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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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

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. 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. 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.

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)](http://arya.mui.ac.ir)
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 ($\geq 126$)], 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. Based on the RASS criteria, the score more than +2 was considered as post-operative incidence of agitation in the patient.

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.

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     |
|---------------------------|------------------------|--------------------------------|-------|
| Age (year)*               | 61.30 ± 8.90           | 61.80 ± 7.90                   | 0.810 |
| EF percent                | 49.10 ± 8.20           | 50.80 ± 8.10                   | 0.340 |
| 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

The mean O₂ 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 CO₂ 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 HCO₃ 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 control 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, O₂, CO₂, HCO₃, and BE was significant (P < 0.001). But the effect of the group has only been significant on pH (P = 0.010), CO₂ (P = 0.020), and BE (P = 0.020).
**Prevention of delirium after CABG**

Table 2. Distribution of the need for blood and its products in two groups of dexmedetomidine 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   |
| Platellet**  | 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 in 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 dexmedetidine 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). The results of this study are consistent with findings of our study.
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 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 |
|------------|-------------------------------|------------------------|-------------------------------|----|-----------------|------------------|
| 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

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 in both dexmedetomidine and control groups

| Variable                          | Group                          | P      |
|-----------------------------------|--------------------------------|--------|
|                                   | Control group (n = 44)         |        |
|                                   | Dexmedetomidine group (n = 44) |        |
| Clamp time (minute)               | Mean ± SD                      | Mean ± SD |
| Pump time (minute)                | 60.20 ± 16.80                  | 55.20 ± 21.70 | 0.230 |
| 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 |
| Delirium occurrence               | No                             | 35 (79.5) | 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 | Yes | 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.

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.13

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. Sival 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.

References

1. Girard TD, Pandharipande PP, Ely EW. Delirium in the intensive care unit. Crit Care 2008; 12(Suppl 3): S3.
2. Ely EW, Stephens RK, Jackson JC, Thomason JW, Truman B, Gordon S, et al. Current opinions regarding the importance, diagnosis, and management of delirium in the intensive care unit: A survey of 912 healthcare professionals. Crit Care Med 2004; 32(1): 106-12.
3. Mac Sweeney R, Barber V, Page V, Ely EW, Perkins GD, Young JD, et al. A national survey of the management of delirium in UK intensive care units. QJM 2010; 103(4): 243-51.
4. Fricchione GL, Nejad SH, Esses JA, Cummings TJ Jr, Querques J, Cassem NH, et al. Postoperative delirium. Am J Psychiatry 2008; 165(7): 803-12.
5. Guenther U, Theuerkauf N, Frommann I, Brimmers K, Malik R, Stori S, et al. Predisposing and precipitating factors of delirium after cardiac surgery: A prospective observational cohort study. Ann Surg 2013; 257(6): 1160-7.
6. Steiner LA. Postoperative delirium. part 2: Detection, prevention and treatment. Eur J Anaesthesiol 2011; 28(10): 723-32.
7. Reade MC, O’Sullivan K, Bates S, Goldsmith D, Ainslie WR, Bellomo R. Dexmedetomidine vs. haloperidol delirium, agitated, intubated patients: A randomised open-label trial. Crit Care 2009; 13(3): R75.
8. Urdan LD, Stacy KM, Lough ME. Thelan's critical care nursing-diagnosis and management. 4th ed Philadelphia, PA: Elsevier Science Health Science Division; 2005.
9. Ganji H. Character evaluation. Tehran, Iran: Savalan Publication; 2001. [In Persian].
10. Tan JA, Ho KM. Use of dexmedetomidine as a sedative and analgesic agent in critically ill adult patients: A meta-analysis. Intensive Care Med 2010; 36(6): 926-39.

11. Urden LD, Stacy KM, Lough ME. Critical care nursing: diagnosis and management. 6th ed. Philadelphia, PA: Mosby/Elsevier; 2010.

12. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. Ann Intern Med 1990; 113(12): 941-8.

13. Thomason JW, Shintani A, Peterson JF, Pun BT, Jackson JC, Ely EW. Intensive care unit delirium is an independent predictor of longer hospital stay: a prospective analysis of 261 non-ventilated patients. Crit Care 2005; 9(4): R375-R381.

14. Zolfaghari M, Arbabi M, Pedram Razi S, Biat K, Bavi A. Effectiveness of a multifactor educational intervention on delirium incidence and length of stay in patients with cardiac surgery. Hayat 2012; 18(1): 67-78. [In Persian].

15. Yapici N, Coruh T, Kehlibar T, Yapici F, Tarhan A, Can Y, et al. Dexmedetomidine in cardiac surgery patients who fail extubation and present with a delirium state. Heart Surg Forum 2011; 14(2): E93-E98.

16. Hipp DM, Ely EW. Pharmacological and nonpharmacological management of delirium in critically ill patients. Neurotherapeutics 2012; 9(1): 158-75.

17. Siobal MS, Kallet RH, Kivett VA, Tang JF. Use of dexmedetomidine to facilitate extubation in surgical intensive-care-unit patients who failed previous weaning attempts following prolonged mechanical ventilation: A pilot study. Respir Care 2006; 51(5): 492-6.