EARLY RECOGNITION AND TREATMENT OF DELIRIUM USING THE CONFUSION ASSESSMENT METHOD FOR THE INTENSIVE CARE UNIT (CAM-ICU) IN A CARDIAC SURGICAL INTENSIVE CARE UNIT

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Summary

Introduction. Delirium is a complex cognitive disorder characterized by a disturbance in attention, awareness and cognition that are not better explained by another preexisting, neurocognitive disorder and that represents a direct physiological consequence of another medical condition, substance/medication intoxication or withdrawal, or exposure to a toxin. Delirium is highly prevalent in the cardiac surgical intensive care unit, as a result of the complexity of the surgical procedure and of the extracorporeal circulation. We report on the changes in the prevalence of delirium after the introduction in our Intensive Care Unit of a systematic assessment of delirium, via the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU).

Materials and methods. We collected and analyzed data using an electronic medical records application (Digistat) and we compared the prevalence of delirium before and after the introduction of a systematic assessment in all admitted patients via the CAM-ICU. Our sample consisted of patients hospitalized in ICU after emergency or elective cardiac surgery in the periods from July 1, 2015 and December 31, 2015 (first group) and from July 1, 2016 and December 31, 2016 (second group). The diagnosis of delirium was formulated, in the first group, through a clinical evaluation by a specialist. In the second group, the diagnosis was formulated through the CAM-ICU.

Results. The first group consisted of 206 patients, of whom 86 (41.5%) showed clinical diagnosis of delirium. The second group consisted of 153 patients, of which only 17 (11.1%) showed a diagnosis of delirium. In our sample haloperidol was the most used drug. There was a low use of atypical antipsychotics and a high use of benzodiazepines. In the second group we showed less use of haloperidol and greater use of dexmedetomidine.

Conclusions. Our study shows a clear reduction in the diagnosis of delirium since the introduction of the CAM-ICU as a standard assessment for all our ICU patients. This reduced prevalence may be due to several factors including the early (i.e., before the development of a full-blown delirium syndrome) recognition and treatment of delirium symptoms. We also cannot exclude that the delirium diagnosis based on a clinical assessment overestimated, and/or that the diagnosis made via the CAM-ICU underestimated, the prevalence of delirium.

Key words: delirium, cardiac surgery; intensive care units; CAM-ICU; early recognition; psychopharmacological treatment

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Introduction

Delirium is a complex cognitive disorder characterized by a disturbance of consciousness with reduced ability to focus, sustain or shift attention. It is also characterized by decreased clarity of awareness of the environment and impaired cognitive functions such as memory deficit, disorientation, language disturbances and perceptual disorders, not justified by a preexisting or evolving dementia. Usually, clinical onset is acute and its course is short and fluctuating. Delirium is a direct consequence of a general medical condition, drug intoxication and/or withdrawal, toxicity exposure or a combination of these events. These deficits are not better explained by the presence of a neurocognitive disorder and do not occur in a context of severe reduction in vigilance, such as coma [1].

Other commonly associated symptoms include sleep disorders, disorders of the psychomotor activity and of emotionality. Patients can be either agitated (hyperactive/hyperkinetic delirium) and lethargic (hypoactive/hypokinetic delirium), and may have fluctuations between agitation and lethargy (mixed delirium) [2].

Delirium is a common postoperative complication, especially in the elderly. It is associated with increased mortality, post-traumatic stress disorder, longer length of hospital stay, extra nursing requirements, increased healthcare costs and substantial cognitive dysfunction for 1 year following surgery [3 4]. It is very common in critical patients and involves up to 80% of intubated patients in intensive care units (ICUs) [5].

Delirium is often a clinical manifestation of a general medical condition for which the treatment must aim at the correcting of the etiological factors that determine its onset. There is also a number of environmental and iatrogenic contributors to delirium such as prolonged immobilization, use of physical restraint, polypharmacy and use of sedative or opioid analgesic drugs, so attention should also be paid to identify and possibly correct these factors [2]. There is a subjective vulnerability correlated to the patient's medical condition, so the onset of delirium in a patient without comorbidity generally requires a number of significant insults, while in a fragile or compromised patient may be sufficient even a single insult of mild entity [6].

Delirium resulting from cardiac surgery is very frequent and represents a serious complication of patients hospitalized in cardiac surgery ICUs. The incidence of delirium after cardiac surgery is estimated to be 26-52% [4], with a significant percentage being hypoactive delirium [7].

The occurrence of delirium after cardiac surgery is associated with worse outcomes. These include increased rate of complications, prolonged duration of mechanical ventilation, prolonged length of stay in ICU and hospital, and increased medical expenses during hospitalization. Other negative outcomes are increased readmission rate, compromised long-term cognitive function, decreased physical ability and life quality, and elevated long-term mortality after hospital discharge [8 9].

The onset of delirium depends on both the patient's vulnerability and triggering factors related to surgery. To assess baseline vulnerability, the most widely used prediction rule for delirium after cardiac surgery was developed and validated by Rudolph et al. in 2009 and includes four items: prior stroke/transient ischemic attack, Geriatric Depression Scale > 4, abnormal albumin, and Mini-Mental State Examination (MMSE) score [10]. Intra-operative risk factors are related to the type and use of general versus local anesthesia, as well as the duration and type of surgery [11-12], reduction of cerebral perfusion linked to pressure imbalances [13], impaired cerebral auto-regulation and permeability of the blood-brain barrier [14].

Other predisposing risk factors include vision impairment, severe illness, cognitive impairment, and serum urea nitrogen: creatinine ratio of 18 or greater [15].

Vascular risk factors have also been strongly associated with development of delirium (tobacco use and vascular surgery), although it is unclear whether the increased risk is due to atherosclerotic burden or the surgical procedure itself [16].

Numerous pathophysiological mechanisms are involved in the genesis of delirium including increased inflammatory mediators and cortical changes [17], neurotransmittal imbalance [18], electrolyte and metabolic alterations [19], cerebral hemodynamic disorders [13] and genetic factors [20].

The development of delirium after cardiac surgery is associated with negative distance effects such as cognitive [21] and functional decline [22], reduced life expectancy [23], increased risk of stroke and mortality [24].

Currently there is no robust evidence demonstrating the effectiveness of various strategies to reduce the incidence of delirium in cardiac surgery[4] however early mobilization of patients is frequently considered to be a useful preventive intervention in non-cardiac surgical ICUs [25].

The use of preventive pharmacological therapy is controversial and usually is not recommended [4]. However, recent studies have shown the usefulness of prophylactic administration of haloperidol in patients

undergoing non-cardiac surgery [26] and risperidone in cardiac surgery patients [27]. Large randomized trials in cardiac surgical patients are needed to confirm the preventive efficacy of antipsychotic administration for the development of delirium [4]. A few studies show that the preoperative use of statins is protective against the development of delirium [28] while there is no evidence for the use of corticosteroids [29] and acetylcholinesterase inhibitors [30]. The choice of sedative therapy may affect the probability of delirium development: benzodiazepines and opioids are associated with increased risk [7], while dexmedetomidine may reduce the incidence and duration of cardiac post-surgery delirium [31].

Delirium treatment is based on the correction of triggering factors and causes removal, however, psycho-pharmacological therapy may be essential to control the symptoms and ensure patient safety. Although haloperidol has been considered the preferred agent for the treatment of delirium in critically ill patients, recent guidelines emphasize that the use of atypical antipsychotic agents may reduce the duration of delirium [2].

Although it's unclear how to manage patients with sub-syndromal delirium who are at high risk for progression to delirium, a recent study has shown the utility of low doses of risperidone (0.5 mg twice die) [32]. Knowing the incidence of delirium in this population can provide better pre- and postoperative planning to efficiently allocate resources and prevent the development of delirium, as well as improve postoperative management, with the least impact that this disorder can cause [33].

Without an appropriate diagnostic tool the diagnosis of delirium risks being not clinically recognized. The Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC) are the most frequently employed reliable diagnostic tools [2].

Materials and methods

The purpose of the study was to evaluate the impact of the introduction of CAM-ICU on the diagnosis of delirium in a cardiac surgical ICU.

We considered patients hospitalized at the cardiac surgical ICU in the University Hospital of Siena, and compared the prevalence of delirium diagnosis before and after the introduction of CAM-ICU.

The CAM-ICU is a diagnostic scale for delirium diagnosis that is based on four features: 1) acute onset and fluctuating course, 2) inattention, 3) altered level of consciousness, 4) disorganized thinking. The patient is diagnosed as delirious (CAM-ICU positive) if he/she has both features 1 and 2 and either feature 3 or 4.

A 2012 meta-analysis considered nine studies evaluating CAM-ICU (969 patients) and concluded that this is an excellent diagnostic tool in critically ICU patients and has a global sensitivity of 80% and a specificity of 95.9% [34].

The third feature of the CAM-ICU requires the assessment of alteration of level of consciousness. This could be done by administering the Richmond Agitation Sedation Scale (RASS). Positive RASS scores denote positive or aggressive symptomatology ranging from +1 (mild restlessness) to +4 (dangerous agitation). The negative RASS scores differentiate between response to verbal commands (scores -1 to -3) and physical stimulus (scores -4 and -5). If the patient's RASS score is -4 or -5 or not arousable by verbal commands, no further evaluation for delirium is performed, because the patient is comatose and is unable to be assessed for delirium. For patients who are arousable (RASS scores of -3 and higher), delirium can be assessed with the ICD-SC or by the CAM-ICU. RASS has demonstrated high reliability and diagnostic validity for patients of various intensive medical, surgical, cardiac and neurosurgical fields [35].

This is a retrospective study on the prevalence of diagnosis of delirium in patients hospitalized in ICU after emergency or elective cardiac surgery before and after the introduction into day-to-day clinical practice of CAM-ICU.

The first group corresponds to the patients hospitalized in the period from July 1, 2015 and December 31, 2015 and the second group from July 1, 2016 and December 31, 2016.

In the first group, which corresponds to the period when CAM-ICU had not yet been introduced, the diagnosis of delirium was established by the clinical evaluation of the patient taking into account the presence of at least one of the following symptoms: confusion, agitation, delirium and depression. The choice to introduce among them the symptom of depression derives from the need to recognize hypoactive delirium, very common in intensive care units and often unrecognized for non-clinical presentation.

CAM-ICU has been introduced into the daily routine of cardiovascular surgery unit of our hospital from April 1, 2016. Since then, daily, three times a day, in morning, afternoon and night shifts, CAM-ICU was performed to each patient admitted by the nursing staff, after a one-year training period.

Results

The first group (1 July 2015 - December 31, 2015; pre-CAM) consisted of 206 patients with an average age of 67.4 (± 12.2) years, including 131 male and 75 female. The second group (1 July 2016 - December 31, 2016; post-CAM) consisted of 153 patients with an average age of 68.4 (± 12.5) years, of which 99 were males and 54 were females. The two groups, in addition to the number, did not differ significantly for the clinical features of the subjects (Figure 1). The most common types of patients were cardiac surgeries for valve or coronary intervention, or for double valve and coronary intervention. Other relatively frequent typologies of interventions were those related to ascending aorta and aortic arch. Another frequent type of intervention was the double valve intervention and the ascending aorta. Other cardiac surgery or chest surgery were less represented. Most of the interventions were in the election (87.9% in the first group and 86.2% in the second group). In the first group 17 interventions (8.2%) were in urgency and 8 (3.9%) in emergency; in the second group, urgent interventions were 8 (5.2%) and emergency 13 (8.5%). The diagnosis of delirium was assessed by clinical evaluation in 86 of 206 patients (41.5%) of the first group. In the second group, the diagnosis of delirium was postponed by the outcome of the CAM-ICU in 17 of 153 patients (11.1%) (Figure 2).

There were minimal differences between the two groups. The average duration of the hospitalization was 5.8 days for the first group and 6.6 days for the second group. The number of deaths was 9 for the first group and 16 for the second group.

In the first group there was a high use of haloperidol and benzodiazepines: 11 patients were treated with haloperidol and 12 with benzodiazepines and benzodiazepine analogues (lorazepam, alprazolam or zolpidem). There was a low use of new generation antipsychotics: only one patient was treated with quetiapine. There was a low use of dexmedetomidine (4 patients).

In the second group there was still a high use of benzodiazepines but lower use of haloperidol: 4 patients were treated with the latter and 12 with benzodiazepines and benzodiazepine analogues (lorazepam, alprazolam or zolpidem). Also in the second group there was a low use of new generation antipsychotics: only 2 patients were treated with quetiapine. Compared to the first group, there was a greater use of dexmedetomidine (8 patients).

No patients, both of the first and of the second group, had been treated with an antipsychotic other than haloperidol or quetiapine.

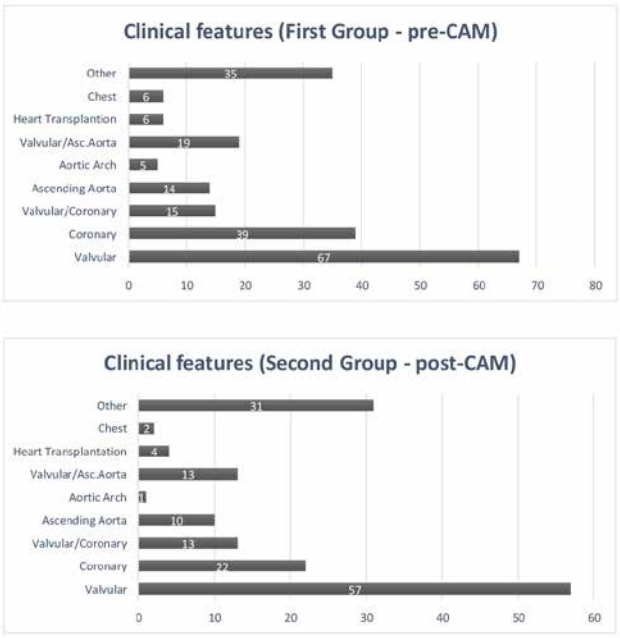

FIGURE 1.
Clinical features of the subjects.

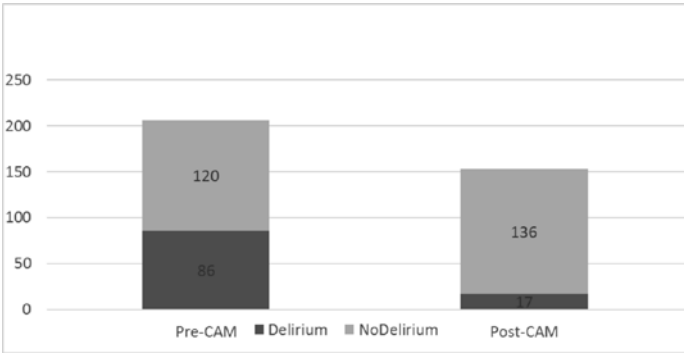

FIGURE 2.
Diagnosis of delirium in the two groups.

Discussion

The results of our study demonstrate a reduction in the diagnosis of delirium in cardiac surgery intensive care units after introduction into the clinical practice of CAM-ICU.

The only intervention that has shown, in randomized trials, to reduce the incidence of diagnosis and the duration of delirium symptoms in intensive care is early mobilization of patients [25] and recent guidelines recommend this intervention to reduce the incidence of delirium[2]. Other environmental and physical interventions, although have demonstrated to reduce the incidence of delirium in therapeutic settings other than intensive care [36], have not been adequately studied in

setting up the cardiovascular ICUs. A recent study on the effectiveness of communication between family members and patients in cardiac surgery has shown how the reassurance from the caregivers can reduce the incidence of postoperative delirium [37].

Evidence of the effectiveness of preventive drug therapy is controversial although some studies demonstrate the efficacy of low doses of risperidone in prophylaxis of delirium in patients undergoing cardiac surgery and haloperidol in prophylaxis of delirium in non-cardiac surgical intensive care [26 27]. However, recent guidelines do not recommend pharmacological interventions for the prevention of delirium in intensive care unit. The same guidelines underline the importance of the use of specific diagnostic scales such as CAM-ICU and ICDSC for delirium diagnosis [2].

The results of our study confirm the importance of CAM-ICU in the diagnosis of delirium and suggest its role in prevention.

We can assume that daily administration of CAM-ICU by nursing staff pays greater attention on the patient and allows early identification of the initial symptoms of delirium by allowing correction of triggers and appropriate therapy for both underlying causes and neuropsychiatric symptoms. The prevalence of delirium in the first group of patients in our study (41.5%) is very high but is in line with that one of other studies conducted within the same cure setting [6]. The prevalence of delirium in the second group of patients (11.1%) is very low, far below the average of other studies, although this does not result in a consequent reduction in the number of complications or mortality and in the duration of the hospitalization.

To our surprise, an earlier assessment and identification/diagnosis of delirium was not correlated with a shorter length of hospitalization or to a lower degree of mortality and complications. We argue that this could be due to the fact that other factors, such as the type of surgery that was performed, play a bigger role. Also, several conditions that contribute to delirium (e.g, electrolyte imbalance, anemia, etc) were likely addressed in both groups, independent on an early diagnosis of delirium.

In our sample, there was a high use of benzodiazepines, low use of atypical antipsychotics and, among other antipsychotics, preferential, if not exclusively, haloperidol use. These data contradict the suggestions of the latest guidelines on delirium in ICUs that conclude that there is no evidence for the efficacy of haloperidol in reducing delirium duration, while atypical antipsychotics may reduce the duration [2]. The same guidelines do not recommend the use of benzodiazepines in the treatment of delirium in intensive care unit except for cases of alcohol or sedatives withdrawal [2], while in our sample is highly utilized.

A difference that we found between the first and second group of patients was a less frequent use of haloperidol in the second group and greater use of dexmedetomidine in the latter. Dexmedetomidine is a selective agonist of $\alpha 2$ adrenergic receptors with sedative, anxiolytic and sympathetic properties [38]. In Italy, is approved for sedation of patients in intensive care units requiring a deeper level of sedation than awakening in response to verbal stimulation (corresponding to the score between 0 and -3 of the RASS). The main side effects are hypotension and bradycardia, while not leading to significant respiratory compromise [2]. Dexmedetomidine causes different sedation than classical sedatives, so patients are more easily awake and interactive [39].

Dexmedetomidine has also an analgesic effect that can reduce the need for opioids. There are many evidences that underline the importance of maintaining a light sedation level in intensive care patients and avoiding benzodiazepines among sedatives, in order to reduce the duration of assisted ventilation, the duration of the hospitalization and the incidence of delirium and cognitive decline. The use of dexmedetomidine as a sedative drug for the control of agitation may allow a reduced use of benzodiazepines and may favor a light sedation level, indirectly reducing the incidence of delirium [2]. Some evidence underlines the benefits of dexmedetomidine in comparison with benzodiazepines and propofol in reducing the risk of delirium after cardiac surgery [40]. We may also hypothesize that a greater use of dexmedetomidine in second group of our study, in addition to the introduction of CAM-ICU, may have contributed to a small reduction in the prevalence of delirium.

Although the results of the study favor a possible role of CAM-ICU in the prevention of delirium it can not be excluded that the reduced prevalence of delirium diagnosis in the second group of patients depends rather on the fact that clinical evaluation overestimates while the CAM-ICU underestimates the diagnosis of delirium.

Conclusions

The findings of this study confirm the importance of routine screening for the diagnosis of delirium in cardiac surgery through the use of accurate and reliable diagnostic tools such as CAM-ICU and suggest the possible positive impact on delirium prevention.

However, it is not possible to exclude with certainty that the reduced prevalence of delirium diagnosis after the introduction of CAM-ICU depends on the fact that the test diagnosis underestimates the diagnosis of delirium with respect to the clinical diagnosis.
Drug use data demonstrate that there is still no uniformity to the guidelines and how there is still a high use of benzodiazepines and a low use of different sedative medicines such as dexmedetomidine for control of agitation in cardiac surgery.

Conflict of interest

None.

References

1 American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 5th ed. Arlington, VA: American Psychiatric Publishing 2013

2 Barr J, Fraser GL, Puntillo K, et al.; American College of Critical Care Medicine. *Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit.* Crit Care Med 2013;41:263-306.

3 Li T, Yeung J, Li J, et al.; RAGA-Delirium Investigators. *Comparison of regional with general anaesthesia on postoperative delirium (RAGA-delirium) in the older patients undergoing hip fracture surgery: study protocol for a multicentre randomised controlled trial.* BMJ Open 2017;7:e016937.

4 Brown C. *Delirium in the Cardiac Surgical Intensive Care Unit.* Curr Opin Anaesthesiol 2014;27:117-22.

5 McNicoll L, Pisani MA, Zhang Y, et al. *Delirium in the intensive care unit: Occurrence and clinical course in older patients*. J Am Geriatr Soc 2003;51:591-8.

6 Gottesman R, Grega M, Bailey M, et al. *Delirium after coronary artery bypass graft surgery and late mortality.* Ann Neurol 2010;67:338-44.

7 McPherson JA, Wagner CE, Boehm LM, et al. *Delirium in the cardiovascular ICU*. Crit Care Med 2013;41:405-13.

8 Witlox J, Eurelings LS, de Jonghe JF, et al. *Delirium in elderly patients and the risk of post discharge mortality, institutionalization, and dementia: a meta-analysis*. JAMA 2010;304:443-51.

9 Koster S, Hensens AG, van der Palen J. *The long-term cognitive and functional outcomes of postoperative delirium after cardiac surgery.* Ann Thoric Surg 2009;87:1469-74.

10 Rudolph JL, Jones RN, Levkoff SE, et al. *Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery.* Circulation 2009;119:229-36.

11 Pandharipande P, Pun B, Herr D, et al. *Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial.* JAMA 2007;298:2644-53.

12 Sieber F, Zakriya K, Gottschalk A, et al. *Sedation depth during spinal anesthesia and the development of postoperative delirium in elderly patients undergoing hip fracture repair.* Mayo Clinic Proc 2010;85:18-26.

13 Siepe M, Pfeiffer T, Gieringer A, et al. *Increased systemic perfusion pressure during cardiopulmonary bypass is associated with less early postoperative cognitive dysfunction and delirium*. Eur J Cardiothorac Surg 2011;40:200-7.

14 Pfister D, Siegemund M, Dell-Kuster S, et al. *Cerebral perfusion in sepsis-associated delirium*. Crit Care 2008;12:R63.

15 Inouye S. *Delirium in older persons.* N Engl J Med 2006;354:1157-65.

16 Rudolph JL, Jones RN, Rasmussen LS, et al. *Independent vascular and cognitive risk factors for postoperative delirium.* Am J Med 2007;120:807-13.

17 Cerejeira J, Firmino H, Vaz-Serra A, et al. *The neuroinflammatory hypothesis of delirium.* Acta Neuropathol 2010;119:737-54.

18 Hshieh TT, Fong TG, Marcantonio ER, et al. *Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence.* J Gerontol A Biol Sci Med Sci 2008;63:764-72.

19 Caplan JP, Chang G. *Refeeding syndrome as an iatrogenic cause of delirium: a retrospective pilot study.* Psychosomatics 2010;51:419-24.

20 Adamis D, van Munster BC, Macdonald AJ. *The genetics of deliria*. Int Rev Psychiatry 2009;21:20-9.

21 Saczynski JS, Marcantonio ER, Quach L, et al. *Cognitive trajectories after postoperative delirium*. N Engl J Med 2012;367:30-9.

22 Rudolph J, Inouye S, Jones R, et al. *Delirium: an independent predictor of functional decline after cardiac surgery.* J Am Geriatr Soc 2010;58:643-9.

23 Koster S, Hensens AG, Schuurmans MJ, et al. *Consequences of delirium after cardiac operations.* Ann Thorac Surg 2012;93:705-11.

24 Martin BJ, Buth KJ, Arora RC, et al. *Delirium: a cause for concern beyond the immediate postoperative period*. Ann Thorac Surg 2012;93:1114-20.

25 Schweickert WD, Pohlman MC, Pohlman AS, et al. E*arly physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial*. Lancet 2009;373:1874-82.

26 Wang W, Li H-L, Wang D-X, et al. *Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery.* Crit Care Med 2012;40:731-9.

27 Prakanrattana UU, Prapaitrakool SS. *Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery.* Anaesth Intensive Care 2007;35:714-9.

28 Katznelson R, Djaiani GN, Borger MA, et al. *Preoperative use of statins is associated with reduced early delirium rates after cardiac surgery*. Anesthesiology 2009;110:67-73.

29 Dieleman JM, Nierich AP, Rosseel PM, et al. *Intraoperative high dose dexamethasone for cardiac surgery: a randomized controlled trial.* JAMA 2012;308:1761-7.

30 Gamberini M, Bolliger D, Lurati Buse GA, et al. *Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery - A randomized controlled trial*. Crit Care Med 2009;37:1762-8.

31 Maldonado JR, Wysong A, van der Starre PJA, et al. *Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery.* Psychosomatics 2009;50:206-17.

32 Hakim S, et al. *Early treatment with risperidone for subsyndromal delirium after on-pump cardiac surgery in the elderly.* Anesthesiology 2012;116:987-97.

33 Javedan H, Tulebaev S. *Management of common postoperative complications: delirium.* Clin Geriatr Med 2014;30:271-8.

34 Gusmao-Flores D, Salluh JIF, Chalhub RÁ, et al. *The confusion assessment method for the intensive care unit (CAM-ICU) and intensive care delirium screening checklist (ICDSC) for the diagnosis of delirium: a systematic review and*

meta-analysis of clinical studies. Crit Care 2012;16:R115.

[35] Sessler CN, Gosnell MS, Grap MJ, et al. *The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients*. Am J Respir Crit Care Med 2002;166:1338-44.

[36] Inouye S, Bogardus S, Charpentier P, et al. *A multicomponent intervention to prevent delirium in hospitalized older patients*. N Eng J Med 1999;340:669-76.

[37] Eghbali-Babadi M, Shokrollahi N, Mehrabi T. *Effect of Family-Patient Communication on the Incidence of Delirium in Hospitalized Patients in Cardiovascular Surgery ICU*. Iran J Nurs Midwifery Res 2017;22:327-31.

[38] Nelson S, Muzyk AJ, Bucklin MH, et al. *Defining the role of dexmedetomidine in the Prevention of Delirium in the Intensive Care Unit*. Hindawi Publishing Corporation BioMed Research International 2015. http://dx.doi.org/10.1155/2015/635737.

[39] Triltsch AE, Welte M, von Homeyer P, et al. *Bispectral index-guided sedation with dexmedetomidine in intensive care: a prospective, randomized, double blind, placebo-controlled phase II study.* Crit Care Med 2002;30:1007-14.

[40] Djaiani G, Silverton N, Fedorko L, et al. *Dexmedetomidine versus propofol sedation reduces delirium after cardiac surgery: a randomized controlled trial.* Anesthesiology 2016;124:362-8.