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Role of Remifentanyl for the Prevention and Treatment of Delirium in Intensive Care Unit Patients (Case Reports)

Emine KURUCA ÖZDEMİR | Nurse Güven Hospital Department of Anesthesiology and Intensive Care

Nedim ÇEKMEN, MD | Güven Hospital Department of Anesthesiology and Intensive Care

ABSTRACT

Delirium is one of the most common causes of the acute end-organ dysfunction across hospital settings, occurring in as high as 80 % of critically ill patients that require intensive care unit. Delirium, defined as an acute fluctuating change in mental state, with consciousness and cognitive impairment, has been found to have a high incidence in hospitalised patients, as well as being associated with increased morbiditiy and mortality, prolonged stays in the intensive care unit and in hospital an higher costs. Remifentayl use may, therefore, be especially recommended for patients with delirium in the intensive care unit. We aimed to evaluate the effect of remifentanyl for the prevention and treatment in patient with delirium in intensive care unit.

KEYWORDS | Delirium, Confusıon Assesment Method-ICU (CAM-ICU), Remifentanyl, intensive care unit (ICU)

Introduction

Delirium is a common and serious complication in critically ill patients, with a reported prevalence reaching 80 % in some intensive care unit (ICU)(1-3). The incidence ranging from 16 % to 87 % depends on different population studied and different assesment instruments used (2-4). Delirium can be further characterised as hypoactive, hyperactive or mixed (4-6). Hypoactive delirium, often unrecognized, is characterized by symptoms of lethargy and minimal psycomotor activity. Hyperactive delirium, by contrast, is marked by significant agitation. Individual with mixed expresions fluctuate between hypoactive and hyperactive expressions (5-7).

Pathophysiological mechanism of delirium are poorly understood and likely related both to anatomic deficits and imbalances in the neurotransmitters modulating the control of cognitive function, behavior and mood. Impairment of cerebral metabolism, primary intracranial disease, secondary brain infection, hypoxemia, systemic ilnesses, metabolic disturbances, exogenous toxic agents, withdrawal substances of abuse, sedatives, hypnotics or psychoactive drugs such as benzodiazepines and narcotics are the main causal factors of the above derangements (5,7-11). In general, risk factors for delirium development may be divided into 3 categories: preexisting host factors, acute illness-related, and iatrogenic or enviromental. (Table 1)_(7-11).

In addition to non-pharmacological methods in treatment of delirium, benzodiazepines, norepileptics, antipsychotics, sedatives and opioids such as pharmacological method can be applied. Once delirium occurs, non-pharmacological interventions should be considered as the first-line of delirium management in ICU. This approach should address all evident causes, providing supportive care and preventing complications and treating behavioral problems (7,9,12-18). Opioids indicated treatment on delirium in the ICU. Remifentanyl is a μ-opioid agonist with rapid onset and peak effect, and short duration of action. Unlike other opioids, remifentanyl is rapidly metabolized by hydrolysis of the propanoic acid-methyl ester linkage by nonspecific blood and tissue esterases. Use of remifentanyl is associated with apnea and respiratory depression. Remifentayl use may, therefore, be especially recommended for patients with delirium in the ICU (16-20). We aimed to evaluate in three patients the effect of remifentanyl for the prevention and treatment in patient with delirium in ICU.

Case 1

A 57 year-old male patient was admitted to ICU because of hypoxemic respiratory insufficiency dependent on acute respiratory distress syndrome (ARDS) as a result of hypoxemia progress happened in 2nd day of postoperative process after left lower lobectomy surgery related with bronchial carcinoma. Coronary artery disease (CAD), laryngectomy and coronary artery bypass graft (CABG) take place in patient history. In physical examination, decreasing of breath sound in both lungs and crepitant rales has been detected. Diffuse bilateral infiltration, ground-glass appearance and pleural effusion have been found in patient's thorax computerized tomography (CT) scans**.**

General medical condition was bad, conscious of patient was confused, Glasgow Coma Scale (GCS) of the case related with agitation was 13, Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 16, multiple organ dysfunction syndrome **(**MODS**)** was 2. His fever was 37.1 C^0, his pulse was 98 beats/min, blood pressure was 110/67 mmHg, respiratory rate was 40 per minute and oxygen saturation (SpO_2) was 81 %.

As a result of hypoxemia happened during the process of 6 L/min O_2 moving in arterial blood gas with mask; noninvasive mechanical ventilation (NIMV) has been applied. Undulation in conscious, agitation, refusing treatment, aggressive behaviours, plucking monitor cables off, violent visual and auditory hallucinations have been observed in the 4th day of patient follow-up. To be able to decrease agitation and provide ventilator interaction with patient who was diagnosed as hyperactive delirium with the help of Confusıon Assesment Method for the ICU (CAM-ICU) scale, remifentanyl infusion treatment has been started with 0.05-2 mcg/kg/min dose. After 2 hours, patient had hemodynamic stability. Patient was observed as sedated, potion had been set up as GCS 13-15 and patient was evaluated regularly according to Richmond Agitation Sedation Scale. Remifentanyl treatment had been applied to patient pharmacological and this treatment had been supported by non-pharmacological methods like reorientation, reducing stimulus and early mobilization.

During the treatment proceeds; persistent fever, increment in levels of leucocytosis and procalcitonin and deepening in hypoxemia have been observed so that when culture of patient indicated existence of gr (-) bacillus then treatment had been continued with sepsis chart. Continue NIMV had been ap-

plied to patient because of refractory hypoxemia. During the treatment delirium had continued in patient with a decreasing rate. From the 8th day in ICU, the treatment had been continued with nasal O_2 support by separating patient from NIMV in periods. In 12th day of follow-up, hypoxemia of patient was cured and became radiological normal. Delirium chart of patient became fixed by regressing with hemodynamic stability and patient became conscious, cooperative and oriented that's why the patient was transferred to service without need of external oxygen device support.

Case 2

A 76 year-old female patient was admitted to ICU because of hypercarbic respiratory insufficiency dependent on chronic obstructive pulmonary disease (COPD) and pneumonia. In patient case history COPD and Diabetes mellitus (DM) take place. In physical examination, decreasing of breath sound in lungs, rough-crepitant rale, rhoncus and wheezing have been detected. On posterior-anterior chest x-ray, diffuse pneumonic infiltration has been detected in right middle and lower lobes. General medical condition was bad, con**s**cious of patient was confused, GCS of the case related with agitation was 12, APACHE II score was 18, MODS was 4. His fever was 37.3 C^0, his pulse was 132 beats/min, blood pressure was 183/64 mmHg, respiratory rate was 41 per minute and SpO_2 was 68 %. As a result of observing characteristic hypoxemia and hypercarbia during the process of 6 L/min O_2 moving in arterial blood gas with mask; elective intubation has been proceed and has been connected to mechanical ventilator. Aggressive agitations, nonadherence with ventilator, biting tube and attempts of pulling catheter have been observed at 4th hour after intubation. Patient was diagnosed as hyperactive delirium with the help of CAM-ICU scale.

To be able to decrease agitation and providing ventilator interaction with patient who was diagnosed as hyperactive delirium with the help of CAM-ICU scale, remifentanyl infusion treatment has been started with 0.05-2 mcg/kg/min dose. After 2 hours, patient had hemodynamic stability.

Patient was observed as sedated, potion had been set up as GCS 13-15 and patient was evaluated regularly according to Richmond Agitation Sedation Scale. Remifentanyl treatment had been applied to patient pharmacological and this treatment had been supported by non-pharmacological methods like reorientation, reducing stimulus and providing regular sleep pattern.

After these treatments conscience, cooperation and orientation of patient became normal. Adaptation of patient to ventilator had been established and it was observed that delirium chart of patient became fixed by regressing. Patient has been extubated with weaning method in 96th hour as a result of fixed hypoxemia and normalization of radiological appearance. Patient achieved hemodynamic stability and patient became conscious, cooperative and oriented that's why the patient was discharged from ICU in 7th day.

Case 3

A 73 year-old male patient was admitted to ICU because of treatment purpose and close patient follow-up postoperative after esophagojejunostomy surgery dependent on oesophageal cancer. In patient case history, CAD, Hypertension, DM and Mobitz type AV block take place. In 2nd day of postoperative period patient pulled nasogastric catheter and in 5th day of postoperative period, confusion started, deterioration in cooperation and orientation were observed. In physical examination, decreasing of breath sound in both lungs and rough-crepitant rale has been detected. On posterior-anterior chest x-ray, diffuse infiltration in right basal and consolidation has been detected in right middle and lower lobes. With an increasing agitation, GCS of the patient was 13, APACHE II score was 18, MODS was 3. His fever was 37.1 C^0, his pulse was 148 beats/min, blood pressure was 95/54 mmHg, respiratory rate was 28 per minute and SpO_2 was 93 %. Behaviours like undulation in conscious, characteristic orientation disorder, agitation, aggressive behaviours, attempt of jumping from bed, plucking monitor cables off and chewing them have been observed. From time to time excessive sleepiness has been observed in patient so that patient could not respond deep and verbal stimuli.

Patient was diagnosed as mixed type of delirium with the help of CAM-ICU scale. To be able to decrease agitation and providing ventilator interaction with patient who was diagnosed as delirium, remifentanyl infusion treatment has been started with 0.05-2 mcg/kg/min dose. After 2 hours, hemodynamical pulse was 124 beat/min in 102/67 mmHg. Patient was observed as sedated, potion had been set up as GCS 13-15 and patient was evaluated regularly according to Richmond Agitation Sedation Scale.

Remifentanyl treatment had been applied to patient pharmacological and this treatment had been supported by non-pharmacological methods like reorientation, reducing stimulus, providing regular sleep pattern and early mobilization. It was observed that during the treatment process delirium chart of patient became fixed with regressing and in the 9th day of ICU, pneumonia of patient was cured.

Patient achieved hemodynamic stability and patient became conscious, cooperative and oriented that's why the patient was discharged from intensive care unit in 7th day. Patient became conscious, cooperative and oriented with hemodynamic stability that's why the patient was transferred to service without need of external oxygen device support.

Discussion

Delirium is commonly observed in critically ill patients an is associated with negative outcomes. The pathophysiology of delirium is not fully understood, and the condition might arise through a variety of different pathogenic mechanisms. Current evidence suggests that drug toxicity, inflammation and acute stress responses can all contribute markedly to disruption of neurotransmission, and, ultimately, to the development of delirium. Neurotransmitters with possible roles in delirium include acetylcholine, dopamine, 5-hydroxytryptamine, norepinephrine, and gamma-aminobutyric acid (GABA). However; alterations to neurotransmitters, especially acetylcholine and dopamine, inflamatory pathways and aberrant stres response are proposed mechanisms leading to ICU delirium. Detection of delirium using a validated delirium assesment tool makes early treatment possible, which may improve prognosis. Patients at high risk of delirium, especially those with cognitive decline and advanced age, should be identified in the first 24 hours admissıon to the ICU (1-3,5-7).

Over the past 10 years several tools have appeared in the literature for the assesment of delirium in the ICU. Two commonly used instruments with robuts validity are the CAM-ICU and the Intensive Care Delirium Screening Check List (ICDSC). The CAM-ICU was adapted for use in ICU patients from the CAM, a tool widely used in the geriatric population, which relies on a 4 feature assesment (12-14).

Delirium can result from multiple etiologies, and outcome is usually unfavorable. Delirium is associated with high morbidity and mortality. Delirium may lead to aspiration pnemonia, inadequate fluid intake, physical injury, permanent cognitive impairment, electrolyte imbalance. Although delirium research in critical care is rapidly maturing, the weight of evidence already demonstrates that critical care clinicals can not afford to ignore this form of organ disfunctions in our patients (2-6). It is potentially preventable and treatable, but poor understanding of its pathophysiology and the complexities that occur in the brain during delirium have limited the development of successfull treatment. The role of impairment cholinergic transmission, inflamation, and impairment oxidative metabolism have been implicated in the development of delirium (3-5,6-12).

If we are to be comprehensive in our approach to monitoring

and managing organ disfunctions, the brain be a very active component of our daily discussion at the bedside in the ICU. An estimated 30–40 % of cases of delirium are preventable, and prevention is the most effective strategy for minimizing the occurrence of delirium and its adverse outcomes. Once delirium occurs, non-pharmacological interventions should be considered as the first-line of delirium management in ICU. Non-farmacological measures are recommended, such as noise reduction and frequent orientation (15-19). ICU care and its potential to trigger and/or exacerbate delirium should not be overlocked. Drugs such as benzodiazepines or anticholinergics and other known precipitants of delirium should generally be avoided. All ordered interventions (eg, blood draws, catheters, respiratory treatments) should be rewieved and discontiuned if unnecessary. This strategy is particulary important at night to minimize unnecessary interruptions and allow time for sleep in addition, attempts should be made to coordinate care when multiple medical procedures are conducted on the same patients. (1) In patients with postoperative delirium and patient with delirium in the ICU, mortality may be increased, as well as length of postoperative hospital stay and associated heathcare costs (4-8, 14-19).

In addition to non-pharmacological methods in treatment of delirium, benzodiazepines, norepileptics, antipsychotics, sedatives and opioids are such as pharmacological method could be applied. It is indicated in a metaanalysis, in which prospective randomize studies were evaluated about mixing different antipsychotic agents with each other and with placebo for delirium treatment, that most commonly used agent is haloperidol and this agent specifically has extrapyramidal side effects (10-17).

As a farmacological measures are recommended, combined sedative, analgesic, physical therapy and delirium protocols seem to improve patients outcomes and reduce the burden of delirium. Recognizing patients with a high risk of delirium provides and opportunity to start prophylactic treatment. However, more research regarding the safety and efficacy of pharmacological prophylaxis is reguired. When patients develop delirium, symptomatic treatment with antipsycotics can be started. There is no evidence that one class of antipsycotic drugs is more efficacious in the treatment of ICU delirium than another. As haloperidol can be addimistered intravenously, it remains the drug of first choice (16-18,21-23). In the search of finding alternative medicines in delirium treatment, remifentanyl has started being used as an alternative to haloperidol, atypical antipsychotics and alfa-2 agonists in late few years. Whether these high risk patients benefit from remifentanyl treatment deserves further study

In another metaanalysis, effectiveness of atypical antipsychotics in delirium treatment was searched through evaluating prospective randomize controlled studies and in these studies olanzapine, risperidone, quetiapine, ziprasipone and aripiprazole have been used. According to these studies and metaanalysis, it is indicated that that these medicines have less extrapyramidal side effects respect to haloperidol, yet haloperidol is more effective then these medicines about preventing delirium agitations. In addition, it is indicated that; agents like ziprasidone and aripiprazole are insecure because of inducing arrhythmia, olanzapine is worsening delirium, quetiapine and risperidone cause hypotension frequently (17-19). In ICU many types of alternative medicines have been used on delirium treatment studying, however, it cannot be suggested that any of these medicines are better than one another when benefit-loss rates of these medicines have considered. We preferred using remifentanyl on ICU follow-up patients with many systemic problems instead of haloperidol because of many advantages of remifentanyl even if haloperidol is usually preferred as first choice (17-22).

Devlin et al (21) have used 3 types of medicines in treatment of delirium table developing in ICU. In this study, they showed that their first choice was haloperidol in 76 % rate, their second choice was antipsychotics in 14 % rate and their third choice was benzodiazepines in 10 % rate. Girard et al (22) have used 3 types of medicines in treatment of delirium table developing in ICU. For 1st group of patients haloperidol, for 2nd group of patients ziprasidone and for 3rd group of patients placebo was used. In another study, Skrobik et al (23) have used 2 types of medicines in treatment of delirium table growing in ICU. Haloperidol has been applied to first group of patients and olanzapine has been applied to second group of patients. Because of these advantages, we preferred using remifentanyl on ICU follow-up patients with many systemic problems.

Several studies have determined predictors for post-operative delirium or have reported an association between opioids and delirium (17-20). Remifentanyl has a number of benefits in the ICU. Remifentanyl effectively controls analgesia/sedation in mechanically ventilated ICU patients. (18-20) Remifentanyl offers precise control of analgesia for painfull procedures ın ICU patients and its rapid, predictable, recovery facilitates neurological assesments. Remifentanyl offers control in special populations such as patients with hepatic and renal impairment so that there is no need for initial dose adjusment (19,20). Because of these advantages, we preferred using remifentanyl on ICU follow-up patients with many systemic problems.

Even if there are studies in which remifentanyl has been used as intraoperative on purpose of anesthesia in order to induce incidence of postoperative delirium (19), Radtke et al (20) used remifentanyl against intraoperative fentanyl for reducing incidence of postoperative delirium in 752 patients. As a result of this study, they indicated that remifentanyl reduces incidence of delirium much more in early postoperative period. We applied 0.05-2 mcg/kg/min dose remifentanyl to patients accepted to ICU with different diagnosis with different clinical developed delirium.

Double blind, placebo controlled randomized trials are needed to further study prophylaxis and treatment of delirium in critically ill patient. Future research in ICU delirium should focus on pharmacological prevention, pharmacological treatment and multicomponent intervention strategies that reveal subgroup of patient with greatest potential to benefit, such as high risk patients or those with subsyndromal delirium (4-8,16-18,20-22).

In conclusion, delirium is a serious cause and complication of hospitalization in elderly patients and should be considered to be a medical emergency until proven otherwise in ICU. Irrespective of the specific etiology, this condition has the potential to markedly affect the overall outcome and prognosis of severely ill patients, as well as substantially increasing healthcare utilization and costs. For these reasons, prevention, early recognition and effective treatment of delirium are essential. Currently available evidence suggests that remifentanyl is a promising agent, not only for prevention, but also for treatment of ICU-associated delirium. However, larger, well-designed trials are warranted to define the role of remifentanyl in preventing and treating delirium in the ICU.

REFERENCES

1-Vasilevskis EE, Han JH, Hughes CG, Ely EW. Epidemiology and risk factors for delirium across hospital settings.Best Pract Res Clin Anaesthesiol. 2012;26(3):277-87. | 2-Wang C, Wu Y, Yue P, Ely EW, Huang J, Yang X, Liu Y. Delirium assessment using Confusion Assessment Method for the Intensive Care Unit in Chinese critically ill patients.J Crit Care. 2013;28(3):223-9. | 3-Heymann A, Radtke F, Schiemann A, Lütz A, MacGuill M, Wernecke KD, Spies C. Delayed treatment of delirium increases mortality rate in intensive care unit patients.J Int Med Res. 2010;38(5):1584-95. | 4-Zaal IJ, Slooter AJ. Delirium in critically ill patients: epidemiology, pathophysiology, diagnosis and management.Drugs. 2012;72(11):1457-71. | 5-Ali S, Patel M, Jabeen S, Bailey RK, Patel T, Shahid M, Riley WJ, Arain A. Insight into delirium.Innov Clin Neurosci. 2011 Oct;8(10):25-34 | 6-Morandi A, Pandharipande PP, Jackson JC, Bellelli G, Trabucchi M, Ely EW. Understanding terminology of delirium and long-term cognitive impairment in critically ill patients.Best Pract Res Clin Anaesthesiol. 2012;26(3):267-76. | 7-Morandi A, Jackson JC. Delirium in the intensive care unit: a review.Neurol Clin. 2011;29(4):749-63. | 8-Gunther ML, Morandi A, Ely EW. Pathophysiology of delirium in the intensive care unit.Crit Care Clin. 2008;24(1):45-65 | 9-Colombo R, Corona A, Praga F, Minari C, Giannotti C, Castelli A, Raimondi F. A reorientation strategy for reducing delirium in the critically ill. Results of an interventional study.Minerva Anestesiol. 2012;78(9):1026-33 | 10-Young J, Murthy L, Westby M, Akunne A, O'Mahony R; Guideline Development Group. Diagnosis, prevention, and management of delirium: summary of NICE guidance. BMJ. 2010;341:c3704. | 11-Girard TD, Ely EW. Delirium in the critically ill patient.Handb Clin Neurol. 2008;90:39-56. | 12-Pun BT, Devlin JW. Delirium monitoring in the ICU: strategies for initiating and sustaining screening efforts.Semin Respir Crit Care Med. 2013 Apr;34(2):179-88 | 13-Morandi A, Brummel NE, Ely EW. Sedation, delirium and mechanical ventilation: the 'ABCDE' approach.Curr Opin Crit Care. 2011;17(1):43-9 | 14-Pun BT, Boehm L. Delirium in the intensive care unit: assessment and management.AACN Adv Crit Care. 2011;22(3):225-37. | 15-Pelland C, Trudel JF. Atypical antipsychotic efficacy and safety in managing delirium: a systematic review and critical analysis. Psychol Neuropsychiatr Vieil. 2009;7(2):109-19. | 16-Campbell N, Boustani MA, Ayub A, Fox GC, Munger SL, Ott C, Guzman O, Farber M, Ademuyiwa A, Singh R. Pharmacological management of delirium in hospitalized adults--a systematic evidence review.J Gen Intern Med. 2009;24(7):848-53. | 17-Swan JT, Fitousis K, Hall JB, Todd SR, Turner KL. Antipsychotic use and diagnosis of delirium in the intensive care unit.Crit Care. 2012;16(3):R84. | 18-Guenther U, Radtke FM.Delirium in the postanaesthesia period.Curr Opin Anaesthesiol. 2011;24(6):670-5. | 19-Battershill AJ, Keating GM. Remifentanil : a review of its analgesic and sedative use in the intensive care unit Drugs. 2006;66(3):365-85. | 20-Radtke FM, Franck M, Lorenz M, Luetz A, Heymann A, Wernecke KD, Spies CD. Remifentanil reduces the incidence of post-operative delirium.J Int Med Res. 2010;38(4):1225-32. | 21-Devlin JW, Bhat S, Roberts RJ, Skrobik Y. Current perceptions and practices surrounding the recognition and treatment of delirium in the intensive care unit: a survey of 250 critical care pharmacists from eight states.Ann Pharmacother. 2011;45(10):1217-29. | 22-Girard TD, Pandharipande PP, Carson SS, Schmidt GA, Wright PE, Canonico AE, Pun BT, Thompson JL, Shintani AK, Meltzer HY, Bernard GR, Dittus RS, Ely EW; MIND Trial Investigators. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial.Crit Care Med. 2010;38(2):428-37. | 23-Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting.Intensive Care Med. 2004;30(3):444-9