JMMS 2015, 2(1): 43- 54. **Research article**

Alcohol withdrawal – therapeutical management in surgical patients with upper intestinal bleeding

Bălălău Cristian[1], Cobani Oana Denisa[2], Trambitasu Gloria[1], Popescu Bogdan[3], Carolina Negrei[4], Scăunașu Răzvan Valentin [3]

[1] Carol Davila University of Medicine and Pharmacy, Department of General Surgery, St. Pantelimon Hospital
[2] St. John Emergency Hospital, Bucur Maternity, Bucharest
[3] Carol Davila University of Medicine and Pharmacy, Colțea Clinical Hospital, Bucharest
[4] Carol Davila University of Medicine and Pharmacy, Faculty of Pharmacy, Department of Toxicology
Corresponding author: Bălălău Cristian, e-mail: dr.balalau@gmail.com

Running title: Alcohol withdrawal and upper intestinal bleeding
Keywords: upper intestinal bleeding, alcohol withdrawal, surgical patients, psyhological/ psychiatric symptoms

www.jmms.ro 2015, Vol. II (issue 1): 43- 54.
Date of submission: 2014-11-19; **Date of acceptance**: 2015-01-16

Abstract

Psychological dependence involves a desire to use a drug to avoid the unpleasant withdrawal syndrome that results from cessation of exposure to it. Alcohol withdrawal syndrome is one of the most feared complications of alcohol addiction and sometimes can be fatal if not treated properly. Withdrawal syndrome is characterized by neurological hyperexcitability, which can lead to severe psychological and neurological symptoms. A survey was conceived in order to monitor the efficiency of several drug associations (Clonidine, Midazolam, IV ethanol), which were administered at the beginning of intensive therapy admission of achohol addicts. By comparing the postoperative evolution parameters and complications incidences for these patients (such as the hospitalization duration in AIT department, the tracheobronchitis incidence, complications as sepsis, pneumonia and cardiac complications), we managed to determine which treatment is the most beneficial for these cases. Benzodiazepines are frequently used for pharmacological therapy of alcohol addicted patients. In our study Midazolam was very efficient, compared to other therapies. When administered for a maximum of 7 days, the inccidence of side effects remains minimal.

Introduction

Alcohol withdrawal syndrome is one of the most feared complications of alcohol addiction and sometimes can be fatal if not treated properly, mortality reaching up to 15%. Withdrawal syndrome is characterized by neurological hyperexcitability due to reduced GABA-ergic activity and increased glutaminergic and noradrenergic activity.

Excess alcohol consumption is a serious health problem, that not only affects the mental health of the persons concerned, but may contribute to multi-systemic structural and/ or functional alterations, such as digestive tract organs and annexes, heart and so forth.

In this study we intend to establish the benefit of the multiple mesures and drugs administered in order to prevent complications for these high risk patients.

Matherials and Methods:

A survey was conceived in order to monitor the efficiency of several drug associations, which were administered at the beginning of intensive therapy admission (Clonidine, Midazolam, i.v. ethanol). By comparing the postoperative evolution parameters and complications incidences for these patients (such as the hospitalization duration in AIT department, the tracheobronchitis incidence, complications as sepsis, pneumonia and cardiac complications), we managed to determine which treatment is the most beneficial for these cases.

Postoperative withdrawal syndrome prevention and treatment have been tested by substitution with alcohol (1-2 mg/dl), monotherapy with Midazolam (0.2-0.4mg/kg/h) or Clonidine (1-2mg/dl). 150 patients were classified in 3 groups whom was administered one of the 3 forms of treatment. The results of group which received alcohol substitution were considered reference for the comparison.

Results:

Statistical analysis of the results revealed that the group that received Midazolam monotherapy, showed best postoperative results, followed by a reduced number of withdrawal syndrome symptoms (with 45%), a shorter duration of hospitalization in AIT department (with 5.2 days), less respiratory complications, delirium tremens and lower mortality (6% versus 12%), when compared with i.v. achohol group.

The patients in the group that received Clonidine, necessitated supplementary sedation, usually with benzodiazepines. Even so, the results were still better then the group with received alcohol sustitution, with 32% reduction of withdrawal syndrome symptoms,a shorter duration of hospitalization in AIT department (with 4.5 days)and lower mortality (8% versus 12%).

Discusions

Alcohol addiction prevalence in surgical patients is very high. Addiction is a compulsion for rewarding stimuli (associated with positive reinforcement), which is essentially an intense desire or craving. Psychological dependence involves a desire to use a drug or perform a behavior to avoid the unpleasant withdrawal syndrome (negative reinforcement) that results from cessation of exposure to it (1, 2, 3). Alcohol withdrawal syndrome is one of the most feared complications of alcohol addiction and sometimes can be fatal if not treated properly, mortality reaching up to 15% (1, 4). Addicted patients have a higher morbidity and exhibitmore complications, such as infections and cardiovascular complications. In these patients, the alcohol recede during hospitalization, the surgical stress, the hypotension, the hypoxia or the perioperative pain, may hasten the onset of withdrawal syndrome (1, 5, 6).

Surgeons tend to under-recognize psychiatric disorders until they interfere with evaluation and treatment. Often, a patient’s psychiatric history is not obtained or considered until problems arise post-

operatively. Chronic alcohol abuse and withdrawal syndrome, are associated with severe postoperative complications as pneumonia, infections, difficult healing, sepsis, cardiac complications (heart failure, ischemia, arrhythmias) (7). They also develop severe hemorrhages and require a higher volume of blood for transfusions (7, 8).

Withdrawal syndrome is characterized by neurological hyperexcitability due to reduced GABAergic activity and increased glutaminergic and noradrenergic activity. There are also numerous mechanisms of cortical inhibitory pathways depression, leaving the excitatory pathways to function uncontrolled (1, 9, 10).

In these patients, postoperative complications risk can be minimized. Tonnensen proved in one survey, that a month withdrawal program that includes disulfiram, before surgery, decreases postoperative complications in patients that undergo gastrointestinal surgery (11). Minimizing intraoperative stress also decreases postoperative morbidity (12). Also, an important part belongs toadministrationof agents that decrease the production of cortisol (small alcohol doses, morphine, ketoconazole, propofol) (13).

Postoperative withdrawal syndrome prevention in patients with UIB

Part of the patients with UIB requires emergency surgery and therefore withdrawal syndrome prevention shortens the hospitalization in AIT department. During a survey, were used and compared more drug associations, which were administered at the beginning of intensive therapy admission: flunitrazepam-clonidine, chormethiazol-halperidol, flunitrazepam-haloperidol or ethanol, then being appreciated the hospitalization duration in AIT department, the tracheobronchitis incidence, complications as sepsis, pneumonia and cardiac complications. The patientswith chlormethiazol-haloperidol, developed tracheobronchitis (14). Although benzodiazepines are recommended as first line treatment in withdrawal syndrome prevention, administration of iv ethanol, represents a prophylactic alternative in many AIT departments. Many claim that it would realize prevention, without excessive

sedation as benzodiazepines. A comparison survey was realized, focusing on sedative effects. The survey conclusion was that ethanol has no advantage as against diazepam and that its efficiency was not proved (2, 15). Another survey proved that ethanol vapors inhalation, may reduce postoperative ethanol withdrawal syndrome symptoms if diazepam treatment doesn't work (16). Clonidine efficiency has been evaluated in intrathecal or oral administration as a supplement to spinal anesthesia with lidocaine, in postoperative withdrawal syndrome prevention. The conclusion was that 150 mg of intrathecal/oral clonidine prevent the onset of postoperative withdrawal syndrome, better than 10 mg of oral diazepam (17, 18).

Treatment for the patient hospitalized for UIB, that presents ethanol withdrawal syndrome

An important percentage of the patients with UIB, presents at hospital admission or develop during hospitalization ethanol withdrawal, due to the high rate of chronic ethanol consumption in this group of patients.

Severe withdrawal syndrome risk factors are: the chronic alcohol consumption, history of generalized convulsions or delirium tremens, while symptoms as anxiety, unrest, tremor, excessive perspiration, altered state of consciousness, hallucinations, show a severe withdrawal syndrome (19). Supportive measures have a major part in ethanol withdrawal patient management. Reevaluation of the patient's state has to be done repeatedly, since many symptoms of the withdrawal coexist, can be mimed or complicated by other conditions, infections, trauma, metabolic disorders, hepatic failure, digestive hemorrhages. When we confront with altered mental state without a defined cause, we have to perform a lumbar puncture or a CT scan, in order to exclude other diagnostic possibilities, especially in patients with fever and withdrawal syndrome.

The patients need to be placed into a quiet place, in lateral position (swimmer position). It may be necessary for those patients who suffer from delirium tremens, for their protection and for those who

take care of them. Blood volume deficits have to be calculated and replaced; if there are no contraindications, isotonic i.v. fluids are administered until the patients become clinically euvolemics. Before administering solutions that contain glucose, Thiamine 100 mg iv or im have to be administered in order to decrease the risk of Wernicke encephalopathy or Korsakoff syndrome.

Table I

Syndrome	Clinincal menifestations	Time
Minor symptoms: They ameliorate in 24-48 h	Tremors, anxiety, headaches, diaphoresis, palpitations, gastrointestinal symptoms, diarrhea, anorexia	6-36 h
Convulsions- in 3% of the chronic alcohol drinkers	Generalized convulsions, tonic-clonics, rare status epileptic (3% of those with seizures)	6-48
Hallucinations – start in 12-24h of abstinence and disappear in 24-48 h (when delirium tremens starts)	The hallucinations are frequently visual; they can also be acoustic and tactile.	48-96 h
Delirium tremens- in 5%; mortality 5% especially because of the arrhythmias or the aspiration pneumonia	Delirium tremens produces hallucinations, disorientation, tachycardia, arterial hypertension, fever, unrest, and diaphoresis. The patients are dehydrated because of the diaphoresis, hyperthermia, vomit, and tachypnea. Hypokalemia is frequent.	

Multivitamins and folate are used as a regular base. Potassium, magnesium, glucose, phosphate deficiencies have to be corrected if necessary. Among the criteria that lead to AIT admission, are:

- Patients older than 40 years, with concurrent diseases like heart failure, myocardial ischemia and pectoral angina;

- Hidroelectrolytic imbalances with EEG alterations, alterations of the acid base balance;
- Hemodynamic instability, respiratory failure, hypoxemia, hypercapnia;
- Severe infections;
- Gastrointestinal pathology, pancreatitis, superior digestive hemorrhage, peritonitis, persistent hyperthermia;
- Rhabdomyolysis, renal failure, delirium tremens history.

Table II- Doses

Drug name	Dose in mg
Chlordiazepoxide	25
Diazepam	5
Lorazepam	0.75-1
Oxazepam	15

"Clinical Institute Withdrawal Assessment for Alcohol" revised score (CIWA-Ar) uses 10 terms to quantify the severity of withdrawal syndrome and allows the classification of the patients in 3 different categories: mild (no hospitalization required), moderate, severe. Severe forms require hospitalization in AIT hospital department (20, 21, 22).

This score is useful but not sufficient, most of the patients having associated comorbidities. It does not take in consideration delirium tremens, which could have other etiologies beside ethanol withdrawal. It's a numeric scale which assigns to symptoms a value regarding their severity, but it's quite subjective (23, 24, 25). In refractory withdrawal, barbiturates are associated, especially phenobarbital. Propofol may be also used. The usage of phenobarbital and propofol, requires AIT monitoring and mechanical ventilation (26). Among other pharmacological agents which have been proposed is Baclofen, a selective agonist of the GABA – B receptor and owns antispasmodic effects through this mechanism. It seems to be efficient as benzodiazepines (27).

The most used antipsychotics are phenothiazines and butirophenones, which decrease convulsions but have to be used with extreme caution. Antiepileptic drugs: in studies is used

carbamazepine which is thought to be as efficient as lorazepame, but there is not enough evidence to certify its use (23, 28, 29, 30).

Chlormethiazole is a drug related to thiamine, which acts as a sedative-hypnotic, muscle relaxant and anticonvulsant. Other proposed agents are sodium valproate, gabapentin, gama-hydroxybutyrate (1, 31, 32). Other drugs, as beta-agonists or neuroleptics might bring some benefits, but cannot be used in monotherapy (33).

Beta-blockers increase the risk of hallucinations and clonidine increases the frequency of nightmares, while their efficiency is not well enough documented. Neuroleptic drugs increase the risk of convulsions. Magnesium sulfate or meprobamate have numerous side effects and their usage is not recommended. There are no specific recommendations regarding hydration. Excessive intake of sodium containing solutions, increases the risk of pulmonary edema in patients with cardiac diseases. B1 vitamin deficiency is frequent and may cause severe complication, that's why oral intake of B1 vitamin is recommended, in high doses, in order to compensate poor absorption. IV administration is preferred if the patient has a seriously altered nutritional status or in severe complications as Gayet-Wernicke encephalopathy, even if there were reported important anaphylactic reactions after vitamin injection.

Reestablishing proper hydroelectrolitic balance, along with continuous monitoring of vital functions and respiratory support, if necessary, has the effect of decreasing mortality in delirium tremens below 3% (19, 34- 36).

Conclusions

Benzodiazepines are frequently used for pharmacological therapy of alcohol addicted patients. In our study Midazolam was very efficient, compared to other therapies. When administered for a maximum of 7 days, the inccidence of side effects remainsminimal (19). They act on GABA-ergic receptors. Lorazepam, Oxazepam or Tamazepam are used frequently in patients with advanced hepatic

diseases, because they lack metabolic effects and they have a short half-life. Oral administration is the preferred way of administration. If bewildered, the i.v. way is used. If not possible, Lorazepam i.m. is used. Young patients with little comorbidity may be only slight sedated. Old patients, with comorbidities must be sedated and monitored in AIT department. Symptomatic therapy is reserved for withdrawal symptoms and represents the choice for young patients. They receive lower doses of benzodiazepines and the treatment period is shorter.

Acknowledgment

„This paper was co-financed from the European Social Fund, through the Sectorial Operational Programme Human Resources Development 2007-2013, project number POSDRU/159/1.5/S/138907 "Excellence in scientific interdisciplinary research, doctoral and postdoctoral, in the economic, social and medical fields - EXCELIS", coordinator The Bucharest University of Economic Studies”.

References

1. Subedi A, Bhattarai B. Intraoperative Alcohol Withdrawal Syndrome: A Coincidence or Precipitation? *Case Rep Anesthesiol. 2013*, 2013: 761527.
2. Spies CD, Rommelspacher H. Alcohol withdrawal in the surgical patient: prevention and treatment. *Anesth Analg. 1999*, 88(4): 946-54.
3. Malenka RC, Nestler EJ, Hyman SE. "Chapter 15: Reinforcement and Addictive Disorders". In Sydor A, Brown RY. Molecular Neuropharmacology: A Foundation for Clinical Neuroscience (2nd ed.) , 2009, New York: McGraw-Hill Medical. pp. 364–375. ISBN 9780071481274.
4. Claudia S, Hans R. Alcohol withdrawal in the surgical patient: prevention and treatment. *Anesthesia and Analgesia 1999*, 88: 946–954.
5. Spies CD. Kip MJ. Neumann T. New strategies to detect alcohol use disorders in the preoperative assessment clinic of a german university hospital. *Anesthesiology 2008*, 109(2): 171–179.

6. Spies C, Tønnesen H, Andreasson S, Helander A, Conigrave K. Perioperative morbidity and mortality in chronic alcoholic patients. *Alcoholism 2001,* 25(5): 164S–170S.
7. de Wit M, Jones DG, Sessler CN, Zilberberg MD, Weaver MF. Alcohol-Use Disorders in the Critically ill Patient. *Chest 2010,* 138(4): 994–1003.
8. Spies C, Tønnesen H, Andreasson S, Helander A, Conigrave K. Perioperative morbidity and mortality in chronic alcoholic patients. *Alcohol Clin Exp Res. 2001,* 25(5): 164S–170S.
9. Littleton J. Neurochemical mechanisms underlying alcohol withdrawal. *Alcohol health and research world 1998*, 22(1): 13- 24.
10. Patkar AA, Gopalakrishnan R, Naik PC, Murray HW, Vergare MJ, Marsden CA. Changes in plasma noradrenaline and serotonin levels and craving during alcohol withdrawal. *Alcohol and Alcoholism 2003,* 38(3): 224–231.
11. Tonnesen H, Rosenberg J, Nielsen HJ, Rasmussen V, Hauge C, Pedersen IK, Kehlet H. Effect of preoperative abstinence on poor postoperative outcome in alcohol misusers: randomised controlled trial. *BMJ. 1999*, 318(7194): 1311- 1316.
12. Spies C, Eggers V, Szabo G, Lau A, von Dossow V, Schoenfeld H, Althoff H, Hegenscheid K, Bohm B, Schroeder T, Pfeiffer S, Ziemer S, Paschen C, Klein M, Marks C, Miller P, Sander M, Wernecke KD, Achterberg E, Kaisers U, Volk HD. Intervention at the level of the neuroendocrine-immune axis and postoperative pneumonia rate in long-term alcoholics. *Am J Respir Crit Care Med. 2006*, 174(4): 408–414.
13. von Dossow V, Baur S, Sander M, Tonnesen H, Marks C, Paschen C, Berger G, Spies CD. Propofol increased the interleukin-6 to interleukin-10 ratio more than isoflurane after surgery in long-term alcoholic patients. *J Int Med Res. 2007*, 35(3): 395–405.
14. Spies CD, Dubisz N, Funk W, Blum S, Müller C. Prophylaxis of alcohol withdrawal syndrome in alcohol-dependent patients admitted to the intensive care unit after tumour resection. *Br J Anaesth. 1995*, 75(6): 734-9.

15. Weinberg JA, Magnotti LJ, Fischer PE, Edwards NM, Schroeppel T, Fabian TC, Croce MA. Comparison of intravenous ethanol versus diazepam for alcohol withdrawal prophylaxis in the trauma ICU: results of a randomized trial. *Postgrad Med. 2006*, 119(2): 46-55.
16. Zhang P, Yang Z, Zhao Y, Liu Y, Zhang L, Shao G. Inhalation of alcohol vapor driven by oxygen is a useful therapeutic method for postoperative alcohol withdrawal syndrome in a patient with esophageal cancer: a case report. *Alcohol Alcohol. 2011*, 46(4): 424-6.
17. Dobrydnjov I, Axelsson K, Berggren L, Samarütel J, Holmström B. Intrathecal and oral clonidine as prophylaxis for postoperative alcohol withdrawal syndrome: a randomized double-blinded study. *Anesth Analg. 2004*, 98(3): 738-44.
18. Ip Yam PC, Forbes A, Kox WJ. Clonidine in the treatment of alcohol withdrawal in the intensive care unit. *Chirurg. 1998*, 69(1): 72-6.
19. Alcohol withdrawal syndrome: how to predict, prevent, diagnose and treat it. Prescrire Int. 2007 Feb, 16(87): 24-31.
20. Ramos R, Mallet T, Divittis A, Cohen R. Predictors of Severity of Alcohol Withdrawal in Hospitalized Patients. *J Clin Med Res. 2013*, 5(5): 376–380.
21. Bayard M, McIntyre J, Hill KR, Woodside J Jr. Alcohol withdrawal syndrome. *Am Fam Physician. 2004*, 69(6): 1443–1450.
22. Myrick H, Anton RF. Treatment of alcohol withdrawal. *Alcohol Health Res World. 1998*, 22(1): 38-43.
23. Shiven B. Chabria Inpatient management of alcohol withdrawal: a practical approach. *Signa Vitae 2008*, 3(1): 24- 29.
24. Sullivan JT, Sykora K, Schneiderman J, Naranjo CA, Sellers EM. Assessment of alcohol withdrawal: The revised Clinical Institute Withdrawal Assessment for Alcohol scale (CIWA-Ar). *Br J Addict 1989*, 84: 1353- 7.
25. Bostwick JM, Lapid MI. False positives on the clinical institute withdrawal assessment for alcohol-revised: is this scale appropriate for use in the medically ill? *Psychosomatics 2004*, 45: 256-61.

26. McCowan C, Marik P. Refractory delirium tremens treated with propofol: A case series. *Crit Care Med 2000*, 28: 1781- 4.
27. Muzyk AJ, Leung JG, Nelson S, Embury ER, Jones SR. The role of diazepam loading for the treatment of alcohol withdrawal syndrome in hospitalized patients. *Am J Addict. 2013*, 22(2): 113-8.
28. Carlson RW, Keske B, Cortez A. Alcohol withdrawal syndrome: alleviating symptoms, preventing progression. *J Crit Illness 1998*, 13(5): 311- 7.
29. Saitz R, O'Malley SS. Pharmacotherapies for alcohol abuse. Withdrawal and treatment. *Med Clin North Am 1997*, 81: 881-907.
30. Mayo-Smith MF, Beecher LH, Fischer TL, Gorelick DA, Guillaume JL, Hill A, Jara G, Kasser C, Melbourne J; Working Group on the Management of Alcohol Withdrawal Delirium, Practice Guidelines Committee, American Society of Addiction Medicine.et al, editors. Management of alcohol withdrawal delirium: an evidence-based practice guideline. *Arch Intern Med 2004*, 164: 1405-12.
31. Morgan MY. The management of alcohol withdrawal using chlormethiazole. *Alcohol 1995*, 30: 771-4.
32. Myrick H, Malcolm R, Brady KT. Gabapentin treatment of alcohol withdrawal. *Am J Psychiatry 1998*, 155: 1632.
33. Perry EC. Inpatient management of acute alcohol withdrawal syndrome. *CNS Drugs. 2014*, 28(5): 401-10.
34. Muzyk AJ, Leung JG, Nelson S, Embury ER, Jones SR. The role of diazepam loading for the treatment of alcohol withdrawal syndrome in hospitalized patients. *Am J Addict. 2013*, 22(2): 113-8.
35. Moore RD, Bone LR, Geller G, Mamon JA, Stokes EJ, Levine DM. Prevalence, detection, and treatment of alcoholism in hospitalized patients. *Journal of the American Medical Association 1989*, 261(3): 403–407.
36. Huber FT, Bartels H, Siewert JR. Treatment of postoperative alcohol withdrawal syndrome after esophageal resection. *Langenbecks Arch Chir Suppl II Verh Dtsch Ges Chir. 1990*: 1141- 3.