et al. [15] study showed that diazepam was successful in treatment of vertigo in 88.9-100% of cases based on patients' positions. In the clinical trial carried out by Barzegari et al. [25] intravenous diazepam showed higher effectiveness in treatment of acute peripheral vertigo compared to methyl prednisolone. Neuroinhibitory effects of diazepam leads to inhibition of vestibular response through gamma-aminobutyric acid receptors [24].

5. LIMITATIONS

The most important limitation of this study was the lack of patients' cooperation for the use of other therapies or their simultaneous use of other drugs to relieve dizziness. However, with the notifying and training of patients in this regard, possible problems were resolved.

6. CONCLUSIONS

This study showed that promethazine and diazepam had similar effectiveness in the treatment of BPPV. With respect to the difference observed between study medications regarding their effects on secondary outcomes, diazepam could be more frequently used in the treatment of BPPV in the emergency department.

CONSENT

As per international standard or university standard, patient's written consent has been collected and preserved by the authors.

ETHICAL APPROVAL

As per international standard or university standard, written approval of Ethics committee has been collected and preserved by the authors.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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