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ORIGINAL ARTICLE

Symptom-triggered alcohol vapor inhalation for postoperative alcohol withdrawal syndrome in patients with gastroesophageal carcinoma

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Summary

Purpose: *The purpose of this study was to investigate the feasibility and efficacy of alcohol vapor inhalation during fasting time for cancer patients with alcohol withdrawal symptoms (AWS) after surgery.*

Methods: *The data of 51 patients after esophagectomy or gastrectomy for gastroesophageal carcinoma in two hospitals from January 2011 to December 2016 was retrospectively analyzed. These patients were diagnosed with AWS with Clinic Institute Alcohol Withdrawal Syndrome Scale (CIWA-Ar) score ≥ 9 in two hospitals during fasting time from January 2011 to December 2016, and they were accordingly divided into alcohol vapor group (n=25) and diazepam group (n=26). As oral intake of wine was forbidden in the first 7 postoperative days, these patients received either alcohol vapor inhalation or intravenous administration of diazepam every 12 hrs. The difference in scores of CIWA-Ar, Riker Sedation-Agitation Scale (SAS), side effects and complications were registered and analyzed.*

Results: *The patients in both groups gained satisfactory efficacy which was indicated by CIWA-Ar scores after therapy, without obvious difference in terms of surgery-related complications, chest and abdominal drainage, serum biomarkers of hepatic function or postoperative hospital stay. However, the patients treated with alcohol vapor inhalation displayed lower alcohol craving and sleepiness, more significant decreased CIWA-Ar scores, as well as encouragingly higher degree of satisfaction, comparing with the diazepam group.*

Conclusion: *Alcohol vapor inhalation is feasible and effective to alleviate AWS timely, which is reliable for patients to get through the fasting time after surgery.*

Key words: *alcohol vapor, alcohol withdrawal syndrome (AWS), inhalation, gastroesophageal cancer*

Introduction

The alcohol withdrawal syndrome (AWS) is a well-known condition occurring after abrupt discontinuation of alcohol in alcohol-dependent individuals. Nonetheless, diagnosis and treatment of AWS are often delayed until dramatic symptoms occur. Awareness of the early manifestations of AWS and the appropriate management are essential [1]. AWS occurs in 16-31% of intensive care unit (ICU) patients when sedation is discontinued [2]. AWS begins mainly 6-24 hrs after the last intake of alcohol, whose manifestations include tremors, agitation, sweating, hallucinations, tachycardia and hypertension. Approximately a third of AWS patients suffer from severe symptoms such as respiratory failure, delirium tremens, infections or gastrointestinal bleeding. Besides, mortality of untreated patients has been estimated to be 15% vs 2% in treated patients. Further-

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more, AWS patients admitted to the ICU have a higher mortality rate, longer hospital stay, longer duration of ventilator support, and higher costs vs patients without alcohol dependence [3,4]. The most severe complications of AWS are withdrawal seizures and delirium tremens. Drinking history and physical examination of the patients are usually sufficient for diagnosis [5].

Alcohol dependence and a history of withdrawal are significant risk factors for the occurrence of AWS. The benefit of withdrawal prophylaxis for patients is unproven, and in addition, the optimal means of identification, prevention and treatment of AWS remain uncertain [6]. The survival factors of AWS include the intensity of clinical manifestations and the presence of associated comorbidities [7]. Treatment of AWS aims to minimize or prevent severe manifestations such as seizure and delirium, and to facilitate long-term abstinence from alcohol for the patients [8]. AWS therapy should be standardized, individualized and based on symptom-triggered administration [2]. Benzodiazepines are the recommended first-line therapy for AWS. Intravenous ethanol is an alternative therapy in ICUs for emergency, however, it offers no advantage over diazepam with respect to efficacy or adverse sedative effects [9]. Other medications including carbamazepine, oxcarbazepine, valproic acid and gabapentin have less abuse potential but do not prevent seizures [10]. Although benzodiazepines remain the mainstay of treatment, patients with symptoms refractory to them may require addition of a rescue therapy [11].

A study reporting the effect of performance status, dysphagia and serum albumin level on the prognosis of esophageal cancer patients revealed that appropriate nutritional support could increase the probability of attaining complete tumor resection [12]. During the fasting period after surgery, the enteral nutrition tube might be removed by the patient when AWS occurs, thus, timely alleviation of the severe manifestations and cooperation of the patients are essential for nutrition support, which is beneficial for postoperative recovery. Pharmacotherapy may not always achieve satisfactory efficacy, therefore, alcohol vapor inhalation and enteral alcohol intake could be considered. But enteral alcohol intake might be a risk factor of anastomotic fistula, gastrointestinal bleeding, and stress ulcer.

As demonstrated in a case report, alcohol inhalation driven by oxygen is an effective and feasible method for postoperative AWS [13]. It is also beneficial in making expectoration easy. However, whether high concentration alcohol damages the pulmonary bronchial mucosa and the walls of pulmonary alveoli is a concern, and the blood alcohol concentration should be monitored during treatment [13]. As comparative studies between alcohol vapor and benzodiazepine for AWS are rare, a retrospective evaluation is presented herein for discussion, regarding efficacy and safety of alcohol vapor inhalation for AWS patients.

Methods

This study was approved by the Institutional Review Board of Xuzhou Central Hospital. As the patients with AWS were mentally unstable initially, the ethical and legal issues became ambiguous for clinical study, therefore, the informed consents were obtained from the guardians of the patients.

Selection of cases and general information

The gastroesophageal cancer patients, aged 61-75 years and treated in two hospitals (January 2011 to December 2016) were analyzed. Alcohol consumption of the patients was discontinued 1 day before surgery. Esophagectomy or gastrectomy were performed subsequently, then the patients were transferred to the surgical ICU with clear consciousness, stable respiratory function, heart rate, blood pressure and saturation of oxygen. All of the patients experienced 2-3 days of total parenteral nutrition, followed by 4-5 days of enteral nutrition, because oral feeding begun 7 days after the operation. Oxygen inhalation via nasal catheter, total parenteral nutrition, expectorant and proton pump inhibitor were also administered daily. Vital signs including respiratory rate, heart rate, blood pressure and saturation of oxygen were stable.

These patients presented with sweating, tremor, headache and anxiety 6-12 hrs after the operation. Chest X ray excluded obvious surgery-related complications. The patients were diagnosed as alcohol-dependent according to the Diagnostic and Statistical Manual of Mental Disorders (4th Edn, American Psychological Association, 1994). The revised Clinical Institute Withdrawal Assessment for Alcohol Scale (CIWA-Ar) and the Riker Sedation-Agitation Scale (SAS) were used for evaluation. The patients were routinely treated using diazepam in one hospital, as diazepam was their standard therapy, while the patients in the other hospital were treated regularly using alcohol vapor inhalation. Meanwhile, 1 patient did not respond to diazepam, and alcohol vapor was used for him, followed by significant efficacy, thus he was enrolled in alcohol vapor group accordingly. Therefore, data of 51 patients diagnosed as AWS was collected, with CIWA-Ar scores higher than 9, requiring timely treatment.

There was no history of medication for AWS before surgery, mental illness, hypertension, heart disease or other drug abuse. Patients suffering from acute delirium, epilepsy, other drug addictions, psychic trauma, kidney or liver damage were excluded. The general information of these patients was displayed in Table 1.

Therapeutic regimens

The enrolled patients received either diazepam intravenously or alcohol vapor inhalation after the onset of AWS. For patients in the alcohol vapor group, during the fasting time of 7 days, liquor for drinking containing different concentrations of alcohol was added to an oxygen humidification bottle instead of distilled water, which was driven by moderate flow of oxygen. Fifty ml of 60% alcohol was used twice a day in the first day after surgery. The patients calmed down quickly after the alcohol-oxygen vapor inhalation, and the CIWA-Ar scores dropped below 8 points. Then 50 ml of 30% alcohol was used twice a day in days 2-3. After that, the dose was changed to 50 ml of 15% alcohol in the next 3 days, which was used when the CIWA-Ar score raised above 8 and the patient asked for therapy, according to symptom-triggered procedure.

For patients in the diazepam group, the initial medication of 10 mg was given intravenously to alleviate the acute syndrome, and if the patient did not respond timely, another 20 mg would be given, until the patient was calmed down. Then diazepam was administered as symptom-triggered procedure thereafter. In detail, 5 mg of diazepam was chosen for patients with a score of 4-5, 10 mg for 6-9 and 20 mg for 10 or higher, while the daily maximum dosage was 60 mg. A rescue protocol was available if the patient did not respond to alcohol vapor and the CIWA-Ar scores remained higher than 9, and consisted of 10-20 mg diazepam administration.

Outcome measures

The primary outcomes were the change of manifestations and AWS scores from day 1 to day 7 in each group. Secondary outcomes included postoperative complications, chest or abdominal tube dwell time, length of postoperative hospital stay, and mental status during the fasting time. Besides, serum biochemical changes such as aspartate aminotranferases (AST), alanine aminotranferases (ALT) and alkaline phosphatase (ALP) were evaluated regularly. Furthermore, safety parameters were monitored daily by recording the vital signs, incidence and severity of adverse events, and postoperative complications. Meanwhile, the Epworth Sleeping Scale (ESS) was utilized for the evaluation of diazepam-related sleepiness.

Statistics

Continuous variables were recorded as mean± standard deviation , and the Student's t-test or Mann-Whitney U test were used for comparison of continuous variables between groups, while x^2 or the Fisher's exact test were used for categorical variables and enumeration data, using SPSS, version 19.0, statistical software (IBM, Armonk, NY, USA). A p value <0.05 was considered as statistically significant.

Table 1. Baseline characteristics of the patients before therapy

Characteristics	*Alcohol Vapor group (n=25) mean±SD*	*Diazepam group (n=26) mean±SD*	*p value*
Age (years)	61.8±8.1	62.0±7.4	0.670
Gender, n			0.984
Female	1	0	
Male	24	26	
Body Mass Index	26.7±4.6	25.9±5.1	0.533
Drinking history (years)	20.9±5.8	21.5±7.1	0.365
Family history of alcoholism, n	2	1	0.972
Surgical procedure, n			0.637
Esophagectomy	17	15	
Gastrectomy	8	11	
CIWA-Ar score	13.3±3.4	13.1±2.7	0.886
CIWA-Ar grade			0.941
Moderate (9-14 scores)	19	21	
Severe (≥15 scores)	6	5	
SAS score	5.3±0.6	5.2±0.6	0.770
ESS score	3.8±1.1	3.6±1.0	0.455
Serum biochemistry			
ALT (U/L)	70.4±41.6	72.8±49.1	0.511
AST (U/L)	119.6±90.1	110.7±60.5	0.627
ALP (U/L)	50.4±41.6	45.8±49.1	0.096

Continuous variables were presented by mean±standard deviation. CIWA-Ar: the revised Clinical Institute Withdrawal Assessment for Alcohol Scale. SAS: the Riker Sedation-Agitation Scale. ESS: the Epworth Sleeping Scale. AST: aspartate aminotranferase, ALT: alanine aminotranferase, ALP: alkaline phosphatase

Results

Patients of the two groups did not vary in terms of socio-demographic and clinical characteristics, initial AWS onset scores (ASA, CIWA-Ar), age, body mass index, family history of alcoholism, years of alcohol consumption and hepatic indices at baseline (ALT, AST, GGT) (Table 1).

Therapeutic efficacy

The patients in both groups showed good compliance. Renal function indices such as serum creatinine and blood urea nitrogen of the patients were within normal range during therapy. As for the patients in the alcohol vapor group, the AWS were alleviated in just 10-30 min after alcohol inhalation, and the patients showed clear consciousness, mild nausea and anxiety, without vomiting or hallucinations 3 days after therapy.

From day 2 to day 7, all patients in each group showed a significant decrease in scores of the SAS and CIWA-Ar, comparing with the scores in day 1, with a marked decrease in the severity of sweating, tremors, anxiety and agitation.

The patients in the alcohol vapor group showed significant difference with regard to the extent of decreased scores of CIAW-Ar, comparing with the diazepam group, and this advantage lasted from day 2 to day 7 after the operation (p=0.024, 0.006, 0.014, 0.001, 0.007 and 0.001, respectively) (Figure 1). However, no notable differences were revealed in terms of SAS scores, length of postoperative hospital stay, chest and abdominal drainage, and hepatic indices such as AST, ALT and GGT between the two groups (Table 2).

No patient asked for diazepam more than the maximum dose of 60 mg per day. In the present study, patients in the alcohol vapor group did not need a rescue diazepam. On discontinuation of treatment 7 days after surgery, no withdrawal symptoms were observed, and scores of the CIWA-Ar as well as SAS were mainly within normal range.

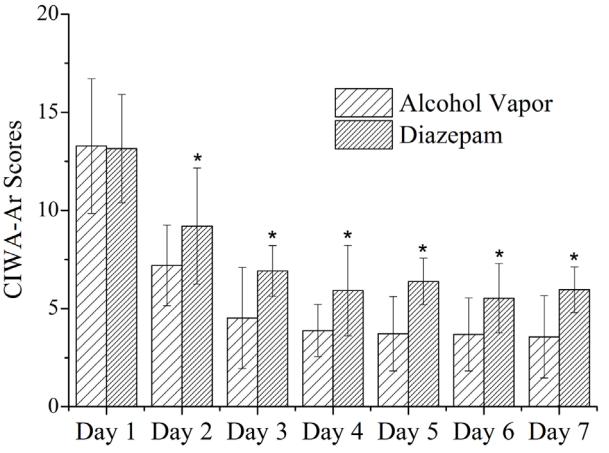

Figure 1. CIWA-Ar scores of the patients using alcohol vapor inhalation or diazepam during the fasting time of 7 consecutive days. * Compared with diazepam group, the difference was significant (p<0.05).

Table 2. Clinical parameters of the patients 7 days after therapy

Parameters	*Alcohol Vapor group (n=25) mean±SD*	*Diazepam group (n=26) mean±SD*	*p value*
Serum biochemistry			
ALT (U/L)	47.4±21.5	42.7±29.6	0.620
AST (U/L)	96.5±40.2	97.1±30.7	0.393
ALP (U/L)	35.1±21.9	40.8±26.1	0.078
SAS	4.2±0.5	4.6±0.8	0.049
Complications			0.600
Anastomotic fistula	0	1	
Respiratory infection	1	1	
Obvious esophageal reflux	2	2	
Atrial fibrillation	3	5	
ESS grade of sleepiness (scores)			0.002
Mild (7-11)	1	9	
Moderate (12-16)	0	2	
Severe (17-24)	0	1	
Chest drainage (days)	4.3±1.2	4.5±1.6	0.276
Abdominal drainage (days)	1.5±1.1	1.4±1.7	0.915
Postoperative hospital stay (days)	8.7±3.6	9.0±2.7	0.122
Satisfaction of patients, n (%)	24 (96.0)	16 (61.5)	0.008

Continuous variables were presented by mean±standard deviation

Safety and tolerability

No statistical differences were found in terms of postoperative surgery-related complications, such as anastomotic fistula, respiratory infection, obvious esophageal reflux or atrial fibrillation. However, the patients using diazepam showed distinctly higher ESS scores of sleepiness (Table 2), comparing with the patients receiving alcohol vapor, which is mainly ascribed to diazepam-related side effects. Furthermore, the amount of alcohol and diazepam could be gradually reduced along with the decreased AWS scores, in accordance with symptom-triggered approach, which might be useful to diminish the side effects and potential harm to patients. However, it could not be elucidated in this study for lack of long-term follow up.

Discussion

Patients admitted to the ICU with AWS have an increased hospital stay and mortality. Guideline regarding this issue is not available, leading to tremendous variability in clinical practice. A certain proportion of patients are benzodiazepines-resistant, and an early multimodal approach might be beneficial for these patients [14]. Patients at risk for AWS can be safely and effectively managed with a standardized, symptom-triggered approach, and moreover, this approach decreases the amounts of benzodiazepines and haloperidol administered to patients at risk for AWS [15]. Furthermore, symptom-triggered treatment is recommended by German guidelines on alcoholism, which could improve the quality of patient care [16].

Severe alcohol withdrawal symptoms are often refractory to standard doses of benzodiazepines, which requires aggressive treatment. A review indicates that benzodiazepines remain a treatment choice, with diazepam having the most favorable pharmacokinetic profile, however, the roles of phenobarbital, dexmedetomidine, and ketamine remain unclear [17]. It is reported that inflammation and nonspecific immune activation are correlated with depression and cancer growth [18]. Therefore, timely psychological intervention along with alcohol vapor therapy might be beneficial to cancer patients.

Inhalation of alcohol vapor driven by oxygen changes the surface tension of the foam, which could be used to alleviate acute pulmonary edema [19]. When AWS occurs, intake of some alcohol is proved to be very effective [20]. But a certain fasting time is necessary for patients after esophagectomy or gastrectomy, in order to diminish the risk of gastroesophageal anastomotic fistula. Additionally, intravenous ethanol in the treatment of AWS could be potentially dangerous and unsafe [21], as intravenous alcohol has a relatively narrow therapeutic window, which leaves patients at risk for ethanol toxicity. A study comparing the efficacy of lorazepam and ethanol for alcohol withdrawal prevention revealed that cardiac and AWS complications in patients using enteral ethanol and lorazepam were similar [22].

On the other hand, alcohol-dependent patients have significantly higher risks of a comprehensive spectrum of somatic diseases and mortality, comparing with the general population [23]. Besides, alcohol exposure is associated with increased lung infections and decreased mucociliary clearance [24]. Furthermore, inhaled alcohol initially bypasses first-pass metabolism and rapidly reaches the circulation and the brain, suggesting that the route of administration may be associated with increased risk of addiction [25]. A review indicates that alcohol vapor inhalation results in measurable biomarkers of acute alcohol exposure, without significantly elevated blood alcohol concentrations, but the vulnerable adolescents may be at risk of alcohol associated problems [25]. However, studies regarding long-term effect of inhaled alcohol in humans is truly insufficient. It is noteworthy that the occurrence of esophageal squamous cell carcinoma is associated with alcohol consumption [26]. Therefore, the most appropriate goal for the majority of people affected with AWS is permanent abstinence from alcohol. Psychosocial intervention should be considered, in addition to pharmacotherapy. Besides, internet-based remote intervention is helpful to alleviate surgery-related pain after esophagectomy [27], which could be utilized for AWS patients to dry out gradually during post-discharge follow-up.

Benzodiazepines are still the first-line therapy for patients experiencing moderate to severe AWS under most circumstances [28]. However, for those patients who do not respond to the first-line management, alcohol vapor could be considered. The patients with AWS will be mentally unstable initially, and, as a result, the ethical and legal issues are ambiguous for clinical trial [29], therefore, studies in terms of alcohol vapor inhalation are limited.

In summary, the short-term feasibility and safety of alcohol vapor inhalation for AWS was tentatively evaluated in this retrospective analysis. Nevertheless, multicenter studies concerning inclusion/exclusion criteria, standard for risk-benefit evaluation, long-term advantages and potential harm of alcohol vapor are required.

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Conflict of interests

The authors declare no confict of interests.

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