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Comparison of the incidence and severity of delirium and biochemical factors after coronary artery bypass grafting with dexmedetomidine: A randomized double-blind placebo-controlled clinical trial study

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Original Article

Abstract

BACKGROUND: One of the most common postoperative problems, such as open heart surgery, is delirium, which is responsible for increased mortality and morbidity. Therefore, it is necessary to find a way to cure this disease. The purpose of this study was to assess the effect of dexmedetomidine administration on the prevention of delirium after coronary artery bypass grafting (CABG) surgery.

METHODS: This randomized double-blind placebo-controlled clinical trial was performed on 88 patients (44 in the intervention group and 44 in the control group) undertaking CABG surgery. The intervention group was subcutaneously treated with doses of 1 µg/kg of dexmedetomidine for 10 minutes, and 0.2-0.7 µg/kg in hour infusion was applied. The control group underwent normal saline infusion as a placebo. Chi-square and analysis of variance (ANOVA) tests were used to compare the data.

RESULTS: Administration of dexmedetomidine in intervention group significantly decreased delirium (P = 0.040) and delirium intensity (P = 0.001). Moreover, patients treated with dexmedetomidine had more stability in laboratory variables and vital signs, and also the duration of hospitalization in these patients was significantly lower than control group (P = 0.002).

CONCLUSION: Considering the efficacy of dexmedetomidine on preventing the incidence and severity of delirium and reducing mortality and morbidity, it is recommended that another study with the larger sample size, with different doses and different prescribing methods be conducted to better understand the effect of this drug and achieve a safe dose with maximum efficacy.

Keywords: Delirium, Coronary Artery Bypass Grafting, Dexmedetomidine

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Introduction

One of the most common problems after surgery including open heart surgery is delirium, which causes increased mortality and morbidity.[1-4] Delirium is a cognitive-behavioral disorder and its causes after surgery include change in the normal nervous activity, secondary to systemic disorders including impaired cholinergic system. Although postoperative delirium may occur in all individuals, however, some people are at high risk including older people (> 70 years of age), those with diabetes, smoking and narcotics, lung surgery, history of high blood pressure, pulmonary disease, atrial fibrillation (AF), and electrolyte disturbances including sodium and hypoglycemia.[5,6]

According to researches, the prevention and treatment of fast-acting delirium after surgery can reduce mortality and morbidity.[7] Several drugs have been designed for delirium after heart surgery including endonestrone, haloperidol, ketamine, rivastigmine and dexmedetomidine, midazolam, and morphine.

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The purpose of the prescribing drugs is sedation, prevention, and treatment of delirium, blood pressure control, rapid patient extubation, reduction of cognitive impairment, and consequently reduced mortality and morbidity.

Selective treatment of delirium after surgery is haloperidol.[1] However, a specific drug is not a selective drug for the prevention of delirium, and many studies have been conducted on various drugs to evaluate the effectiveness of the treatment of delirium after surgery. The purpose of this research is to find a more effective drug with less complication. Haloperidol and dexmedetomidine are two of the most effective drugs in the prevention of delirium that have been studied in the studies. One of the studies in this field was conducted by Reade et al., comparing dexmedetomidine and haloperidol, which showed that intensive care unit (ICU) duration and delirium induced by dexmedetomidine administration was less than haloperidol.[7] In a study by Urden et al., comparing dexmedetomidine and haloperidol, the duration of hospitalization in the ICU with dexmedetomidine was lower than haloperidol, but there was no difference in the incidence of delirium[8]

Considering the high prevalence of delirium after surgery including cardiac surgery and the preventive effect of dexmedetomidine on mortality and morbidity, and according to research conducted in comparison it with other drugs and the contradictory results of the studies, the aim of this study is to assess the efficacy of dexmedetomidine in preventing and controlling delirium after cardiac surgery.

Materials and Methods

This was a randomized double-blind clinical trial. In order to prevent possible errors and biases during data collection and evaluation, clinical and analytic caregivers were unaware of the assignment of the study group. Subjects of this study included all patients undergoing coronary artery bypass grafting (CABG) surgery who referred to Shahid Chamran Hospital in Isfahan, Iran, in 2016-2017. The sample size of this study was calculated using the sample size estimation formula for outbreak studies. The 95% confidence interval (CI) level was considered, the prevalence of agitation after CABG surgery was considered to be 0.5, which included 44 persons (in each group). The probability of loss of subjects in each group would be 50 people. Sampling was done in a non-probable and randomized manner (Figure 1).

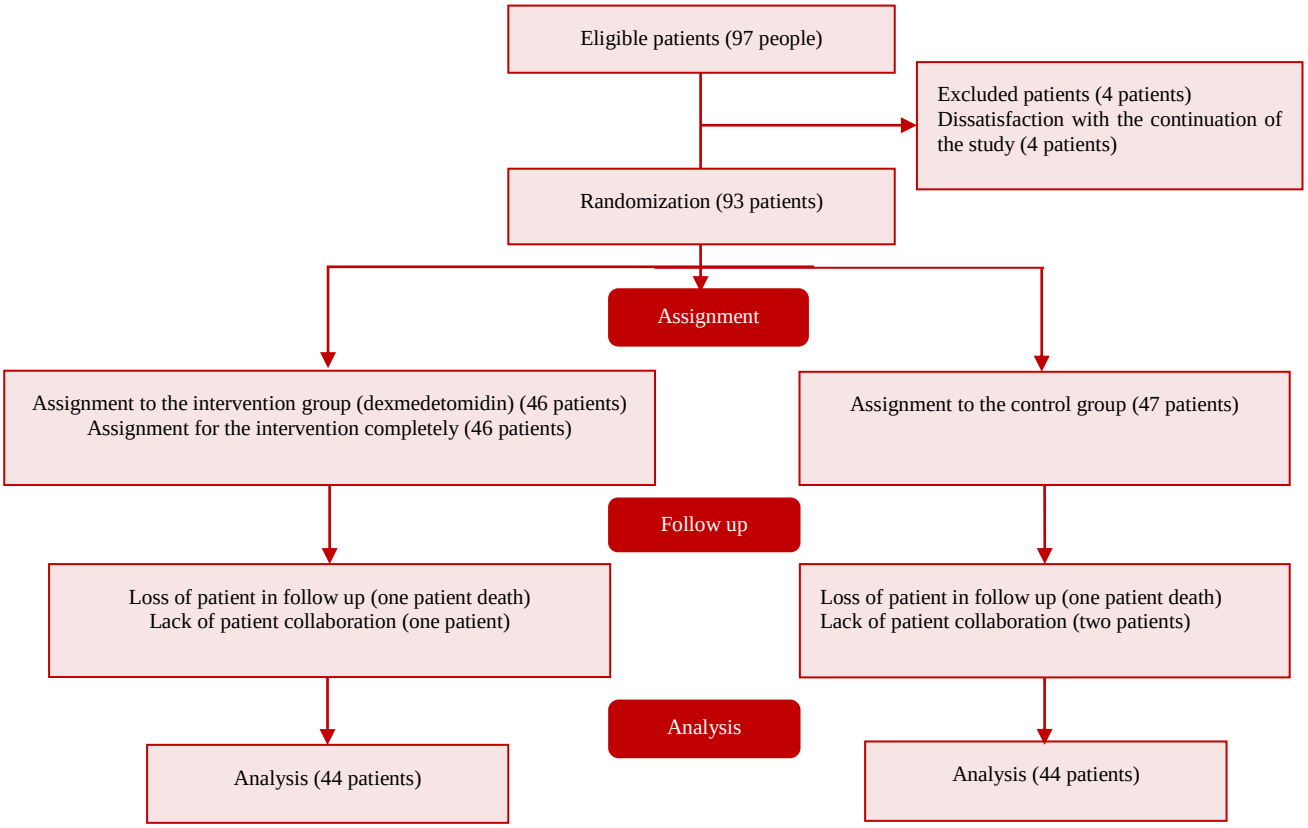

Figure 1. Study flowchart (CONSORT format)

The inclusion criteria included living patients aged 40-80 years who were candidates for CABG surgery and approved to participate in the study and had no history of mental illness and dementia. Exclusion criteria included a person's lack of cooperation, defect in the examined data, the need for re-operation due to hemorrhage after entering ICU, excessive sensitivity to haloperidol and phenothiazines, having Parkinson's disease (resting shaking) and weakness in the central nervous system (CNS), glaucoma, history of seizure, and receiving anti-seizure, anti-Parkinson, or lithium medication.

After obtaining permission from the Medical Ethics Committee of Isfahan University of Medical Sciences, Isfahan City, and the registration of the trial with IRCT20171104037209N1 code number at the Iranian Center for Clinical Trials and performing the necessary coordination, candidates for CABG surgery referring to Shahid Chamran Hospital were selected. After obtaining their informed consent to participate in the study, their demographic information including age, sex, weight, level of education, history of diabetes [diagnosed by a medical history and taking diabetic drugs or high blood glucose (≥ 126)], hypertension disease (diagnosed by a medical history and taking blood pressure drugs), addiction to cigarette, narcotics and alcohol, history of using psychiatric drugs, and the personality type [that is divided into two categories A and B which having personality type A was considered as a risk factor for cardiovascular disease (CVD) due to being aggressive, impatient, and competitive; this variable is evaluated by a completed questionnaire Ganji[9] was prepared and recorded in a data collection form. Additionally, the newest amount of laboratory variables including hemoglobin (Hb) (g/dl), white blood cell (WBC) (/mm^3), blood urea nitrogen (BUN) (mg/dl), creatinine (mg/dl), sodium (mg/l), and potassium (mg/l) (measured with kits of Parsa and ParsAzmun and electrolyte analyzer device) before surgery was extracted from the case and recorded. Patients were assigned in two groups of intervention and control using random allocation software. The intervention group received 1 µg/kg doses of dexmedetomidine immediately within 10 minutes and the infusion of 0.2-0.7 µg/kg/h of dexmedetomidine in a volume equivalent to 50cc by the syringe pump, and the control group underwent infusion of normal saline with the same volume by the syringe pump as placebo. In the event of agitation, both control and intervention groups received haloperidol (0.5 mg intramuscular) and in the intervention group, the administration of dexmedetomidine continued until that the conditions for separating the patients from the ventilator were obtained.

The patients were followed up to 72 hours after the operation and the daily amounts of Hb (g/dl), WBC (/mm3), BUN (mg/dl), creatinine (mg/dl), sodium (mg/l), and potassium (mg/l) up to 72 hours after surgery were recorded. The incidence of delirium, delirium intensity, prescription dose, duration of administration, side effects, duration of hospitalization in ICU, sedation rate, and duration of intubation was extracted and recorded in each patient's profile.

The frequency of occurrence of post-operative agitation was determined using the Richmond Agitation-Sedation Scale (RASS) and patient's review every 24 hours for up to 72 hours. A RASS questionnaire consists of 10 levels, which according to a researcher's clinical evaluation categorizes patients from aggressive to unresponsive to stimuli levels. Then, patients were divided into two groups of A and B (aggression and non-aggression) based on this criterion. The validity and reliability of the questionnaire was confirmed,[10,11] and the percentage of delirium occurrence was determined by treatment group. Based on the RASS criteria, the score more than +2 was considered as post-operative incidence of agitation in the patient.

The Confusion Assessment Method for ICU (CAM-ICU) was also studied in this study. This tool was introduced by Inouye et al.[12] and Thomason et al.,[13] and has been proven to be effective in detecting confusion and monitoring of delirium in ICU patients. Moreover, the validity of the Persian version of this tool with a specificity of 99.1% and sensitivity of 66.7% was confirmed.[14]

All patients' information including demographic factors and laboratory findings were recorded in a checklist made by the registrar and entered into SPSS software (version 18, SPSS Inc., Chicago, IL, USA). To compare the mean of quantitative variables [the normal distribution of them investigated by the Kolmogorov-Smirnov test (K-S test)] independent t-test was used and to compare the frequency distribution of nominal qualitative variables, chi-square test and if necessary, Fisher's exact test were used. Moreover, to compare the frequency distribution of ordinal qualitative variables the Mann-Whitney U test was used.

Results

Among 88 patients who were candidates for open heart surgery, 72 (81.8%) were men and 16 (18.2%)

were women, the mean age of the subjects was 61.55 ± 4.80 years. In our study, it was found that the overall prevalence of delirium in patients undergoing open heart surgery was 13 patients (14.77%).

Independent t-test revealed that there was no significant difference in mean age (P = 0.810) and ejection fraction (EF) percent (P = 0.340) between the two groups. The Mann-Whitney test showed that there was no significant difference in the level of education between the two groups (P = 0.490). Also, chi-square test showed that there was no significant difference in the distribution of personality type between two groups (P = 0.590). Chi-square test showed that there was no significant difference between the two groups in high blood pressure (P = 0.520), smoking (P = 0.370), alcohol consumption (P = 0.250), and narcotics use (P = 0.190) (Table 1).

Fisher's exact test showed that there was no significant difference in incidence of arrhythmias between the two groups before ICU (P = 0.340) and after ICU (P = 0.330).

There was no significant difference between the mean pH before of the pump until the first day of the ICU between the two groups (P > 0.050), but in the second day (P = 0.002) and third day (P = 0.020) of the ICU, it was significantly higher in the control group than the dexmedetomidine group.

The mean O_2 after the pump (P = 0.030) in the dexmedetomidine group and in the first day of ICU (P = 0.001) in the control group was significantly higher than the other group; but in other times, there was no significant difference between the two groups (P > 0.050). The mean of CO_2 during the pump (P = 0.007), the first day (P = 0.010), and the second day (P = 0.020) of the ICU in the dexmedetomidine group was significantly higher than the control group but at other times there was no significant difference between the two groups (P > 0.050). The mean HCO_3 before the pump (P = 0.030) in the control group and at the first day of the ICU (P = 0.010) in the dexmedetomidine group was significantly higher than the other group, but it did not differ significantly between the two groups at other times (P > 0.050). The mean base excess (BE) before the pump (P = 0.005) and on the second day (P = 0.004) and the third day (P = 0.030) of the ICU in the control group was significantly higher than dexmedetomidine group, but at other times no significant difference was observed between the two groups (P > 0.050).

After Bartlett's test of sphericity, the repeated measures test showed that the effect of time on pH, O_2, CO_2, HCO_3, and BE was significant (P < 0.001). But the effect of the group has only been significant on pH (P = 0.010), CO_2 (P = 0.020), and BE (P = 0.020).

Table 1. Frequency distribution of demographic factors and risk factors in the two groups of dexmedetomidine and control

Variable	Control group (n = 44)	Dexmedetomidine group (n = 44)	P
	Mean ± SD	Mean ± SD	
Age (year)*	61.30 ± 8.90	61.80 ± 7.90	0.810
EF percent*	49.10 ± 8.20	50.80 ± 8.10	0.340
	n (%)	n (%)	
Diabetes**	21 (47.7)	21 (47.7)	> 0.990
Hypertension**	17 (38.6)	20 (45.5)	0.520
Smoking**	13 (29.5)	17 (38.6)	0.370
Alcohol consumption	0 (0)	2 (4.5)	0.250
Narcotics use**	7 (15.9)	12 (27.3)	0.190
Level of education***			0.490
Illiterate	28 (63.6)	32 (72.8)	
Under diploma	9 (20.5)	4 (9.1)	
Diploma	5 (11.4)	6 (13.6)	
Above diploma	2 (4.5)	2 (4.5)	
Personality type**,£			0.590
A	28 (64.0)	30 (68.0)	
B	16 (36.0)	14 (32.0)	

* T-test; ** Chi-square test; *** Mann-Whitney test; £ The personality type is divided into two categories A and B, having personality type A is a risk factor for cardiovascular disease (CVD) due to being aggressive, impatient, and competitive. This variable is evaluated by a completed questionnaire.
SD: Standard deviation; EF: Ejection fraction

Table 2. Distribution of the need for blood and its products in two groups of dexmedmotidine and control before entering the intensive care unit (ICU) and in the ICU

Variable	Time	Control group (n = 44)	Dexmedetomidine group (n = 44)	P
		n (%)	n (%)	
Packed* cell	During surgery	22 (50.0)	13 (29.5)	0.048
	In the ICU	29 (65.9)	22 (50.0)	0.130
FFP*	During surgery	3 (6.8)	3 (6.8)	> 0.990
	In the ICU	13 (29.5)	15 (34.1)	0.650
Cryo**	During surgery	1 (2.3)	0 (0)	0.500
	In the ICU	3 (6.8)	5 (11.4)	0.360
Platlet**	During surgery	1 (2.3)	1 (2.3)	> 0.990
	In the ICU	3 (6.8)	1 (2.3)	0.310

* Chi-square test; ** Fisher's exact test
FFP: Fresh frozen plasma; Cryo: Cryoprecipitate; ICU: Intensive care unit

Chi-square test showed that the frequency of the need for packed cell before entering ICU was significantly higher in control group than the dexmedetomidine group (P = 0.048), but there was no significant difference in ICU between the two groups (P = 0.130) (Table 2).

Independent t-test showed that there was no significant difference between the mean of BUN before entering ICU (P = 0.25) and in the first day of ICU (P = 0.86) between the two groups, but in the second day (P = 0.007) and the third day (P = 0.001) of ICU, it was significantly higher in the control group than in the dexmedetomidine group. There was no significant difference in the pre-operative sodium level in the second day of ICU between the two groups (P > 0.050), but on the third day of ICU, it was significantly higher in the control group than the dexmedetomidine group (P = 0.003). The mean of potassium before entering the ICU was completely identical in both groups, but after the first day of ICU in the control group, it was significantly higher than the dexmedetomidine group (P < 0.050). After Bartlett's test of sphericity, the repeated measures test showed that the effect of time on Bun, creatinine, Hb, sodium, and potassium was significant (P < 0.001). But the effect of the group has only been significant on Bun (P = 0.030), sodium (P = 0.004), and potassium (P = 0.002) (Table 3).

Independent t-test showed that the mean duration of hospitalization in ICU (P = 0.002) and pump (P = 0.030) in control group was significantly higher than the dexmedetomidine group.

Chi-square test showed that the delirium frequency in the ICU was significantly higher in the control group than in the dexmedotine group (P = 0.040). The Mann-Whitney test showed that the severity of delirium in the ICU was significantly higher in the control group than the dexmedetomidine group (P < 0.001) (Table 4).

Our results verified that there was no significant difference between two groups before ICU and after separation from the pump in receipt of inotropic drugs (P > 0.050).

The mean of arterial blood pressure before surgery (P = 0.500) and in the third day of ICU (P = 0.530) did not show significant difference between the two groups, but in the first day (P = 0.002) and the second day (P < 0.001) of the ICU, it was significantly lower in the control group than in the dexmedetomidine group. There was no significant difference in mean heart rate at any time between two groups (P > 0.050).

Discussion

The results of our study revealed that the administration of dexmedetomidine significantly reduced the delirium and also the severity of delirium in the affected patients. On the other hand, our study showed that patients receiving dexmedetomidine had more stability in laboratory variables [sodium, potassium, and arterial blood gases (ABGs)] and the vital signs including blood pressure, and the duration of hospitalization in these patients was significantly lower. Therefore, based on the results of our study, it can be concluded that dexmedetomidine significantly reduces delirium and increases the stability of vital signs in patients.

A study by Thomason et al. revealed that delirium after using dexmedetomidine was less than haloperidol use (54% vs. 76%, P < 0.001).[13] The results of this study are consistent with findings of our study.

Table 3. Evaluation of some laboratory variables in patients in both dexmedetomidine and control groups

Variable	Time	Control group (n = 44)	Dexmedetomidine group (n = 44)	P	P effect of time	P effect of group
		Mean ± SD	Mean ± SD			
Bun*	Before entering ICU	34.80 ± 11.30	32.40 ± 8.03	0.250	< 0.001	0.030
	First day in ICU	28.90 ± 8.10	29.20 ± 9.70	0.860		
	Second day in ICU	37.10 ± 10.50	31.60 ± 8.10	0.007		
	Third day in ICU	43.20 ± 11.70	34.80 ± 11.40	0.001		
Creatinine*	Before entering ICU	1.04 ± 0.20	1.02 ± 0.19	0.590	< 0.001	0.390
	First day in ICU	1.03 ± 0.19	1.05 ± 0.21	0.530		
	Second day in ICU	1.15 ± 0.31	1.11 ± 0.16	0.470		
	Third day in ICU	1.10 ± 0.24	1.01 ± 0.14	0.020		
Hb*	Before entering ICU	13.90 ± 2.30	13.70 ± 1.80	0.610	< 0.001	0.380
	Before the pump	12.20 ± 2.30	12.90 ± 2.20	0.140		
	During the pump	8.30 ± 1.40	9.40 ± 1.40	0.360		
	After the pump	9.50 ± 1.60	10.02 ± 1.10	0.080		
	First day in ICU	10.60 ± 1.50	10.20 ± 1.30	0.130		
	Second day in ICU	10.30 ± 1.10	10.40 ± 1.10	0.650		
	Third day in ICU	10.30 ± 0.90	10.60 ± 0.90	0.150		
Sodium*	Before entering ICU	140.80 ± 3.90	138.40 ± 3.80	0.150	< 0.001	0.004
	Before the pump	138.80 ± 5.10	138.60 ± 2.50	0.820		
	During the pump	133.70 ± 5.50	131.80 ± 3.60	0.260		
	After the pump	134.70 ± 4.20	134.20 ± 3.20	0.510		
	First day in ICU	140.90 ± 4.20	140.50 ± 3.20	0.650		
	Second day in ICU	141.02 ± 4.50	140.30 ± 2.90	0.360		
	Third day in ICU	141.02 ± 3.70	137.70 ± 4.40	0.300		
Potassium*	Before entering ICU	4.40 ± 0.50	4.40 ± 0.40	> 0.999	< 0.001	0.002
	Before the pump	4.10 ± 0.90	3.70 ± 0.40	0.004		
	During the pump	5.10 ± 0.90	4.80 ± 0.70	0.045		
	After the pump	5.50 ± 0.90	4.90 ± 0.70	0.001		
	First day in ICU	4.70 ± 0.80	4.40 ± 0.50	0.030		
	Second day in ICU	4.40 ± 0.50	4.30 ± 0.50	0.370		
	Third day in ICU	4.10 ± 0.50	4.20 ± 0.40	0.640		

* T-test and repeated measures test

BUN: Blood urea nitrogen; Hb: Hemoglobin; ICU: Intensive care unit; SD: Standard deviation

In a study by Tan and Ho comparing dexmedetomidine and haloperidol, the duration of hospitalization in the ICU with dexmedetomidine was lower than haloperidol, but no difference was observed in the delirium incidence.[10]

Table 4. Evaluation of the conditions of operation, incidence and severity of delirium, and the administration of haloperidol in the event of delirium in patients of both dexmedetomidine and control groups

Variable		Group		P
		Control group (n = 44)	Dexmedetomidine group (n = 44)	
		Mean ± SD	Mean ± SD	
Clamp time (minute)*		60.20 ± 16.80	55.20 ± 21.70	0.230
Pump time (minute)*		100.90 ± 25.80	89.10 ± 31.50	0.030
Duration of surgery (hour)*		4.70 ± 0.60	4.80 ± 1.00	0.730
Mechanical respiration duration (hour)*		10.50 ± 4.04	10.50 ± 3.40	> 0.990
Duration of admission to ICU (day)*		2.70 ± 0.70	2.30 ± 0.60	0.002
The onset of a diet (day)*		11.40 ± 4.20	10.70 ± 3.00	0.480
		n (%)	n (%)	
Delirium occurrence**	No	35 (79.5)	40 (90.9)	0.040
	Yes	9 (20.5)	4(9.1)	
CAM-ICU (delirium intensity)***	Step 1	2 (4.5)	16 (36.4)	0.001
	Step 2	33 (75.0)	25 (56.8)	
	Step 3	4 (9.1)	2 (4.5)	
	Step 4	5 (11.4)	1 (2.3)	
Receiving haloperidol in the event of delirium		9 (20.5)	2 (4.5)	0.020

* T-test; ** Chi-square test; *** Mann-Whitney test

SD: Standard deviation; ICU: Intensive care unit; CAM-ICU: Confusion assessment method for intensive care unit

Study results concerning the reduction of hospital stay in the ICU is consistent with our findings, but the lack of superiority to dexmedetomidine contradicts our study results. The reason for the difference in the results of our study and the mentioned study may be due to the difference in the sample size, the demographic characteristics, the type of disease, and the applied dose of drugs. But in a study by Girard et al. dexmedetomidine, comparing with other drugs, was highly effective in reducing the incidence of delirium.[1] The results of this study are consistent with findings of our study.[1]

In 2010, Yapici et al. suggested that dexmedetomidine was a selective drug in treating delirium after cardiac surgery because of side effects of other drugs including haloperidol.[15]

Although Hipp and Ely introduced haloperidol as the preferred drug for treating delirium, they reported that dexmedetomidine was safer and also depletion of delirium and more effective treatment of delirium with the administration of dexmedetomidine were reported.[16] The results of these studies are consistent with the findings of our study. Siobal et al. stated that dexmedetomidine was less complicated and the incidence of delirium decreased with the administration of dexmedetomidine.[17] The results of this study are consistent with the findings of our study.

Conclusion

The results of our study showed that the administration of dexmedetomidine significantly reduced the delirium and also the severity of delirium in the affected patients. On the other hand, our study showed that patients receiving dexmedetomidine had more stability in laboratory variables and vital signs including blood pressure. On the other hand, the duration of hospitalization was significantly lower in these patients. Due to the high incidence of delirium after surgery, the diagnosis, screening, and successful treatment of this disease by dexmedetomidine with the least complication after open heart surgery is very important.

Study limitations: One of the limitations of the study was the impossibility of using different doses and different methods of administering dexmedetomidine in the studied patients, which was due to the lack of sample size at the time of the study. Therefore, considering the efficacy of dexmedetomidine, another study with the larger sample size and with different doses and different prescribing methods can be used to better understand the effect of this drug and achieve a safe dose with maximum efficacy. Also, in our study, the long pump and the need for packed cell more in the haloperidol group are two confounding factors. Therefore, another study with a larger sample size is recommended to overcome these two confounding factors.

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Conflict of Interests

Authors have no conflict of interests.

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