Case Report

Crit Care & Shock (2011) 14:84-88

Prolonged dexmedetomidine infusion to facilitate drug detoxification and withdrawal in patients with multiple drugs addiction

Surjya Prasad Upadhyay, Piyush Narayan Mallick, Waleed Mohamed Elmatite, Raj Kumar Singh

Abstract

Many patients are admitted to intensive care unit for acute intoxication, serious complication of overdose or withdrawal symptoms of illicit drugs. Acute withdrawal of drug with addiction potential is associated with sympathetic over-activity leading to marked psychomimetic disturbances. Acute intoxication or withdrawal of such drugs are often associated with life threatening complication which requires ICU admission and necessitates prolonged sedative-analgesic medications, whereas weaning from which is often complicated by withdrawal and other psychomimetic symptoms. Dexmedetomidine, an α2 agonist has been used successfully to facilitate withdrawal and detoxification of various drugs and also to control delirium in ICU patients. Herein we reported two cases of chronic substance abuse patients admitted with acute overdose complication leading to prolonged ICU course requiring sedative-analgesic, and later the drug withdrawal related symptoms further complicated the weaning process. Dexmedetomidine infusion was successfully used as sedative-analgesic to control the withdrawal related psychomimetic symptoms and to facilitate smooth detoxification and weaning from opioid and other sedatives

Key words: Opioid dependence, substance abuse, facilitate, withdrawal symptoms, dexmedetomidine.

Introduction

Substance abuse is considered a maladaptive pattern of substance dependent. The most severe form of abuse is characterized by physiological and behavior symptoms related to substance use. Most common illicit drugs are alcohol, marijuana, cocaine, opioids, benzodiazepine and amphetamine. The presenting symptoms are often multiple, misdiagnosed and often inconsistent because of variable dosage and adulteration of drugs, mixed-intoxication-withdrawal state and sometime adverse or idiosyncratic reactions. Acute withdrawal of these illicit drugs are associated with agitation, restlessness, insomnia, generalized muscle and joint pain anxiety, dysphoria and various psychomimetic disturbances (1) and most of these symptoms are caused by central nervous system (CNS) hyperactivity and are very distressing which frequently leads to relapse to drug use. (2,3) Acute intoxication and withdrawal of some illicit drugs are often associated with severe and life threatening complication such as rhabdomyolysis, (4) acute renal failure, (4,5) neurological complication, (5) acute pulmonary edema, (6) ARDS, (6,7) etc, which not only prolonged the ICU stay but also make the withdrawal and detoxification process complex. In addition, critically ill patients who received long-term sedative-analgesic therapy in ICU developed functional tolerance and experience withdrawal symptoms similar to those of patients addicted to narcotics, alcohol or other stimulant drugs. (8-10) So far, we don't have standard guideline or recommendation on the use of sedation-analgesia in patients with drug addiction problems or prone to have addiction.

From Al Jahra Hospital, MOH, Kuwait (Surjya Prasad Upadhyay, Piyush Narayan Mallick, Waleed Mohamed Elmatite, and Raj Kumar Singh)

Address for correspondence:
Dr. Surjya Prasad Upadhyay
Department of Anesthesia and Intensive Care
Al-Jahra Health district
PO Box 40206, Alsafat 01753, Kuwait
Tel: +965-245-82-040
Fax: +965-245-76-805
Email: run77in@yahoo.com

Dexmedetomidine is gaining popularity as sedative-analgesic in ICU and has been used successfully to control withdrawal symptoms associated with varieties of substance abuse and dependences including withdrawal of prolonged sedation in ICU. (1,2,10-14)

We reported two cases, one of opioid addiction (heroin) and another multiple drug addiction, admitted with acute overdose complication which led to prolonged ICU stay; weaning from the ventilator and other supportive care in ICU was complicated by the withdrawal related symptoms which were managed successfully with prolonged dexmedetomidine infusion.

Case report

Case 1

A 32-year-old male, addicted to heroin for 3 years, was found in semiconscious, unresponsive state in his room and brought by family members to emergency room in a state of shock with gasping respiration. He was hypothermic, hypotensive with blood pressure of 70/45 mmHg, heart rate of 128 per min, shallow respiration with a rate of 12/min, hypoxemic with oxygen saturation 88% on 10 liter oxygen. Initial evaluation was suggestive of acute opioid overdose as patient was a known heroin addict; there were pin point pupil with hypoventilation and hypothermia. Blood sample were sent for toxicology laboratory. After 0.4 mg of intravenous naloxone in increment of 0.1 mg boluses, patient's sensorium level improved and respiration became more normal with improvement in oxygen saturation, but he remained hypotensive. Fluid resuscitation was continued, vasopressor (noradrenaline infusion) added and an infusion of naloxone was started. Patient was shifted to intensive care unit (ICU) for further observation and treatment. Blood gas analysis showed persistent metabolic acidosis. Hematological parameters were normal but biochemistry revealed signs of acute rhabdomyolysis with marked raise in creatinine kinase, hyperkalemia, high blood urea nitrogen (BUN) and creatinine. Aggressive hydration with alkalinazation and force diuresis started. Despite the aggressive therapy for about 3 hours, patient went into anuria with marked rise in creatinine. Patient started to be agitated, restless, with complained of generalized body and joint pain and his respiration became labored, auscultation revealed bilateral diffuse crepitation. Patient was intubated and connected to mechanical ventilator with propofol and remifentanil infusion as sedative-analgesic. Urgent chest x ray confirmed acute pulmonary edema. Nephrology consultation was sought for urgent dialysis, naloxone infusion was stopped. Although the metabolic parameters improved after urgent dialysis but the ventilatory parameters worsened requiring higher oxygen and high level of positive end expiratory pressure (PEEP). Echocardiographic evaluation revealed normal cardiac function. The lung condition worsened further over the next couple of days with severe hypoxemia consistent with acute respiratory distress syndrome (ARDS). Patient was managed with lung protective ventilatory strategy with infusion of methyl prednisolone 1 mg/kg/day along with other supportive care in the form of regular dialysis, antibiotic, nutritional support, chest physiotherapy etc. In view of prolonged ventilatory support, the sedation-analgesia regime was changed into midazolam and morphine. After about 10 days, respiratory parameters were gradually improved, and kidney function started to recover. Patient was successfully extubated and liberated from ventilator when he passed spontaneous breathing trial (SBT) on day 15. Few hours after extubation patient started to show signs of opioid withdrawal with agitation, generalized aches and pain all over the body, lacrymation, increasing restlessness, tachypnea, tachycardia and hypertension. Trial of intravenous haloperidol failed to control his agitation. Patient was reloaded with shorter acting opioid: remifentanil, to which he responded. His psychomimetic and other physical symptoms were modestly controlled with 400 microgram/hour of remifentanil, but he required increasing doses of remifentanil and used to be restless, agitated on slightest reduction of remifentanil infusion. Trial of midazolam and propofol infusion failed to reduce the remifentanil requirement. On day 18; dexmedetomidine infusion was added after a loading dose of 50 microgram over 30 min, and remifentanil infusion was successfully tapered off over 4 hours. Patient was managed with continuous infusion of dexmedetomidine 0.7 microgram/kg/hr, and lorazepam added for night comfort. On day 5 of dexmedetomidine infusion, we added oral clonidine 25 microgram every 4 hour and slowly tapered off dexmedetomidine over the next 2 days. Patient remained conscious, oriented and calm throughout the dexmedetomidine treatment. Finally he was shifted to rehabilitation centre on oral clonidine.

Case 2

A 28-year-old male with known history of alcoholism and multiple substance abuse, was brought to emergency room in comatose state and shock with vital signs: pulserate 94/min, BP 70/50 mmHg, oxygen saturation 75% on room air, and respiratory rate 20/min. Chest auscultation revealed bilateral diffuse crepitations. Blood gas analysis (BGA) showed severe lactic acidosis (lactate 5.7 mmol/L) with severe hypoxemia (our BGA machine was calibrated with lactate measurement). Patient was intubated without any sedative or analgesic as he was deeply comatose; there were visible food particles in the hypo-pharynx suggestive of aspiration of gastric content. An empty strip of diazepam tablet was found in his pocket. Blood and urine sample were taken for toxicology, gastric lavage was done, intravenous flumazenil (0.5mg) was given at a dose of 0.1 mg every 3 min. Patient responded partially to fluid and flumazenil and started to fight with the tube and ventilator. He was paralyzed with cisatracurium and sedated with propofol and sufentanil. A low dose noradrenaline infusion was started to maintain his blood pressure. Chest x ray was suggestive of massive aspiration (bilateral infiltrate, more on right); echocardiography revealed no cardiac abnormality with normal ejection fraction. Haemogram, liver and kidney profile were normal. Patient's lungs condition worsened over 2-3 days with features suggestive of ARDS. He was managed with lung protective ventilatory strategy, along with antibiotic, methyl prednisolone 1 mg/kg/day and other supportive care.

His blood and urine sample were positive for benzodiazepine, opioid (heroin), alcohol and cocaine. In view of prolonged ventilatory support the sedation-analgesia regimen was changed into morphine-midazolam combination. The respiratory parameters improved significantly over 10 days. For the weaning process, daily SBT after interruption of sedation-analgesia was tried. Patient used to be very restless, agitated, and delirious like state with marked tachycardia, tachypnea, and hypertension necessitating resumption of sedation and sometime even needed paralysis too. The sedation-analgesia regimen was changed into shorter acting propofol and remifentanil combination for easy titration. Many attempts of SBT to wean from ventilator went into vain. On day 15 dexmedetomidine infusion was added at a rate of 0.7 microgram/kg/hr after a loading dose of 0.5 microgram/kg over 15 min. Propofol-remifentanil infusion was gradually tapered off over 6 hours. Long acting benzodiazepine (lorazepam) 2 mg was added for night sedation. The patient was maintained on dexmedetomidine infusion for a couple of days. Finally he passed SBT and was successfully extubated on day 18. Patient was maintained on dexmedetomidine infusion for another day before being started of oral clonidine which was bridged with dexmedetomidine infusion. Finally patient was shifted to rehabilitation centre on oral clonidine.

Discussion

One of the problem encountered while treating critical illness on ventilator in patients already addicted to opioid or other drugs of abuse is the development of dependence and withdrawal process itself and these patients are prone to develop delirium in ICU. Unfortunately the drugs of choice such as benzodiazepine and opioid are similar to ones that are abused. Once patient's primary condition improved, smooth withdrawal of sedative-analgesic without psychomimetic symptoms become the limiting factor for the recovery of the patient. Alpha-2 (α2) agonist has been successfully used to attenuate the hypertension, tachycardia, agitation, anxiety and fever occurring during withdrawal of benzodiazepine and opioid. (14-18) Clonidine has been used to attenuate the symptoms of withdrawal from alcohol, narcotics and naloxone-induced hypertension for more than 20 years. Dexmedetomidine, a selective α2-adrenergic agonist with an affinity of 8 times more than that of clonidine resulting in more selective α2 activation and exerts the desired effects of sedation, analgesia, anxiolysis and sympatholysis with less respiratory depression (13) with negligible effects on α1 stimulation (19) and it has been used to facilitate withdrawal of various drugs dependencies such as alcohol, (20,21) cocaine, (17,22) opioid, (11,12,19) and benzodiazepine. (12) It has also been used successfully even in infant to detoxify opioid and benzodiazepine sedation. (12) Withdrawal from many addictive drugs is characterized by hyperadrenergic state, the α2 agonist decreases the sympathetic outflow and adrenergic activity counteracting the physiological effects of withdrawal, and these effects are largely mediated by post-synaptic α2A subtype receptors in the locus caeruleus. (23-25) α2 agonist and opioid act synergistically on central sympathetic outflow. (26) The mechanism how dexmedetomidine enhances the opioid

analgesia is not yet clear. Maccioli et al has successfully used dexmedetomidine to facilitate cocaine withdrawal and withdrawal from prolonged benzodiazepine infusion. (3) Dexmedetomidine is being increasingly used for long term sedation in ICU and also used for prevention and control of delirium in ICU. (27) Clinical trials that compared dexmedetomidine to benzodiazepine and propofol infusion showed less incidence of delirium and shorter duration of ventilator time. (28-31)

In summary, our observation suggests that dexmedetomidine infusion has a potential role as sedative-analgesic in ICU patients prone to have tendency for drug dependency and addiction and it can be used to prevent, control or treat withdrawal symptoms of many addictive drugs without causing significant neurological, haemodynamic or respiratory compromise. Dexmedetomidine can also be used for withdrawal of iatrogenic-induced tolerance that developed from prolonged use of conventional sedative-analgesics in ICU. Further study with larger sample size is needed to explore its potential as main sedative-analgesic in ICU and control of multiple withdrawal symptoms of addictive drugs.

References

1. Maccioli GA. Dexmedetomidine to Facilitate Drug Withdrawal. Anesthesiology 2003;98:575-7.
2. O'Connor PG, Kosten TR, Stine SM. Management of opioid intoxication and withdrawal. In: Graham AW, Schultz TK, Mayo-Smith MF, et al, editors. Principles of addiction medicine. 3rd ed. Chevy Chase (MD): American Society of Addiction Medicine; 2003. p. 651-68.
3. Jaffe JH. Drug addiction and drug abuse. In: Gilman AG, Rall TW, Nies AS, Taylor P, editors. Goodman and Gilman's the Pharmacological Basis of Therapeutics. 8th ed. New York: Pergamon Press; 1990. p. 522-73.
4. Deighan CJ, Wong KM, McLaughlin KJ, Harden P. Rhabdomyolysis and acute renal failure resulting from alcohol and drug abuse. QJM 2000;93:29-33.
5. Kumar R, West DM, Jingree M, Laurence AS. Unusual consequences of heroin overdose: rhabdomyolysis, acute renal failure, paraplegia and hypercalcemia. Br J Anaesth 1999;83:496-8.
6. Wilson KC, Saukkonen JJ. Acute Respiratory Failure from Abused Substances. J Intensive Care Med 2004;19:183-93.
7. Ridgway ZA, Pountney AJ. Acute respiratory distress syndrome induced by oral methadone managed with non-invasive ventilation. Emerg Med J 2007;24:681.
8. Jenkins DH. Substance abuse and withdrawal in the intensive care unit. Contemporary issues. Surg Clin North Am 2000;80:1033-53.
9. Tobias JD. Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit. Crit Care Med 2000;28:2122-32.
10. Littler C, Scobie SD, Shelly MP. Withdrawal of sedation after long term ventilation on the intensive care unit. Clin Intensive Care 1995;6:83-5.
11. Belgrade M, Hall S. Dexmedetomidine infusion for the management of opioid-induced hyperalgesia. Pain Med 2010;11:1819-26.
12. Finkel JC, Elrefai A. The use of dexmedetomidine to facilitate opioid and benzodiazepine detoxification in an infant. Anesth Analg 2004;98:1658-9.
13. Rahman RA, Azmi MH, Ishak NH, Manap NA, Zain JM. The use of dexmedetomidine for refractory agitation in substance abuse patient. Crit Care Shock 2010;13:59-60.
14. Multz AS. Prolonged Dexmedetomidine Infusion as an Adjunct in Treating Sedation-Induced Withdrawal. Anesth Analg 2003;96:1054-5.
15. Shafer A. Complications of sedation with midazolam in the intensive care unit and a comparison with other sedative regimens. Crit Care Med 1998;26:947-56.
16. Ghignone M, Quintin L, Duke PC, Kehler CH, Calvillo O. Effects of clonidine on narcotic requirements and hemodynamic response during induction of fentanyl anesthesia and endotracheal intubation. Anesthesiology 1986;64:36-42.
17. Kersten JR, Pagel PS, Hettrick DA, Warltier DC. Dexmedetomidine partially attenuates the sympathetically mediated systemic and coronary hemodynamic effects of cocaine. Anesth Analg 1995;80:114-21.
18. Baddigam K, Russo P, Russo J, Tobias J D. Dexmedetomidine in the Treatment of Withdrawal Syndrome in Cardiothoracic Surgery Patients. J Intensive Care Med 2005;20:118-23.
19. Virtanen R, Savola JM, Saano V, Nyman L. Characterization of the selectivity, specificity and potency of medetomedine as an alpha 2-adrenoreceptor agonist. Eur J Pharmacol 1988;150:9-14.
20. Rovasalo A, Tohmo H, Aantaa R, Kettunen E, Palojoki R. Dexmedetomidine as an adjuvant in the treatment of alcohol withdrawal delirium: a case report. Gen Hosp Psychiatry 2006;28:362-3.
21. Darrouj J, Puri N, Prince E, Lomonaco A, Spevetz A, Gerber DR. Dexmedetomidine infusion as adjunctive therapy to benzodiazepines for acute alcohol withdrawal. Ann Pharmacother 2008;42:1703-5.
22. Kontak AC, Wang Z, Arbique D, Victor RG. Central Sympatholysis with Dexmedetomidine is an Effective Countermeasure for Cocaine-Induced Sympathetic Activation and Peripheral Vasoconstriction in Chronic Cocaine Abusers. Circulation 2009;120:S1178.
23. Coupar IM. Effect of alpha 2-adrenoceptor agonists on the expression of morphine-withdrawal in rats. Naunyn Schmiedebergs Arch Pharmacol 1992;345:553-7.
24. Lidbrink P. The effect of lesions of ascending noradrenaline pathways on sleep and waking in the rat. Brain Res 1974;74:19-40.
25. Glass MJ, Pickel VM. Alpha(2A)-adrenergic receptors are present in mu-opioid receptor containing neurons in rat medial nucleus tractus solitarius. Synapse 2002;43:208-18.
26. Maze M, Virtanen R, Daunt D, Banks SJ, Stover EP, Feldman D. Effects of dexmedetomidine, a novel imidazole

sedative-anesthetic agent, on adrenal steroidogenesis: in vivo and in vitro studies. Anesth Analg 1991;73:204-8.
27. Reade MC, O'Sullivan K, Bates S, Goldsmith D, Ainslie WR, Bellomo R. Dexmedetomidine vs. haloperidol in delirious, agitated, intubated patients: a randomised open-label trial. Crit Care 2009;13:R75.
28. Finkel JC, Johnson YJ, Quezado ZM. The use of dexmedetomidine to facilitate acute discontinuation of opioids after cardiac transplantation in children. Crit Care Med 2005;33:2110-2.
29. Venn RM, Newman P, Grounds RM. A phase II study to evaluate the safety and cardiovascular effects of dexmedetomidine for sedation in the medical intensive care unit. Intensive Care Med. In press.
30. Riker RR, Ramsay MAE, Prielipp RC, Jorden V. Long-term dexmedetomidine infusions for ICU sedation: a pilot study. Anesthesiology 2001;95:A383.
31. Szumita PM, Baroletti SA, Anger KE, Wechsler ME. Sedation and analgesia in the intensive care unit: evaluating the role of dexmedetomidine. Am J Health Syst Pharm 2007;64:37-44.