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Preventive Efficacy of Acetaminophen and Dexmedetomidine in Incidence of Postoperative Delirium Following Coronary Artery Bypass Grafting Surgery (CABG) With The Use of Cardiopulmonary Bypass (CPB)

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Keywords:

Acetaminophen; Dexmedetomidine; Coronary Artery Bypass Grafting

1. Abstract

1.1 Introduction: Delirium is a clinical syndrome characterized by acute cognitive dysfunction and altered level of consciousness. These symptoms are common in patients undergoing major surgeries, especially thoracic and cardiac surgeries. The present study aimed to assess the efficacy of acetaminophen and dexmedetomidine in prevention of postoperative delirium following coronary-artery bypass grafting (CABG) with the use of cardiopulmonary bypass (CPB)

1.2. Materials and Methods: This was a double-blind clinical trial. The participants consisted of 70 candidates for CPB surgery. The patients were divided into two groups. Thirty-five patients were assigned in each group. One group was injected intravenously with acetaminophen and the other one with dexmedetomidine. Incidence of delirium was assessed 24, 48 and 72 hours after the surgery in both groups. Collected data was analyzed using SPSS v.23.

1.3. Findings: average ages of the participants were 57.46 ± 9.68 in the dexmedetomidine group and 55.11 ± 8.8 in the acetaminophen group. There was no statistically significant difference between both groups in terms of age. No significant differences were also found between both groups in terms of preoperative ejection fraction, hemoglobin, hematocrit, urea, and creatinine levels (P>0.05). The incidence of delirium significantly reduced in 24 hours after the surgery in the dexmedetomidine group compared to the acetaminophen group (P=0.045). However, there was no significant difference between the two groups in terms of incidence of delirium in 48 and 72 hours after the surgery (P>0.05).

1.4. Conclusion: Dexmedetomidine is superior to other medications in management of hospital-induced delirium. It can also reduce the incidence of delirium in 24 hours following CABG in an effective manner. It is recommended that more detailed studies be carried out by taking into account underlying systemic diseases and higher number of adverse effects of the drug to determine effective dose and timely administration of the drug as well as punctual preoperative and postoperative care to manage postoperative delirium.

2. Statement of the Problem

Delirium is a clinical syndrome characterized by acute cognitive dysfunction and altered level of consciousness. These symptoms are common in the patients hospitalized in the intensive care unit (ICU) [1]. The highest rate of incidence of delirium accounts for postoperative period and seven days after the surgery. Delirium affects 80% of the patients receiving mechanical ventilation [2]. Given the negative consequences of untreated delirium, its timely diagnosis and treatment is important. Although delirium is a com-

mon complication and hazard in the patients undergoing cardiac surgery [3], a high percentage of patients suffering from delirium unfortunately remain undiagnosed and consequently untreated, which increases mortality rates, length of hospitalization, nursing care, and mental disorders [4]. Delirium occurs in up to 80% of critically ill patients, which increases the risk of functional decline, prolongs hospitalization, increases mortality rate, worsens prognosis, and increase treatment costs [5]. Therefore, it is imperative to assess preventive measures and treatment methods to reduce complications, mortality, and patient care costs in an effective manner. The present study aimed to determine efficacy of intravenous injection of dexmedetomidine and acetaminophen on the incidence of post-cardiac surgery delirium.

3. Materials and Methods

This was a double-blind clinical trial. Necessary license was obtained from the Ethics Committee of Shahid Sadoughi University of Medical Sciences. Informed consent forms were also secured. The study was carried out in Afshar Hospital in Yazd in 2018. The participants were candidates for CABG with the use of CPB (n=70). Sample size was determined with 95% confidence interval and 80% power by taking into account 70% occurrence of delirium in the dexmedetomidine group, 35% incidence rate of delirium in the acetaminophen group, and 20% sample loss. Thirty-five patients were assigned to each group. Inclusion criteria were 40 to 75 years of age and >30% ejection fraction. Exclusion criteria were history of seizure, emergency coronary artery surgery, creatinine>2, renal disorder, underlying cognitive impairment (e.g. dementia), alcohol addiction, poor communication and not understanding the Persian, visual and hearing impairment, and continuous use of sedatives, >3h on-pump CABP, use of balloon pumps following CABG, prolonged intubation (>72h) in ICU. One gram paracetamol was infused over 10 minutes prior to induction of anesthesia and repeated every six hours until extubating in the acetaminophen group. In the dexmedetomidine group, 0.6μg/kg/min was infused over 10 minutes. The maintenance dose (0.4g/kg/min) was infused prior to extubating. Research instrument was a three-phase questionnaire. Demographic data and patient records were collected in the first phase. Post-operative complications (e.g. hypotension and bradycardia requiring treatment) were written down in the second phase. Therefore, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), median arterial pressure (MAP), oxygen saturation (O2 SAT%) were monitored. The Mini-Mental State Exam (MMSE) was used in the third phase. It contained 19 questions assessing incidence and severity of delirium. Induction of anesthesia was performed by a singular anesthesiologist using a unique method to avoid biased results. The surgery was also performed by a singular cardiac surgeon. Preoperative medications were intramuscular morphine (0.1mg/kg) and promethazine (0.5mg/kg) injected 45 minutes prior to induction of anesthesia. The medications used for induction of anesthesia were propofol (2-3mg/kg), fentanyl (1-2g/kg), pancuronium bromide (0.1mg/kg), and midazolam (0.05-0.15mg/kg). Propofol (100-200 μg/kg/min) and remifentanil (0.1μg/kg/min) were infused until the end of surgery to maintain anesthesia. The collected data was analyzed using SPSS v.22.

4. Limitations of the Study

Side effects of the both drugs could not be assessed due to small sample size and low number of side effects was found in the study. It was not possible to check for transient and mild cognitive impairment (e.g. decreased alertness) or transient temporal and spatial disturbance in daily monitoring of patients with delirium.

5. Findings

The findings showed no statistically significant difference between both groups in terms of gender (P>0.05). No statistically significant difference was also found between both groups in terms of incidence of diabetes, addiction, and smoking (Table 3-1). Average ages of the participants were 57.46 ± 9.68 years in the dexmedetomidine and 55.11 ± 8.8 years in the acetaminophen group. No statistically significant difference was also found between both groups in terms of age (P = 0.293) (Table 3-2). Ejection fraction was 44.91 ± 10.13 years in the dexmedetomidine group and 47.74 ± 8.83 years in the acetaminophen group. No significant difference was found between both groups in terms of ejection fraction (P = 0.193). Mean hemoglobin level in the dexmedetomidine group was 14.01 ± 2.08 mg/dl and 14.14 ± 1.65 mg/dl in the acetaminophen group. T-test results showed no significant difference in hemoglobin level between both groups (P = 0.737). Mean urea level was 36.68 ± 16.36 in the dexmedetomidine group and 38.68 ± 15.53 in the acetaminophen group. T-test results showed no significant difference in mean urea level between both groups (P <0.603). Mean creatinine level was 1.22 ± 0.61 in the dexmedetomidine group and 1.1 ± 0.19 mg/dl in the acetaminophen group. T-test results showed no significant difference in mean creatinine level between both groups (P = 0.272) (Table 3-3) (Figure 3-1). The incidence of delirium was significantly lower in the dexmedetomidine group than in the acetaminophen group in 24 hours after the surgery (P = 0.045). However, there was no significant difference in incidence of delirium between both groups in 48 and 72 hours after the surgery (P>0.05).

6. Side Effects

Postoperative bradycardia was detected in one patient in the dexmedetomidine group and two patients in the acetaminophen group (PR<40). Postoperative hypotension was also detected in one patient in the dexmedetomidine group (SBP<90mmHg for more than 5 minutes).

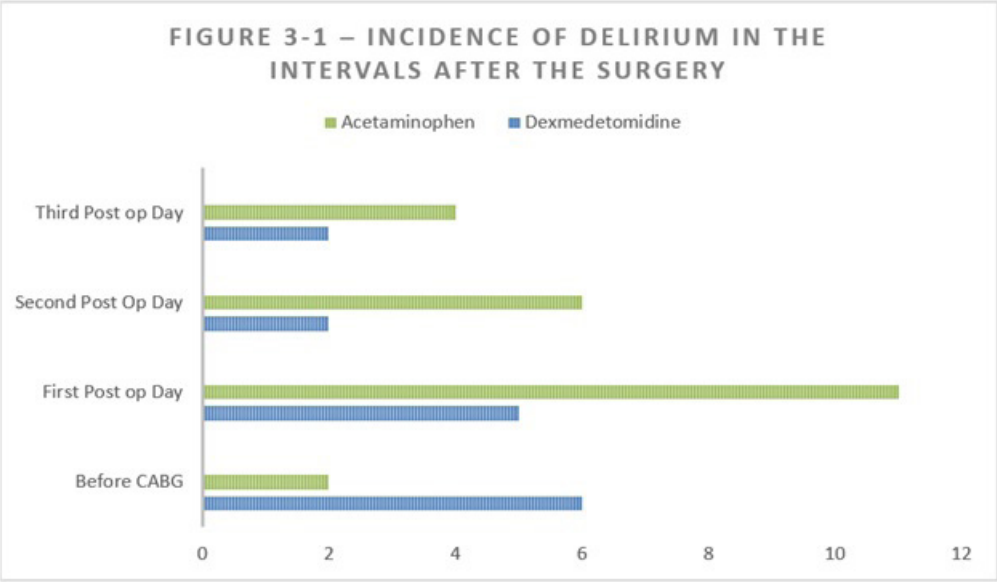

Figure 3-1: Incidence of Delirium in the intervals after the Surgery

Table 3-1: Comparison of gender, diabetes, addiction and smoking between both groups

Group Variable		Dexmedetomidine	Acetaminophen	p-value*
Gender	Male	31 (88.6)	28 (80)	0.513
	Female	4 (11.4)	7 (20)	
Addiction	Positive	6 (17.1)	8 (22.9)	0.55
	Negative	29 (82.9)	27 (77.1)	
Diabetes	Positive	17 (48.6)	19 (54.3)	0.632
	Negative	18 (51.4)	16 (45.7)	
Smoking	Positive	17 (48.6)	15 (42.9)	0.631
	Negative	18 (51.4)	20 (57.1)	

Table 3-2: Comparison of average age, ejection fraction, hemoglobin, hematocrit, urea, creatinine level between both groups

Group Variable	Dexmedetomidine	Acetaminophen	p-value*
	Mean ± SD	Mean ± SD	
Age	57.46 ± 9.68	55.11 ± 8.8	0.293
Ejection fraction	44.91 ± 10.13	47.74 ± 8.83	0.197
Hemoglobin	14.01 ± 2.08	14.16 ± 1.65	0.737
Hematocrit	41.19 ± 5.65	41.52 ± 4.68	0.792
Urea	36.68 ± 16.36	38.68 ± 15.53	0.603
Creatinine	1.22 ± 0.61	1.1 ± 0.19	0.272

Table 3-3: incidence of delirium in the interval after the surgery

Intervals	Delirium	Dexmedetomidine	Acetaminophen	p-value
	No. (%)	No. (%)		
Preoperative	Positive	6 (17.1)	2 (5.7)	0.133
	Negative	29 (82.9)	33 (94.3)	
24 hours after the surgery	Positive	5 (14.3)	11 (31.4)	0.045
	Negative	30 (85.7)	24 (68.6)	
48 hours after the surgery	Positive	4 (11.42)	5 (14.28)	0.833
	Negative	31 (88.58)	30 (85.72)	
72 hours after the surgery	Positive	2 (5.71)	1 (2.85)	0.393
	Negative	33 (94.29)	34 (97.15)	

7. Discussion

Delirium is a common and serious disorder in patients with prolonged hospitalization or undergoing major surgeries (e.g. CABG). Various studies have shown that the prevalence of delirium in ICU patients increased by 25% although the incidence of this syndrome was reported 45%-89% in the elderly. Delirium has a significant relationship with mortality, dementia, and sustained cognitive impairment following discharge from the hospital [6-8]. Milbrandt reported treatment cost of delirium as 6.5 to 20.5 billion US dollars in 2004 (9). There are three distinct clinical subtypes of delirium, namely hyperactive, hypoactive and mixed [10]. Hypoactive subtype carries the worst prognosis [11]. Many recent papers and scientists have addressed therapeutic interventions to control delirium and reduce its complications. Gamma-aminobutyric acid (GABA) derivatives (e.g. perpofol and benzodiazepine) were used as a standard treatment to control hospital-induced delirium for decades [12]. However, recent studies have shown that these sedatives can increase the prevalence of postoperative or ICU-induced delirium [13]. Given the rapidly reversible delirium and transient side effect of these sedative, a newer generation of sedative drugs (e.g. dexmedetomidine) was used to control hospital-induced delirium. Dexmedetomidine is a highly selective alpha-2 adrenergic receptor agonist [14, 15]. It exerts hypnotic action through activation of central pre- and postsynaptic α2-receptors in the locus coeruleus [16]. The spinal cord is probably the major site of analgesic action of dexmedetomidine [17]. Therefore, GABA is preferred to dexmedetomidine due to its complex analgesia-inducing mechanism. The present study aimed to compare the efficacy of dexmedetomidine and acetaminophen in prevention of delirium following CABG. The results showed greater efficacy of dexmedetomidine in preventing postoperative delirium. Clinical properties of dexmedetomidine are sedation, analgesia and anxiety reduction [17-19]. Although some side effects including hypotension and bradycardia were reported, dexmedetomidine can reduce pain, nausea, the need for other sedatives, and duration of mechanical ventilation [18]. Therefore, it is often used for treatment of delirium. Although dexmedetomidine had no significant efficacy in preventing delirium in 48 and 72 hours after CABG, the results of similar studies suggested that administration of dexmedetomidine can be effective in reducing the incidence of delirium by one week after the surgery [19]. Kim et al. showed that dexmedetomidine had no significant effect in reducing the incidence of delirium despite effective reduction of post-thoracic surgery agitation. Dexmedetomidine reduces agitation through release of catecholamines and anti-inflammatory processes [20]. Huyan (2019) also showed that preoperative and inoperative administration of dexmedetomidine reduced the incidence and severity of postoperative delirium in the patients undergoing thoracotomy for pulmonary resection. A similar study was conducted on patients with lung cancer in 2019 in China [21]. XIE et al. exerted dexmedetomidine neuroprotective properties and significantly reduced inoperative dose of propofol in China in 2018. The efficacy of this drug was also studied in patients with hip surgery. Preoperative and inoperative administration of dexmedetomidine not only reduced the incidence of delirium, but also preoperative injection of dexmedetomidine reduced inoperative dose of propofol [22]. Another study also showed that dexmedetomidine and sufentanyl reduced the incidence of postoperative delirium. The two drugs also had a significant effect on reducing visual analogue score, sedation agitation score, and plasma levels of stress hormones despite increased postoperative respiratory distress [23]. One study reported significantly lower incidence of postoperative delirium in 24 hours after CABG in the acetaminophen group compared to the dexmedetomidine group. Length of hospitalization in ICU in the acetaminophen group was significantly shorter than the dexmedetomidine group [24]. However, the patients desired higher doses of opioids in the acetaminophen group compared to the dexmedetomidine group [25-27]. Subramaniam et al. claimed that their project was the first published paper on comparison of efficacy of dexmedetomidine and acetaminophen in reducing the incidence of postoperative delirium. They claimed that acetaminophen was more efficacious than dexmedetomidine. However, efficacy of both drugs on delirium aroused controversy in the discussion section of the paper [28-31].

8. Conclusion

The results of this study and its comparison with recent studies showed that dexmedetomidine is superior to other medications for controlling hospital-induced delirium. It can also improve quality of postoperative management of patients undergoing CABG and reduce the incidence of delirium in 24 hours after CABG in an effective manner.

9. Recommendations

It is recommended that more detailed studies be carried out by taken into account underlying systemic diseases and higher number of side effects of the drug to determine effective dosage and timely administration of dexmedetomidine as well as punctual preoperative, inoperative and postoperative care to control delirium after CABG.

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