International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

Randomised Double Blind Study for Comparison of Dexmedetomidine V/S Midazolam for Reduction of Incidence of Delirium Post Cardiac Surgery

Dr Ajay Sharma[1], Dr Reema Meena[2]

Abstract: ***Background: Delirium is a neurobehavioral syndrome caused by the transient disruption of normal neuronal activity secondary to systemic disturbances. Objective: To Compare dexmedetomidine VS midzolam for reduction of incidence of post valvular cardiac surgery delirium. Methods: Patients underwent elective cardiac surgery with a standardrized intraoperative anesthesia protocol, followed by random assignment to one of two postoperative sedation protocols: dexmedetomidine, or midazolam. Results: Dexmedetomidine group (1/30) observed lesser incidence of delirium in comparison to midazolam group (12/30). Conclusion: Dexmedetomidine is a better drug to decrease the incidence of delirium post cardiac surgery over midazolam, with more haemodynamic stability and early extubation time.***

Keywords: Delirium, neurobehavioral syndrome, transisent disruption, neuronal activity

1. Introduction

The World Health Organization (WHO) has defined delirium as "An etiologically nonspecific organic cerebral syndrome characterized by concurrent disturbances of consciousness and attention, perception, thinking, memory, psychomotor behavior, emotion, and the sleep - wake schedule"[1]. Postoperative cognitive dysfunction (POCD) is defined as "more than expected" postoperative deterioration in cognitive domains, including memory, mood, consciousness, and circadian rhythm[2]. Delirium is a neurobehavioral syndrome caused by the transient disruption of normal neuronal activity secondary to systemic disturbances[3]. Postoperative delirium is an acute organic mental syndrome reported to effect up to 57% of cardiac surgery patients[4].

The incidence of delirium is rather high in both medically and surgically ill patients[5], and even higher among intensive care (ICU) patients (up to 80%).[6] To date, no single cause of delirium has been identified. Known risk factors for delirium include advanced age, pre - existing cognitive impairment, medications Introduction 2 (especially benzodiazepines), sleep deprivation, hypoxia and anoxia, metabolic abnormalities, and a history of alcohol or drug abuse[7]. Patients undergoing major surgery, including cardiac surgery, are at increased risk of developing delirium because of the complexity of the surgical procedure, the administration of intra operative and postoperative anaesthetic and other pharmacological agents, and postoperative complications.[8] Cardiac surgery includes various risk factors which are categorised as modifiable and non modifiable[9]. Non modifiable is Direct Myocardial injury caused by surgery itself[10]. Modifiable includes use of cardiopulmonary bypass [11], Temperature management [12], Surgery duration[13], Arterial pressure management[14], Glycemic control[15], Haemodilution[16], Surgical approach [17], Anaesthetic dosage[18]. Failed or premature extubation of such patients leads to the complications which causes Increased length of ICU and Hospital stay[19]. Increased cost of hospital care[20]. Pateints with post operative delirium have increased likelihood of developing dementia[21] and permanent cognitive Impairment in long term. Development of delirium in the ICU shown to be a predictor of increased morbidity and mortality rate[22]. Despite its prevalence and negative clinical impact, delirium is often unrecognized by medical personnel and staff. Several studies have demonstrated that 32% to 84% of delirium patients go unrecognized by physicians[23]. So its utmost important to develop various strategies to prevent post operative delirium. Multimodal strategy to prevent the postoperative delirium covers different aspect respectively Introduction 3 Baseline cognition should be objectively evaluated with a brief screening tool during preoperative evaluation in any patient with risk factors for preexisting cognitive impairment. Patient with history of Alcohol intake, psychomotor drugs, previous stroke, old age and females are taken on high risk for development of post operative delirium. Post - operative essential ventilation is done in ICU in cardiac patient. ICU sedation[24] is important part of management of cardiac surgery patient. ICU Sedation helps to reduce surgical stress, provide Anxiolysis and normalise sleep wake cycle. Dexmedetomidine[25], Propofol[26], Midazolam[25], Morphine[27], Lorazepam[28], Acetaminophen[29] are various drugs used so far for the prevention of the post operative delirium following cardiac surgery. Post operative pain management via regional anaesthesia or drugs also helps in prevention of post operative Delerium cases. Dexmedetomidine, a highly selective alpha2 - receptor agonist, provides excellent sedation and analgesia with minimal respiratory depression[30] it may be a useful adjuvant during general anaesthesia by promoting haemodynamic stability[31] and decreasing the required doses of anaesthetics and analgesics. This Double - blind, prospective, randomized clinical trial was designed to investigate the effects of postoperative sedation on the development of delirium in patients undergoing cardiac - valve operations with cardiopulmonary bypass (CPB). We postulated that sedation with dexmedetomidine may be associated with a lower incidence of delirium, given its particular pharmacological properties when compared with midazolam.

Aims and Objectives

To Compare dexmedetomidine VS midzolam for reduction of incidence of post cardiac surgery delirium

Primary Objective: To Assess and compare the incidence of cases who develop delirium within 72 hrs of post cardiac surgery between the two groups.

Secondary Objective: To assess and compare the: 1) Haemodynamic Variables (SBP/DBP/MAP/HR) at various interval in. both study group 2) Diffrence in time to extubate in both study group.3) Any Side Effect

2. Material and Methods

The study was conducted in the Cardiothoracic and vascular surgery Operation Theatre, Department of Anesthesiology at tertiary center with due permission from the institutional ethical committee number 23/MC/EC/2018 and written informed patient consent after complete explanation about the study protocol and procedure to the patients. This study was Hospital based, prospective, randomised double blind interventional study. This study was completed between October 2018 to Feb 2019 with a sample size of 30 in each group is adequate at 95% confidence and 80% power to verify the expected difference of 47% in patient developing delirium in both groups (3% vs 50%) based upon the differences in means as per article.31

Patients were randomly allocated into 2 groups. (30 patients in each group) GROUP A (n=30): Patients received inj. Dexmedetomidine 0.4mcg/kg IV followed by infusion at the rate of 0.2 µg/kg/hr. Loading dose to be given in dilution of 10 ml saline over 10 minutes. GROUP B (n=30): Patients received inj. midzolam 0.05mg/kg IV followed by infusion at the rate of 0.1 - 0.2 mg/kg/hr. Loading dose to be given in dilution of 10 ml saline over 10 minutes. Participants underwent a preoperative evaluation and neuropsychiatric testing before randomisation. Patients of age group between 18 - 60 years with ASA Grade 2 and 3 posted for cardiopulmonary bypass valvular surgery with Mallampati Grade 1 and 2 with MMSE (HINDI) Score more then 27/30 were included in study. Patients with pre existing diagnosis of dementia, preoperative use of psychomotor drug, recent or active substance abuse, evidence of advanced heart block, pregnancy or documented stroke within last 6 months were excluded from study.

Anaesthesia for the surgical procedure was standardized among all study groups, including induction with etomidate, fentanyl, and rocuronium and maintenance with fentanyl, midazolam, and inhalation agents (e. g., isoflurane, sevoflurane) and vecuronium. Operative procedures were performed via median sternotomy in conjunction with cardiopulmonary bypass (CPB). During CPB, all subjects were anaesthetised with isoflurane (up to 2%). The only difference in management between the two groups occurred at the time of sternal closure. After successful weaning from CPB, patients were started on one of the two randomly assigned, postoperative sedation regimens: Dexmedetomidine: (loading dose: 0.4mcg/kg, followed by a maintenance infusion of 0.2 mcg/kg/hour) or midazolam drip (0.5 mg/kg folllowed by infusion rate of 0.1 - .2mg/kg/hr). Upon arrival at the ICU, a standardized protocol for postoperative care were implemented for all patients. All patients were extubated when deemed clinically appropriate according to respiratory - care protocols. RAMSAY SEDATION SCORE before extubation is 3 and after extubation 2 is maintained and drugs were titrated accordingly. If a patient developed delirium, haloperidol 5 mg every 2–4 hours was used as needed for agitation not responding to redirection, medical management, and adjustments of the assigned sedative drugs during the first 24 hours after surgery. After the first 24 hours, haloperidol (2 mg IV every 6 hours), and lorazepam (for patients not responding to haloperidol alone) 1 mg IV every 6 hours were available, as needed, for agitation. Haloperidol and lorazepam were used only after a diagnosis 30 of delirium was established. All clinical decisions regarding time of extubation, administration of rescue medications (including pain management, neuroleptics, and benzodiazepines), or removal of a patient from the study were made exclusively by the primary treatment team on the basis of the standardized protocol and clinical judgment without influence or input from the research team. Delirium was assessed daily between 0800 and 2000 hours during the first 3 postoperative days and was diagnosed when symptoms consistent with DSM - IV–TR criteria had been present during the previous 24 hours. This model is similar to that used by numerous other researchers/studies, which used, The Intensive care delirium screening checklist can easily be applied by a clinician or a nurse in a busy critical care setting to screen all patients even when communication is compromised. The tool can be utilised quickly and helps to identify delirious patient. Earlier diagnosis may lead to earlier intervention and better patient care. Postoperative Day 1 evaluations were performed on the first day after surgery, with Time Zero being time of sternal closure. The patients were examined each morning between the hours of 0800 and 2000 for secondary objective measures. Daily evaluations consisted of a patient's interview, a review of the nursing record and medical chart, and a review of medications. All patients were followed until discharge from the hospital. Along with delirium screening mean extubation time, mean heart rate and haemodynamics were studied in both the study group. Side effect if any were also noted in all the patients.

Outcome Variables:
1) Incidence of Delirium (ICDSC)
2) Haemodynamic Variables (SBP/DBP/MAP/ HR)
3) Time to extubate
4) Side effect if any

Statistical Anaylsis
Results were summarised as mean +/ - SD or number and percentage. The difference in mean of two groups were analysed using student T test. RESULTS expressed in form of proportions, difference in proportions Statistical analysis was performed with the SPSS, version 21 for Windows statistical software package (SPSS inc., Chicago, IL, USA). The Categorical data was presented as numbers (percent) and were compared among groups using Chi square test. The quantitative data was presented as mean and standard deviation and were compared by student's t - test. Probability was considered to be significant if less than 0.05.

For significance cut off values is as follows → • $p > 0.05$ = not significant • $p < 0.05$ = significant The level of

significance was kept 95% for all statistical analysis.

3. Results

There were no significant differences between two groups with regard to the distributions of Age, sex as kotekar N have conducted a study that females were more prone for post operative delirium than males, American Society of Anaesthesiologists (ASA) grade Jadon et. al showed that higher grade of ASA which means increasing comorbidity results in more cognitive dysfunction, MMSE score baseline, ejection fraction, duration of anaesthesia and duration of surgery. The types of surgical procedures were also similar in both the groups. Patients were independently examined for the development of delirium during the first 3 postoperative days using (ICDSC) Intensive care delirium screening checklist as many studies have determined the highest incidence of postoperative delirium to occur during the first 3 postoperative days after which time Discussion 48 the onset of delirium could not be clearly attributed to the effects of surgery itself nor distinguished from multiple other factors

Table 1: Showing not significant observations

	Group A	Group B	P value
	Mean	Mean	
Mean Age (yrs)	37.43	38.13	0.837 (NS)
SEX	M - 36%	M - 40%	1 (NS)
MMSE Score	28.96	28.8	0.141 (NS)
2D Echo	56.40	56.77	0.252 (NS)
ASA Score	2 - 80% 3=20%	2 - 63% 3=37	0.252 (NS)
CPB Time	99.33	98.33	0.689 (NS)
Total Duration	3.65	3.72	0.291 (NS)
Lowest Temperature	31.57	31.50	0.599 (NS)

Table 2: Extubation time

	Group A		Group B		P value
	Mean	SD	Mean	SD	
Extubation Time (hrs)	5.80	0.50	7.42	0.97	p<0.001 (S)

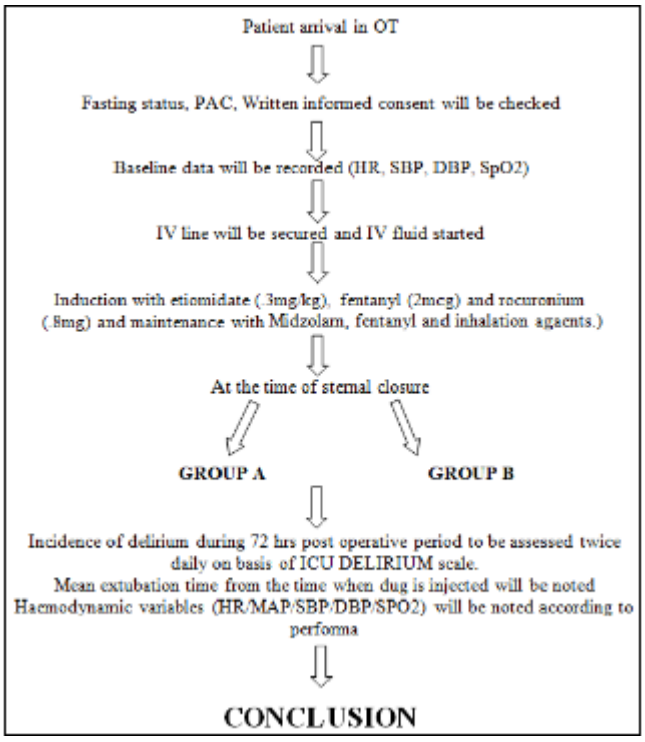
Table 3: Delirium

		Group A (No.)							Group B (No.)							P value
		0	1	2	3	4	5	6	0	1	2	3	4	5	6	
Day 1	1	21	3	4	1		1		18					6	6	0.005
	2	29				1			18				7	5		0.0003
Day 2	1	30							18	1		7	5			p<0.001
	2	30							18		7			5		p<0.001
Day 3	1	30							19	11						0.0001
	2	30							30							-

Table 4: Hemodynamic Parameters

Group A	Group B	P value	Group A	Group B	P value	Group A	Group B	P value	
66	78	<0.0001	78	82	0.12	84	86	0.283	PULSE
80	85	0.09	86	90	0.16	88	92	0.12	MAP

Flow Diagram (Methodology)



4. Discussion

The present study was conducted in the department of Anaesthesiology at tertiary care center with due permission from committee of the research review board.60 patients of either sex belonging to age group of 18 - 60 year with NYHA grade 2 and 3 were scheduled to undergo valvular cardiac surgery were observed. As the patients undergoing intra - cardiac (valvular) surgery are at higher risk of developing delirium, with the assumption that the embolic load to the brain, consisting of particulate matter and air, is higher than in CABG patients, which makes them potentially more vulnerable for postoperative neuropsychiatric deficits. In our study the incidence of delirium for patients undergoing cardiac valvular surgery was 40% in midazolam groups, In contrast the incidence of delirium in pateints receiving dexmedetomidine was 3%, Similar results were observed in the study done by Maldonado et. al showing 50% incidence in midazolam group vs 3% in dexmedetomidine group. Jadon et. al did a clinical study in orthopaedic surgery patient using two groups dexmdetomidine and fentanyl vs midazolam and fentanyl group, Mini mental state examination (MMSE) was performed one day before preoperatively and on 1, 3, and7th day postoperatively. The incidence of POCD was significantly reduced by Dexmedetomidine similar to our study Djaini G et. al compared dexmedetomidine vs propofol sedation, reduction of POCD showed results of dexmedetomidine better than propofol. Dexmedetomidine has high and specific receptor selectivity. Dexmedetomidine does not bind to the GABA receptor and hence has intrinsic delirium - sparing effect as shown by Lin. et. al clinical study Studies have suggested that the likelihood of delirium is increased with the number of neurotransmitter pathways disrupted. Dexmedetomidine asserts its sedative effects by blocking a single neurotransmitter, norepinephrine, via 2 - adrenoceptor binding. Changes in the noradrenergic system have been described as potential causative factors in delirium, with increased levels Discussion of plasma free - MHPG (3 - methoxy - 4 - hydrophenylglycol) concentration observed in some delirium states. In our study oxygen saturation was maintained throughout the study in both the groups, only 6/30 in midazolam group had a oxygen saturation upto 90% in comparision to dexmedetomidine group. Dexmedetomidine produces sedation without respiratory depression Studies have demonstrated that hypoxia and anoxia in the CNS are critical events leading to the biomolecular derangements in delirium. Aakerlund and Rosenberg reported lower postoperative oxygensaturation in post - thoracotomy patients who developed delirium, as compared with patients who did not develop delirium. Dexmedetomidine lacks clinically significant anticholinergic effects. A strong association has been documented between medications with anticholinergic potential and the development of delirium. Dexmedetomidine is believed to promote a more physiologic sleep–wake cycle in the ICU setting. This is important because sleep deprivation and disruption have been implicated in the onset and perpetuation of delirium, In our study sleepwake cycle is one of the factors of screening delirium checklist. Dexmedetomidine has been shown to have neuroprotective effects in humans undergoing cardiac surgery. Zhang Y et. al Studied Effects of different doses of Dexmedetomidine on cognitive dysfunction in elderly patients early after laparoscopic surgery for colorectal cancer found that preferentially 0.5 μg·kg (- 1) ·h (- 1) can reduce the incidence of POCD in elderly patients undergoing laparoscopic surgery for colorectal cancer. Chenj. et. al studied 126 patient who had undergone Discussion 50 laparoscopic cholecystectomy, using clinical interviews showed the role of dexmedetomidine in amelioration of cognitive functions similar to our study. In the present study, we compared the efficacy of dexmedetomidine and midazolam in facilitating extubation (table 9) in patients undergoing cardiac surgery as Mueller in his study showed that time duration of mechanical ventilation is a important factor for prevention of delirium. In our study Extubation time of 5hrs 48min in DEX group and 7hrs 24min in midzolam group (p value ($\leq$0.001)) thus showing early extubation in dexmed group. Similar results were found in the study done by Shehabi32et. al which showed that mean time to extubation was shorter in dexmedetomidine group than midzolam group in critically ill patients (3.7 days vs 5.6 days $P < 0.05$). Venn et al also reported significantly lower heart rate in the dexmedetomidine group (mean [standard deviation] 75 [6] vs.90 [4] beats/min) however, no significant differences were found in arterial pressures between the groups. Shehabi33 et al. also reported a 16% reduction in mean systolic blood pressure and 21% reduction in heart rate over the first 4 h followed by minimal (±10%) changes throughout the infusion. In our Study group Mean arterial pressure were comparable in two groups ($p>0.05$), although in dexmedetomidine group it was lower at 6hrs, 12 hrs and 24 hrs. Our study showed 2 cases of arrhythmia in midazolam group in comparison to no such cases in dexmedetomidine group. Minati choudhary stated that the potent and highly selective dexmedetomidine not only provide unique type of sedation and analgesia, but also provide special anti arrhythmic effect. Limitations of our present study includes the time duration of the study was limited and for shorter duration. Study groups were mostly of younger age group comparatively.

5. Summary

The study was conducted in Department of Anesthesiology; S. M. S. Medical College, Jaipur. Patients were randomly allocated into 2 groups. (30 patients in each group) GROUP A (n=30): patients received inj. Dexmedetomidine GROUP B (n=30): patients received inj. midzolam The primary objective for reduction of Incidence of delirium post cardiac surgery pateients. Dexmedetomidine group (1/30) observed lesser incidence of delirium in comparison to midazolam group (12/30) With p value 0.005. Tracheal extubation time was also recorded shorter in dexmedetomidine group (5.80hrs) in comparison to midazolam group (7.42hrs) with p value statistically significant. Haemodynamically both the groups were moreover similar except for first 24 hrs were stable heart rate was observed in dexmedetomidine group (66/min) on comparison to midazolam group (78/min). Midazolam group was associated with side effect of arrhythmia in few cases which was not seen in dexmedetomidine group. Bradycardia seen with dexmedetomidine was not observed in our study as drug was used in lower dose and administered over a longer duration of time period as shown by Bajwa et al in his study.

6. Conclusion

Our study showed that Dexmedetomidine is a better drug to decrease the incidence of delirium post cardiac surgery over midazolam, with more haemodynamic stability and early extubation time

References

[1] Task Force on DSM - IV. Diagnostic and statistical manual of mental disorders.4th edition. Text revision (DSM - IV - TR). American Psychiatric Association, Washington DC, 2000.
[2] Rasmussen LS (1998). Defining postoperative cognitive dysfunction. European Journal of Anaesthesiology, 15 (6) 761 - 764.
[3] CazaN, Taha R, Qi Y & Blaise G (2008). The effects of surgery and anesthesia on memory and cognition. Progress in Brain Research, 169
[4] Engel GL, Romano J: Delirium: a syndrome of cerebral insuffi - ciency. J Chron Dis 1959; 9: 260–277
[5] Lipowski ZJ: Update on delirium. Psychiatr Clin North Am 1992; 15: 335–346
[6] Maldonado JR: Pathoetiological model of delirium: a compre - hensive understanding of the neurobiology of delirium and an evidence - based approach to prevention and treatment. Crit Care Clin 2008; 24: 789–856
[7] Ely EW, Shintani A, Truman B, et al: Delirium as a predictor of mortality in mechanically - ventilated patients in the intensive care unit. JAMA 2004; 291: 1753–1762
[8] Maldonado JR: Delirium in the acute - care setting: Characteris - tics, diagnosis, and treatment. Crit Care Clin 2008
[9] Smith LW, Dimsdale JE: Postcardiotomy delirium: conclusions after 25 years? Am J Psychiatry 1989;
[10] Burkhart CS, Dell - Kuster S, Gamberini M, Moeckli A, Grapow M, Filipovic M, Seeberger MD, Monsch AU, Strebel SP, Steiner LA: Modi able and nonmodi able risk factors for postoperative delirium after cardiac surgery with car - diopulmonary bypass. J Cardiothorac Vasc Anesth 2010; 24: 555–9
[11] Shroyer AL, Grover FL, Hattler B, Collins JF, McDonald GO, Kozora E, Lucke JC, Baltz JH, Novitzky D; Veterans Affairs Randomized On/Off Bypass (ROOBY) Study Group: On - pump versus off - pump coronary - artery bypass surgery. N Engl J Med 2009; 361: 1827–37
[12] Grocott HP, Mackensen GB, Grigore AM, Mathew J, Reves JG, Phillips - Bute B, Smith PK, Newman MF; Neurologic Outcome Research Group (NORG); Cardiothoracic Anesthesiology Research Endeavors (CARE) Investigators' of the Duke Heart Center: Postoperative hyperthermia is associated with cognitive dysfunction after coronary artery bypass graft surgery. Stroke 2002; 33: 537–41
[13] Van der Mast RC, van den Broek WW, Fekkes D, et al: Incidence of and preoperative predictors for delirium after cardiac surgery. J Psychosom Res 1999;
[14] Siepe M, Pfeiffer T, Gieringer A, Zemann S, Benk C, Schlensak C, Beyersdorf F: 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
[15] Puskas F, Grocott HP, White WD, Mathew JP, Newman MF, Bar - Yosef S: Intraoperative hyperglycemia and cognitive decline after CABG. Ann Thorac Surg 2007; 84: 1467–73
[16] Mathew JP, Mackensen GB, Phillips - Bute B, Stafford - Smith M, Podgoreanu MV, Grocott HP, Hill SE, Smith PK, Blumenthal JA, Reves JG, Newman MF; Neurologic Outcome Research Group (NORG) of the Duke Heart Center: Effects of extreme hemodilution during cardiac surgery on cognitive function in the elderly. ANESTHESIOLOGY 2007
[17] Gu YJ, Mariani MA, Boonstra PW, Grandjean JG, van Oeveren W: Complement activation in coronary artery bypass grafting patients without cardiopulmonary bypass: The role of tissue injury by surgical incision. Chest 1999; 116: 892–8
[18] Silbert BS, Scott DA, Evered LA, Lewis MS, Kalpokas M, Maruff P, Myles PS, Jamrozik K: A comparison of the effect of high - and low - dose fentanyl on the incidence of postopera - tive cognitive dysfunction after coronary artery bypass sur - gery in the elderly. ANESTHESIOLOGY
[19] O'Keeffe S, Lavan J: The prognostic significance of delirium in older hospital patients. J Am Geriatr Soc 1997; 45: 174–178
[20] Pompei P, Foreman M, Rudberg MA, et al: Delirium in hospitalized older persons: outcomes and predictors. J Am Geriatr Soc 1994; 42: 809–815
[21] Murray AM, Levkoff SE, Wetle TT, et al: Acute delirium and functional decline in the hospitalized elderly patient. J Gerontol 1993
[22] Ebert AD, Walzer TA, Huth C, et al: Early neurobehavioral disorders after cardiac surgery: a comparative analysis of coro - nary artery bypass graft surgery and valve replacement. J Car - diothor Vasc Anesth 2001; 15: 15–19
[23] Lewis LM, Miller DK, Morley JE, et al: Unrecognized delirium in ED geriatric patients. Am J Emerg Med 1995; 13: 142–145
[24] Maldonado J, van der Starre PJ, Wysong A: Postoperative seda - tion and the incidence of ICU delirium in cardiac surgery pa - tients. Presented at the American Society of Anesthesiologists, Annual Meeting. San Francisco, CA, Anesthesiology 2003;
[25] Yapici N, Coruh T, Kehlibar T, Yapici F, Tarhan A, Can Y, Ozler A, Aykac Z: Dexmedetomidine in cardiac surgery patients who fail extubation and present with a delirium state. Heart Surg Forum 2011, 14: E93 - 98.20.
[26] Dasta JF, Jacobi J, Sesti AM, McLaughlin TP: Addition of dexmedetomidine to standard sedation regimens after cardiac surgery: an outcomes analysis. Pharmacotherapy 2006, 26 (6): 798 - 805.22.
[27] Abd Aziz N, Chue MC, Yong CY, Hassan Y, Awaisu A, Hassan J, Kamarulzaman MH: Efficacy and safety of dexmedetomidine versus morphine in post - operative cardiac surgery patients. Int J Clin Pharm 2011, 33: 150 - 154.12.
[28] Pandharipande PP, Pun BT, Herr DL, Maze M, Girard TD, Miller RR, ShintaniThompson JL, Jackson JC,

Deppen SA, Stiles RA, Dittus RS, Bernard GR, Ely EW: Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007

[29] Wunsch H, Kahn JM, Kramer AA, Rubenfeld GD: Use of intravenous infusion sedation among mechanically ventilated patients in the United States. Crit Care Med 2009, 37: 3031 - 3039.

[30] Hsu YW, Cortinez LI, Robertson KM, et al: Dexmedetomidine pharmacodynamics, part I: crossover comparison of the respiratory effects of dexmedetomidine and remifentanil in healthy volunteers. Anesthesiology 2004;

[31] Shehabi Y, Ruettimann U, Adamson H, Innes R, Ickeringill M. Dexmedetomidine infusion for more than 24 hours in critically ill patients: Sedative and cardiovascular effects. Intensive Care Med 2004

[32] Maldonado, J. R., Wysong, A., van Der Starre, P. J., Block, T., Miller, C., Reitz, B. A. Dexmedetomidine and the reduction of postoperative delirium after cardiac surgery. Psychosomatics.2009.