

Effect of Preoperative Dexmedetomidine on Prevalence of Postoperative Cognitive Dysfunction in Elderly Patients Candidate for Orthopedic Surgery under General Anesthesia

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ABSTRACT

Background: Postoperative cognitive dysfunction (POCD) is amongst the most critical complications after surgery. This study shows the effect of dexmedetomidine on the prevalence of postoperative cognitive impairment.

Methods: In this double-blinded clinical trial study, patients aged 60-80 years undergoing pelvic and femoral orthopedic surgery were randomly assigned in one of the two groups of the course, i.e., Dexmedetomidine (DEX) or normal saline (NS). We infuse One hour before anesthesia, one $\mu\text{g}/\text{kg}$ dexmedetomidine in the group (DEX), and the same volume of normal saline (NS). Mini-Mental State Examination test (MMSE) was applied to evaluate the patients' cognitive condition, One day before the surgery, 24 and 72 hours after the surgery.

Results: There was no significant difference between the two groups in terms of age, sex, duration of anesthesia, duration of surgery, and the amount of bleeding during operation ($P>0.0$). The postoperative hematocrit level was lower than the preoperative level in the group (DEX) ($P<0.05$). There was no significant difference in MMSE test scores pre and postoperatively between the two groups ($P>0.05$).

Conclusion: Dexmedetomidine infused before surgery has no preventive effect on POCD in elderly patients undergoing pelvic and femoral orthopedic surgery under general anesthesia.

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Postoperative cognitive dysfunction (POCD) is a common complication after the surgery, especially in elderly patients. This complication may manifest itself by memory deficits, disorientation about the place, and persons and disabilities in the process of thought and speech. The pathogenesis of this complication is quite vague [1-3]. The main risk factors for POCD include infection, patient age, type and duration of surgery, the anesthetic drugs, comorbidities, and sleep disorders [4-5]. For instance, its incidence is very high in elderly patients undergoing an operation for removing a malignant tumor because of the inherent long

duration of surgery and postoperative stress responses [6-7]. In addition to decreasing the patient's life quality, POCD can also increase the postoperative mortality rate. The release of cytokines due to the stress response provoked itself may induce malfunctions in the brain and finally represent POCD [8]. The dexmedetomidine is an alpha-2 agonist with central sympatholytic, a potent analgesic, and sedative effects. The Dexmedetomidine acts as an analgesic and anxiolytic [9-13]. Using this drug, depending on its dose can reduce blood pressure and heart rate in old patients. This study can clarify the

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role of dexmedetomidine in improving cognitive disorders after surgery.

Methods

We run this randomized, double-blind clinical trial in the Anesthesiology Department of Firoozgar Hospital, Tehran, Iran. Inclusion criteria are patients with ASA physical class I-III, ages 60-80 years, candidate for pelvic or femoral orthopedic surgery. Exclusion criteria are the history of an allergic reaction to dexmedetomidine, systolic blood pressure less than 90 mmHg, history of mental disorders, history of the central nervous system diseases, the endocrine diseases, electrolyte disturbances, current corticosteroid therapy, and dependency on alcohol or drugs. We evaluate the patients a day before surgery. Also, we measure hematocrit and serum sodium and potassium levels in the day before surgery. We check our patients by the MMSE test before the operation. Mini-Mental State Exam (MMSE) is a widely used cognitive function test among the elderly; it includes orientation, attention, memory, language, and visual-spatial skills [14-15]. Patients are randomly divided into two groups (DEX) and (NS) using a computer-driven random number table in the operation room. Ten minutes before the anesthesia induction, a dose of 1 µg/kg dexmedetomidine diluted in 100 ml normal saline is infused over 10 minutes to group DEX patients. In group NS, 100 ml of isotonic saline is administered. Dexmedetomidine or normal saline injection is performed in each group by strict monitoring of blood pressure and heart rate. When reduction in blood pressure was more than 20% of the primary basal value, we stopped injection, or the heart rate dropped to less than 50/min. Anesthetic drug regimens in both groups are the same. Premedication is Midazolam 25 µg/kg and fentanyl 2 µg/kg. Induction of anesthesia is conducted with Propofol 2 mg/kg, Atracurium 0.5 mg/kg, and lidocaine 1.5 mg/kg. The maintenance of anesthesia medications is similar in both groups. Atracurium 0.2 mg/kg with 30min intervals and propofol 50-150 µg/kg/min titrated by continuous evaluation of hemodynamic parameters. Routine monitoring consists of ECG, NIBP, Pulse oximetry, and capnography. Mandatory minute ventilation is adjusted in each patient according to ET-CO₂ measurements to maintain between 30 and 35 mmHg. During the surgery, any risk factors related to early POCD, such as blood loss, significant hemodynamic changes, operation duration, and anesthesia, are recorded. At the end of the surgery, the neuromuscular block is reversed with 0.04 mg/kg neostigmine and 0.02 mg/kg atropine. Patients are extubated after obtaining adequate tidal volumes and

intact swallowing reflexes. PCA (Patient Controlled Analgesia) pump with 2 grams of Paracetamol in addition to 500 mcg of fentanyl is applied for each patient. In the case of VAS>3, 20 mg Pethidine is injected to control their pain. A day before surgery and 24 and 72 hours after the surgery, each patient's mental status is evaluated by the MMSE test (Mini-Mental State Examination). This test consists of 3 sections with 5 points, three sections with 3 points, one section with 2 points, four sections with 1 point, and the final score ranges between 0 and 30 [16-17]. Despite this test's high usage, it has some deficiencies such as the insensitivity to the frontal lobe and right hemisphere brain damages and significant correlation with the levels of patient's literacy and culture.

Statistical Analysis

SPSS V22 analyzes the study data. The normality of quantitative variables is assessed with the Kolmogorov-Smirnov test. Therefore, to compare quantitative variables in two groups, an independent T or Mann-Whitney U. test is used. Comparing qualitative variables in two groups, chi-square or Fisher exact test is used. Also, to compare hematocrit before and after the operation Wilcoxon test is used, and to compare MMSE test scores before surgery and 24 and 72 hours after the surgery, repeated measure ANOVA test is used. A P-value of less than 0.05 is considered significant.

Results

Seventy patients undergoing pelvic or femoral orthopedic surgery were enrolled in the study, 10 cases were excluded, and finally, the data of 60 (30 cases in each group) patients were analyzed (Figure 1). There was no significant difference in terms of age, sex, level of education, and type of surgery between the two groups ($P>0.05$) (Table 1). There was no significant difference between, duration of anesthesia and intraoperative bleeding between the two groups ($P>0.05$) (Table 2). There was no significant difference between hematocrit before and after the operation between two groups ($P>0.05$). In the dexmedetomidine group, the mean value of postoperative hematocrit decreased ($P<0.05$), but this reduction was not observed in patients receiving saline ($P>0.05$). A comparison between the two groups showed no significant difference in means of MMSE scores in the pre and postoperative periods. ($P>0.05$). Intragroup comparison of MMSE scores with repeated measure ANOVA test in the group (DEX) showed a significant change in this score before and after the surgery. ($P<0.05$), also, this significant difference was observed in the saline group ($P<0.05$) (Table 3).

Figure 1- Patient flow chart

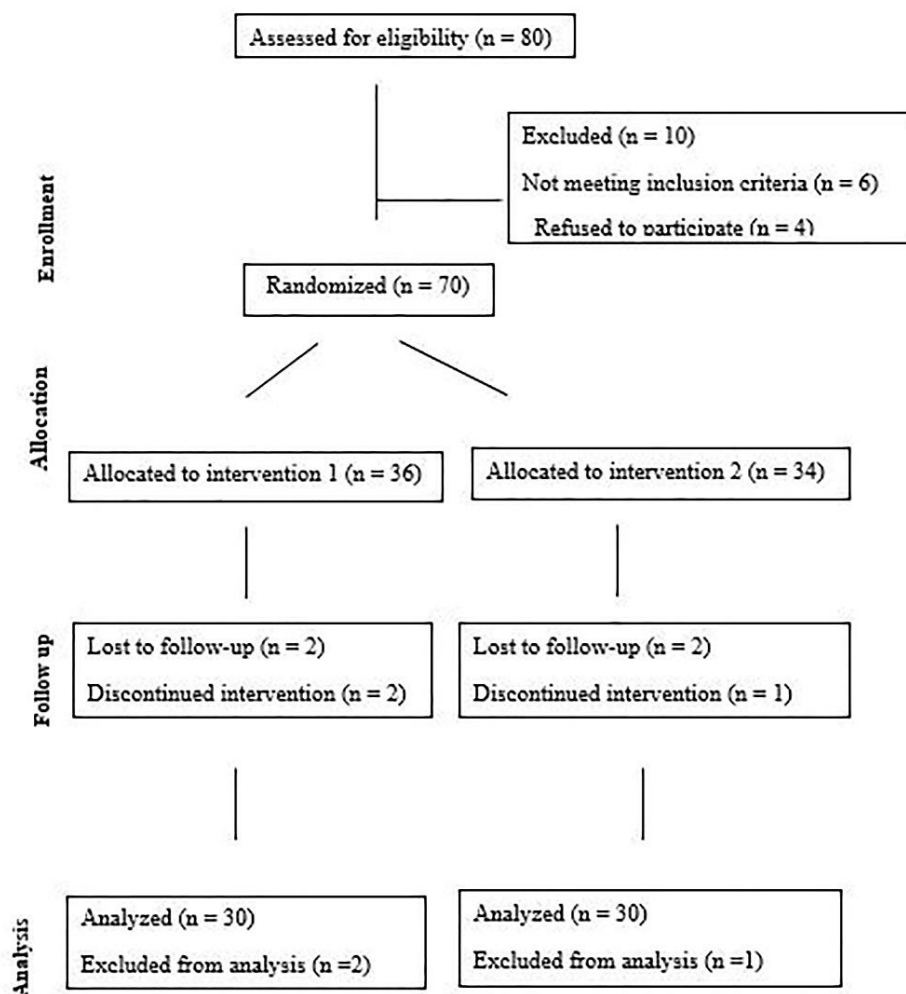


Table 1- Comparison of age, sex, education, and type of surgery in two groups

Variable	Group		P value
	Dexmedetomidine	Normal Saline	
Age, year Mean \pm SD	68.23 \pm 5.73	67.4 \pm 5.95	*0.485
Sex, n (%)			
Male	13 (43.3%)	13 (43.3%)	**1
Female	17 (56.7%)	17 (56.7%)	
Education, n (%)			
Illiterate	13 (43.3%)	12 (40%)	
Middle School	7 (23.3%)	5 (16.7%)	**0.691
Diploma	7 (23.3%)	11 (36.7%)	
Academic	3 (10%)	2 (6.7%)	
Surgery, n (%)			
Femur	18 (60%)	17 (56.7%)	**0.793
Hips	12 (40%)	13 (43.3%)	

*Test: Mann-Whitney U test, **Test: Chi-square

Table 2- Comparison of anesthesia and surgery duration and intraoperative blood loss in two groups

Variable	Group		*P value
	Dexmedetomidine Mean \pm SD	Normal Saline Mean \pm SD	
Duration of anesthesia, min	211.66 \pm 53.69	229.33 \pm 41.26	0.247
Duration of surgery, min	164.33 \pm 50.28	210.33 \pm 146.93	0.366
Intraoperative blood loss, ml	316.66 \pm 202.71	318.66 \pm 202.92	0.994

* Test: Mann-Whitney U test

Table 3- Comparison of Mini-Mental State Examination (MMSE) test scores before surgery, 24 and 72 hours after surgery in two groups

Time	Group		+P ₁ value
	Dexmedetomidine Mean \pm SD	Saline Mean \pm SD	
1MMSE test, n			
Before surgery	27.63 \pm 2.29	27.53 \pm 2.12	0.769
24 hours after surgery	26.76 \pm 2.43	26.6 \pm 2.28	0.754
72 hours after surgery	27.4 \pm 2.48	27.06 \pm 2.16	0.411
++P ₂ value	<0.001	<0.001	

1MMSE: Mini-Mental State Examination, *P₁ value: Comparison between two groups, **P₂ value: Comparison between before and after surgery, +test:Mann-Whitney U test, ++test:Reapeated measure ANOVA test

Discussion

This study showed that the effect of infusion of 1 μ g/kg dexmedetomidine is similar to the infusion of isotonic saline.

Different strategies have been tried to diminish the occurrence and severity of POCD complications [19]. Dexmedetomidine is one of them; however, its efficacy in this regard is still a matter of debate [13-14]. Based on the literature review, there is no study about dexmedetomidine's effectiveness on postoperative cognitive dysfunction after orthopedic surgeries. In some previous studies, similar to our study, dexmedetomidine's ineffectiveness in decreasing postoperative cognitive dysfunction has been reported [14,20-22].

None of the above studies has included any of the significant clinical predisposing risk factors for POCD. But in our study, elderly (high-risk for POCD) patients were assigned who were scheduled to undergo the significant orthopedic operation of femoral or hip surgery. Conversely, in some studies that their results are inconsistent with the current study, the effectiveness of prescribing dexmedetomidine in decreasing the postoperative cognitive dysfunction (based on MMSE test) has been mentioned. Some studies showed the significant effect of dexmedetomidine for PCOD. This inconsistency may be due to the difference in the investigated patients' demographic factors and the type of surgery in studies [23]. Some research found that the patients' MMSE test score under the operation in the dexmedetomidine group was better than the saline group

at three-time intervals one day, three days and seven days after the surgery. It is maybe due to the type of anesthesia and the type of surgery in two studies [13,18].

Patients had lower Hematocrit levels after surgery in the Dexmedetomidine group; the MMSE test results were similar. It cannot be claimed that dexmedetomidine is led to a better cognitive condition in this group because the role of anemia in POCD has not yet been established.

The advantage of this study is that the review was experimental research, and it had a control group.

MMSE test is a plain assay in comparison to the Wechsler memory scale (WMS) test. Because the difference between the two groups was not significant in MMSE analysis, it is recommended to design some studies similar to our research using the WMS test (which is more exquisite and evaluates the memory status more accurately) in the future. Second, the sample size was small in the current study, and it is recommended to take a larger sample size in the subsequent analyses.

Conclusion

According to our study results, Dexmedetomidine injection with a dose of 1 μ g/kg before surgery did not affect the prevention of postoperative cognitive impairment in elderly patients undergoing pelvic and femoral orthopedic surgery under general anesthesia.

Clinical Trial

We registered the study in IRCT (Iranian Registry of Clinical Trials) with the trial ID 34476 and the registration code is: IRCT20140109016151N7.

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