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Benzodiazepine loading versus symptom-triggered treatment of alcohol withdrawal: a prospective, randomized clinical trial☆

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Abstract

Objectives: The objectives were to compare the efficacy of a benzodiazepine loading versus a symptom-triggered protocol in the management of alcohol withdrawal.
Methods: We conducted a prospective, randomized, controlled trial including 47 consecutive patients admitted to one of two tertiary care medical centers who developed alcohol withdrawal syndrome. Patients were randomly assigned to either a benzodiazepine loading protocol or a symptom-triggered treatment protocol. The Clinical Institute Withdrawal Assessment for Alcohol-Revised scale (CIWA-Ar) was recorded throughout the length of stay, along with measures of autonomic system functioning.
Results: The average rate of change of CIWA-Ar scores was −1.5±1.3 for the symptom-triggered group and −2.3±2.5 for the loading group. Average rate of change for systolic blood pressure was −2.7±5.3 for the symptom-triggered group and −2.3±6.4 for the loading group. There was no significant difference between the rates of change for either group on either measure. Similarly, there was no significant difference in total benzodiazepine use between groups. Within 72 h of treatment, 69.6% of patients in the loading group were free of withdrawal symptoms versus 41.7% in the symptom-triggered group, a difference not reaching statistical significance.
Conclusions: This study did not reveal clear evidence of a clinical advantage for choosing either treatment method.

Keywords: Alcohol; Benzodiazepines; Withdrawal; Lorazepam; Diazepam; Symptom triggered; Loading method

1. Introduction

Alcohol use disorder (AUD) is the most serious substance abuse problem in the United States (US) and worldwide [1,2]. In 2008 in the US, slightly more than half (56% or 129 million) of Americans reported being current drinkers of alcohol, while 23.3% participated in binge drinking (i.e., ≥5 on the same occasion on at least 1 day in the 30 days prior to the survey) and 6.9% of the population reported heavy drinking (i.e., binge drinking on at least 5 days in the past 30 days) [3]. Similarly, the Epidemiologic Catchment Area survey found that the lifetime prevalence in the general population of alcohol abuse or dependence is 13.6% [4]. According to a national survey of the Veterans Affairs system, 42% of all veteran inpatients required medications to aid detoxification from alcohol [5]. Alcoholism has been reported in 20% to 50% of hospitalized medical patients [6]. Most alcohol-dependent patients admitted to the general medical wards will develop alcohol withdrawal symptoms, significant enough to require pharmacological intervention regardless of the cause for admission [7]. Alcohol abuse and withdrawal are associated with an increased risk for medical comorbidities (e.g., infections, cardiopulmonary insufficiency, cardiac arrhythmia, bleeding disorders, need for mechanical ventilation) and longer, more complicated hospital and intensive care unit stays [8].

Since their introduction in the 1960s, benzodiazepines have surpassed all other available agents (e.g., barbiturates)

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and have become the first-line treatment for all phases of alcohol withdrawal syndrome (AWS), including prevention of alcohol withdrawal delirium and seizures [9–12]. They have been shown to be the most efficacious available agents and are considered the treatment of choice for alcohol withdrawal [7,9,12–15]. A Cochrane review including 64 trials and a total of 4309 subjects demonstrated that benzodiazepines are superior to placebo for all alcohol withdrawal symptoms, particularly seizures [3 studies, 324 participants, relative risk 0·16 (95% confidence interval 0·04–0·69)] [16]. Yet, there is no consensus as to the best agent from this group to use, as randomized controlled trials have been limited in number and size [11].

There are at least two schools of thought regarding the clinical use of benzodiazepines for the treatment of alcohol withdrawal [10,12]. One such school favors the "loading method." This requires the use of a long-acting agent (e.g., diazepam, onset of action=1–1.5 h, *T*1/2=20–100 h, plus 36–200 additional h of active metabolites) which is administered until there has been significant improvement in withdrawal symptoms [17]. This approach postulates that agents with long half-lives will allow for self-tapering of the drug, translating into ease of administration and avoidance of breakthrough symptoms due to undersedation [18–20]. Critics of this method suggest that some patients may receive unnecessary medication, thus highlighting the possibility of oversedation, which may result in respiratory depression and prolonged hospitalizations [21,22].

The second is the "symptom-triggered" method, which promotes the use of short-acting agents (e.g., lorazepam, onset of action=2–4 h, *T*1/2=10–15 h, no active metabolites) administered in accordance with regular symptom monitoring [e.g., Clinical Institute Withdrawal Assessment for Alcohol-Revised scale (CIWA-Ar)] [23,24]. Symptom-triggered protocols address the potential for under- or overmedicating by assessing symptoms on real-time and administering benzodiazepine dosages only in response to symptom severity [25]. Proponents of this method suggest that it is as safe and effective as loading methods while preventing oversedation, which translates into faster resolution of symptoms, a reduction in the duration of treatment and quantity of medication use, and earlier discharge from the hospital [20,25–29], thus decreasing medical resource utilization and improving the efficiency of treatment [20]. In fact, a study using this symptom-triggered model reported a shorter time to symptom control and a total lower medication needed when compared to a nonprotocol infusion method [30]. Critics highlight problems of "breakthrough" withdrawal, the need for constant monitoring and frequent medication administration, and a potentially greater risk of developing benzodiazepine dependence [14,18,19,31].

The study described in this paper sought to conduct a head-to-head comparison between the two different treatment methods in a "real-life" scenario by comparing the loading method (using a long-acting benzodiazepine agent) to the symptom-triggered method (using a short-acting benzodiazepine) to determine whether there are indeed differences between these different approaches regarding effectiveness, safety or side effects. This was done by design as both the comparison between long- and short-acting agents using the same method and the comparison between two methods (i.e., loading vs. symptom triggered) have been conducted without conclusive results [9,14,16,32–37].

2. Methods

2.1. Study patients

The study was an open, prospective, randomized clinical trial conducted over a 12-month period at two tertiary care medical facilities, Stanford University Medical Center (SUMC) and the Palo Alto Veterans Affairs (PAVA) Healthcare System, in patients who presented with alcohol withdrawal symptoms. Patients were enrolled regardless of the initial reason for hospitalization. Eligible patients were inpatients with a reported history of alcohol withdrawal or dependence, age 18 or older, who had consumed alcohol within 24 h of admission and had the ability to consent to participate in the study. The criteria for exclusion from the study included pregnancy, history of dementia, reported active abuse of other central nervous system (CNS)-depressant agents (e.g., benzodiazepines, barbiturates, opiates), acute intoxication with a CNS-activating agent (e.g., cocaine, amphetamines), severe hepatic dysfunction [e.g., international normalized ratio (INR)>2·0] or unwillingness to participate in the study. Upon meeting eligibility criteria and consenting to participate, baseline characteristics were gathered (Table 1). Patients were randomized by number draw to either a symptom-triggered or loading benzodiazepine treatment protocol (Table 2).

2.2. Outcomes

The primary outcome measure was the baseline scores and rates of change of the CIWA-Ar [24]. The CIWA-Ar is a widely used scale that monitors alcohol withdrawal symptoms of anxiety; agitation; headache; tremor; diaphoresis; nausea and vomiting; orientation; and tactile, auditory and visual hallucinations. Throughout their inpatient stay, patients in both groups were regularly evaluated by the nursing staff using the CIWA-Ar. Additional [i.e., as needed (PRN)] medication could only be administered if the patient's CIWA score was elevated or if vital signs exceeded established parameters (Table 2). In addition, the CIWA-Ar was blindly administered three times per day (at 08:00, 14:00 and 21:00) by one of two medical students trained by the senior author on the administration of the CIWA-Ar. Secondary measures included measures and rate of change of autonomic system functioning (as measured by changes in vital signs). Blood pressure, pulse, temperature and respiratory rate measured by the nursing team were recorded at corresponding times. To facilitate comparison of the usage of