Original Article

The Effect of Dexmedetomidine Infusion vs. Morphine on Duration of Mechanical Ventilation in CABG: A Clinical Trial

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Abstract

Background: No single and ideal method has been proposed so far to decrease the time of mechanical ventilation while maintaining patients' hemodynamic stability after coronary bypass surgery. This study aimed to compare the effect of Dexmedetomidine and Morphine infusion on the latter parameters in patients after coronary artery bypass graft surgery in the intensive care unit.

Materials and Methods: In this clinical trial study, 60 patients undergoing coronary artery bypass graft surgery were divided into two groups (N=30): the first group receiving Morphine and the second group receiving Dexmedetomidine. At admission to the ICU in the first group, Morphine was injected at a dose of 0.25 mg/kg, and in the second group, Dexmedetomidine was injected at a dose of 1 µg/kg for 10 minutes. Hemodynamic parameters and blood gas levels at preoperative cardiac care were compared between the two groups at the time of endotracheal tube withdrawal.

Results: The trend of hemodynamic changes and blood gas levels during the intensive care unit stay did not differ between the two groups. The mean duration of mechanical ventilation in the Morphine group was 10.63/2 2.31 hours and in the Dexmedetomidine group was 9.77/1 1.92 hours, and there was no significant difference between the two groups (p=0.12).

Conclusion: both Morphine and Dexmedetomidine had similar effects on hemodynamic stability and blood gas levels; however, Dexmedetomidine was associated with fewer drug-related side effects; so, it seems wise to consider Dexmedetomidine superior to Morphine in the postoperative period of CABG patients.

Keywords: Coronary artery bypass, Hemodynamic, Extubation of the airway, Dexmedetomidine, Morphine

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Introduction

Following open-heart surgery, patients are directly transferred to the intensive care unit, where they are carefully monitored until they regain consciousness from anesthesia, and adequate oxygenation and hemodynamic stability are achieved (1). Early

extubation is one of the chief measures for reducing complications in the patients and shortening the length of stay in the recovery room (2). Early extubation effectively reduced the detrimental effects of positive pressure ventilation by shortening the duration of mechanical ventilation. Also, its general effects include patient comfort, reduction in respiratory complications, ease of patient monitoring and management, faster patient ambulation and facilitation of movement and activity, and lower hospitalization costs (3). Early extubation results in increased left ventricular filling, improved ventricular function, and consequently, increased cardiac output (3). Moreover, this measure has several positive effects on the respiratory system, including reducing the risk of nosocomial pneumonia and damage to the lung tissue (4).

The alpha-2 agonist Dexmedetomidine has multiple desirable properties, including analgesic effects, inhibition of the sympathetic output, anxiolytic effects, and reduction of norepinephrine levels. These effects contribute to the patient improvement and hemodynamic stability (5, 6). Dexmedetomidine treatment of Oxygen-Glucose deprivation/ reoxygenation (OGD/R) cells promoted cell survival and attenuated OGD/R-induced cell apoptosis, and it might be an effective agent for the treatment of ischemic diseases. Dexmedetomidine protects WRL-68 cells against OGD/R-induced injury by inhibiting inflammation, oxidative stress, and cell apoptosis via the activation of the Nrf2/HO-1 signaling pathway (7).

Morphine is used as an analgesic for pain relief in hospitalized and cardiac patients and against pain during the surgery and in the post-surgery period (8).

The present study was conducted to compare the effects of Dexmedetomidine and Morphine as pain-relief and sedative agents in the intensive care unite (ICU) and to determine which of these two medications involves fewer complications, shorter times to extubation, better ABG parameters, shorter ICU stays, and greater hemodynamic stability in patients after coronary artery bypass graft (CABG). CABG is a lengthy procedure and involves a vital part of the body. Therefore, patients undergoing CABG under general anesthesia are at the risk of a multitude of problems, including hemodynamic instability, imbalances of fluid, electrolytes, and blood gases, coagulation disorders, and late extubation, each of which can affect the quality of the surgery and cause further complications and increase patient mortality (9). Thus, it is hypothesized that using Dexmedetomidine can lead to earlier extubation and improved respiratory parameters, and reduce CABG complications.

Results of this study can contribute to the subject because currently (also where this study did) Morphine is commonly used for post-surgical pain relief, and to date, a few comprehensive studies have been performed to investigate the effects of Dexmedetomidine on patients undergoing CABG surgery.

Methods

The present double-blind clinical trial study was approved by the Ethics Committee of Isfahan University of Medical Sciences (Code: IR.MUI.MED.REC.1398.016), registered at Iran's Clinical Trial Registration Center (Code: IRCT20130311012782N39), and conducted in the years 2017 and 2018 in Shahid Chamran Teaching Hospital in the city of Isfahan. The study population consisted of CABG surgery candidate patients admitted to the hospital.

The criteria for the patients' inclusion in this clinical trial were: candidates for CABG, patient's consent to take part in the study, no addiction to opioids, no use of psychotropic or antidepressant medications, no underlying respiratory diseases, and no use of medications affecting the hemodynamic status.

The exclusion criteria were: pumping time over 120 minutes, patients requiring surgeries other than CABG, the need for aortic balloon pump, return to the operating room due to re-bleeding, patients needing more than two inotropic medications before separation from the cardiopulmonary pump, changes of surgery plan in terms of the surgical techniques, and emergency surgery.

After obtaining written informed consent, patients were visited the night before surgery by the anesthesiologist. In this study, data obtained from the patients were randomized using random allocation

software. To achieve uniformity in the study, the same pre-medication and anesthesia induction and continuation methods were applied in the two groups. After CABG surgery, the patients were transferred to ICU. The first ABG sample was obtained upon the establishment of monitoring and mechanical ventilation.

Baseline systolic and diastolic hemodynamics and pulse rate were recorded. In the first group of patients, 0.25 mg/kg Morphine, dissolved in 50 mL's of normal saline, was administered by infusion over ten minutes at admission to the recovery room. In the second group, one µg/kg of Dexmedetomidine was infused into the patients over ten minutes. The first group was infused with a dose of 50 mL's normal saline, and the second group with one µg/kg of Dexmedetomidine per hour in 50 mL's normal saline. In both groups, three mg of Morphine was administered to the patients that needed more analgesics by orders from the anesthesiologist.

In the present study, the double-blinding method was applied as follows: patients did not know which type of medication they were receiving. Moreover, medications were prepared in coded syringes of similar shape by one of the operating room staff who had no knowledge of this study's particulars and then given to a study operator with no knowledge of the contents of the syringes to be administered.

Hemodynamic parameters, including systolic and diastolic blood pressures, the mean arterial pressure, the heart rate, and the level of the blood gases (Paco2, Pao2, and pH) were determined and recorded before surgery, at admission to ICU, during the stay at the ICU, and during extubation, in both groups of patients. Furthermore, medication side-effects were assessed and recorded, including nausea, vomiting, hemodynamic disturbances (hypertension, hypotension, bradycardia, and tachycardia), and respiratory depression, during the study. Finally, the patients' demographic details, ICU stay duration, blood products, and inotropes received were recorded in data collection forms.

The sample size was determined as 30 patients per group; we considered the following parameters in the calculation: 95% confidence interval, a test power of 80%, an estimated standard deviation of about 1.17 hours for the extubation time, and a minimum significant difference of 0.8 between the two groups. Figure 1 shows the flowchart of the present study.

The collected data were entered into the computer and analyzed in SPSS-24, using Chi-squared test (to compare qualitative and nominal data in the two groups), T-test (to compare quantitative data in the two groups), and variance analysis with repeated measures (to assess the trend of changes in variables over time in the two groups).

Results

In the present study, 60 patients undergoing CABG surgery received either Morphine or Dexmedetomidine in two separate groups (30 patients in each) and were studied. No patients were removed from the study because of unwanted complications. There were no significant differences between the two groups regarding demographic and general variables (Table 1).

Table 1: Demographics and Baseline Variables in Study Groups (Dexmedetomidine & Morphine).

Demographic Variables		P	Case Group	
			Morphine	Dexmedetomidine
Mean Age (year)		0.58	59.2±12.6	60.9±11.9
Gender	Male	1	20(66.7)	20(66.7)
	Female		10(33.3)	10(33.3)
Weight (Kg)		0.6	75.1±16.5	77.1±12.2
Duration of Mechanical Ventilation Pump		0.59	32.8±90.3	94.8±25.7
Duration of Aortic Clamp		0.24	64.3±32.3	55.9±18.8

Table 2: Mean ± Standard Deviation of Blood Pressure and Heart Rate between the two Study Groups (Morphine & Dexmedetomidine).

Hemodynamic Parameters	Time	Group		P
		Morphine	Dexmedetomidine	
Systolic Blood Pressure (mmHg)	Pre –operation	119.5±9.6	116.8±12.1	0.33
	Upon Entering the ICU	112.3±12.2	116.1±9	0.18
	During the ICU Stay	116.1±10.4	116.2±7.5	0.96
	At the time of the Extubation	119.3±14.4	114±1.4	0.62
	P	0.34	0.1	0.061
Diastolic Blood Pressure (mmHg)	Pre –operation	66.7±10	71.8±8.4	0.23
	Upon Entering the ICU	62.8±9.9	61.5±7.4	0.56
	During the ICU Stay	62.7±8.7	5.61±7.4	0.84
	At the time of Extubation	63.7±9.9	69±5.7	0.47
	P	0.31	0.68	0.09
Mean Arterial Pressure (mmHg)	Pre-Operation	82.4±11.7	78.6±9.9	0.2
	Upon Entering the ICU	76.7±12.1	81.5±10.8	0.12
	During the ICU Stay	78.1±8.8	81.1±7.5	0.18
	At the time of Extubation	75.5±11.3	77.5±10.6	0.81
	P	0.81	0.87	0.06
Heart Rate (N/h)	Pre-Operation	84.3±12.3	88.6±10.6	0.15
	Upon Entering the ICU	88±13.5	91.9±10.2	0.21
	During the ICU Stay	91.6±11.2	92.9±11	0.67
	At the time of Extubation	85.3±23.8	87.5±9.2	0.9
	P	0.62	0.19	0.092

Assessment of hemodynamic parameters before surgery, at admission to ICU, during the stay in ICU, and at the time of extubation showed no significant differences between the two groups receiving Morphine and Dexmedetomidine in terms of the systolic and diastolic blood pressures, the mean pressure, and the heart rate. Furthermore, intragroup assessments showed no significant changes in these

Table 3: Mean ± Standard Deviation of Blood Gas Variables between the two Study Groups (Morphine & Dexmedetomidine).

Blood Gas	Time	Group		P
		Morphine	Dexmedetomidine	
pH	Pre-Operation	7.42±0.07	7.4±0.04	0.18
	Upon Entering the ICU	7.26±0.74	7.32±0.55	0.69
	During the ICU Stay	7.36±0.19	7.37±0.16	0.9
	At the time of Extubation	7.45±0.18	7.31±0.01	0.32
	P value	0.11	0.13	0.1
PaO2 (mmHg)	Pre-Operation	96.1±297.7	259.6±151.6	0.2
	Upon Entering the ICU	122.4±310.3	308.8±117.9	0.96
	During of stay in ICU	133.4±51	125.5±45.6	0.53
	At the time of Extubation	119.4±35	91.1±1.6	0.29
	P value	0.99	0.52	0.15
PaCO2 (mmHg)	Pre-Operation	33.9±5.7	34.9±5.2	0.46
	Upon Entering the ICU	34±6.1	34.4±7.4	0.86
	During the ICU Stay	36.9±5.3	40±13.6	0.26
	At the time of Extubation	36.7±11.1	37.8±3.9	0.9
	P value	0.41	0.13	0.09
$HCO3^-$ (mEq/L)	Pre-Operation	24.1±7.2	22.1±1.6	0.13
	Upon Entering the ICU	22±1.9	22±1.7	0.92
	During of stay in ICU	23.5±4.2	22.1±1.7	0.09
	At the time of Extubation	22.7±2.3	22±1.3	0.65
	P value	0.23	0.11	0.09

Table 4: Blood Products' Use, Inotropes and Postoperative Complications between the two Study Groups (Morphine & Dexmedetomidine).

Variables	Time	Group		P value
		Morphine	Dexmedetomidine	
Receipt of Blood Products	Packed Cells	12(40%)	12(40%)	1
	FFP	5(16.7%)	6(20%)	0.99
	Platelet	1(3.3%)	2(6.7%)	0.99
	Crayo	0(0%)	0(0%)	1
Receipt of Inotrop	Adrenaline	2(6.7%)	0(0%)	0.49
	Dobutamine	3(10%)	0(0%)	0.24
	Noradrenaline	3(10%)	1(3.3%)	0.61
Post-operation side effects	Vomit	5(16.7%)	1(3.3%)	0.2
	Nausea	6(20%)	0(0%)	0.024

parameters within the groups over time. Finally, intergroup assessments revealed no significant difference between the two groups regarding the trend of changes in hemodynamic parameters (Table 2).

The mean duration of mechanical ventilation in the Morphine receiving group infusion was 10.63±2.31 hours, and in the Dexmedetomidine receiving group infusion was 9.77±1.92 hours. Thus, the difference between the two groups in terms of ventilation duration was negligible and not significant (p=0.12). Assessment of blood gases showed no significant difference between the Morphine and Dexmedetomidine groups for the mean levels of blood gases PaO2, PaCO2, HCO3, and pH. Moreover, intragroup and intergroup assessments showed no significant differences within the groups or between the two groups in the trends of change in blood gases (Table 3).

Table 4 presents the frequency distribution of receiving blood products and inotropes and post-surgery complications in the Morphine and Dexmedetomidine groups. The results showed no significant difference between the two groups in terms of receiving inotropes and blood products. Most importantly, regarding post-surgery complications, the vomiting frequency was significantly higher in the Morphine group (p=0.024).

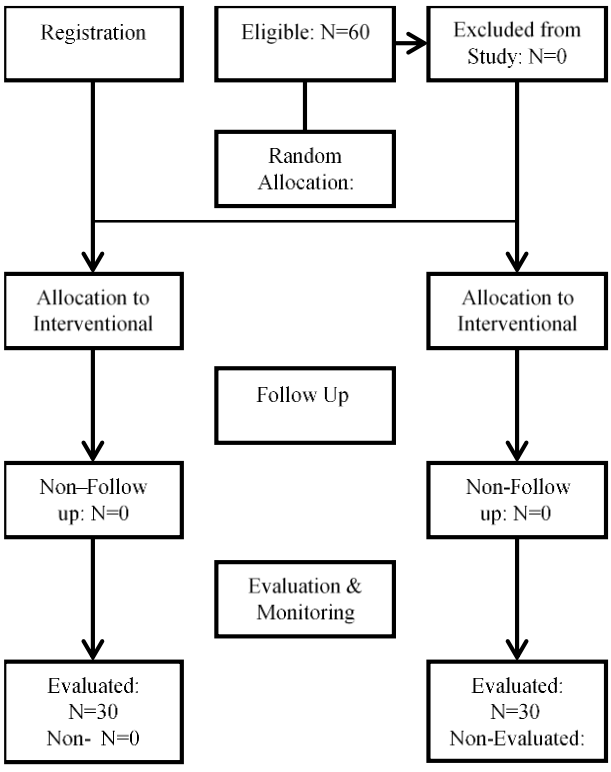

Figure 1. Study Flowchart.

Discussion

The present study found fewer complications, shorter extubation times, improved blood gas analysis parameters, shorter ICU stay, and improved hemodynamic stability in CABG patients receiving dexmedetomidine compared with morphine in the postoperative period; while there was no significant difference between the two groups in terms of demographic and baseline variables. However, the results showed neither morphine nor dexmedetomidine do not adversely affect the regaining of respiratory function in the patients. The results of the present study are consistent with several

other studies regarding the severity of post-surgery pain and the needed rescue analgesics (10), postoperative need for beta-blockers, and antiemetics (11), duration of mechanical ventilation (12), psychological, hemodynamic, and coagulative outcome measures (13), myocardial oxygenation, cardiac oxygen demand, myocardial protection, and post-surgical mortality (5-6), the need for a postoperative required dose of sedatives and analgesics (14); besides, there are numerous studies which have assessed the molecular mechanism of Dexmedetomidine leading to the latter clinical outcomes; which could support the clinical findings.

The research of cellular and molecular of Dexmedetomidine's effects show that the protection of Dexmedetomidine against Oxygen-Glucose deprivation/reoxygenation Injury-Induced Apoptosis via the p38 MAPK/ERK Signaling Pathway show that Dexmedetomidine treatment of OGD/R cells promoted cell survival and attenuated OGD/R-induced cell apoptosis. It also activated the p38 MAPK/ERK signaling pathway, increased the levels of Bcl-2, and decreased the levels of Bax and cleaved caspase-3. Treatment with the p38 MAPK/ERK inhibitor CV-65 inhibited p38 MAPK/ERK activation and abrogated the Dexmedetomidine-induced effects on cell survival and apoptosis. Moreover, as a result, Dexmedetomidine protects N2A cells from OGD/R-induced apoptosis via the p38 MAPK/ERK signaling pathway activation. Dexmedetomidine might be an effective agent for the treatment of ischemic diseases (7).

Also, in other cellular and molecular research, Dexmedetomidine promoted cell viability and suppressed cell apoptosis in OGD/R-treated WRL-68 cells. It reduced TNF-α, IL-6, IL-1β, ROS, and MDA production, whereas it increased SOD and GSH-Px in OGD/R-treated WRL-68 cells. Moreover, Nrf2, HO-1, and Bcl-2 expression were upregulated, whereas, in contrast, transcripts for Bax, caspase3, and caspase9 were downregulated following Dexmedetomidine treatment under OGD/R. Knockdown of Nrf2 reversed the Dexmedetomidine, effects on cell proliferation, apoptosis, and expression of TNF-α, IL-6, IL-1β, ROS, MDA, SOD, and GSH-Px. Dexmedetomidine protects WRL-68 cells against OGD/R-induced injury by inhibiting inflammation, oxidative stress, and cell apoptosis via the activation of the Nrf2/HO-1 signaling pathway, suggesting that it may be a potential protector against hepatic injury (15).

Dexmedetomidine has been administered worldwide in the last few years. Some studies suggest positive effects of this medication in maintaining the patients' hemodynamic balance. Although using Morphine can also be beneficial, it seems that the benefits of Dexmedetomidine outweigh Morphine in patients undergoing CABG, especially the elderly and those with underlying diseases.

Given the limitations of the present study, including the small sample size, it is recommended that future studies investigate larger samples and use the findings of the present study as a basis for further investigations on the effect of Dexmedetomidine use on the duration of mechanical ventilation and the maintenance of hemodynamic stability. Furthermore, the present study focused on the impact of Dexmedetomidine in CABG surgery; however, it is recommended that the effects of this medication in other types of surgery are also studied.

Conclusion

The results show that both Morphine and Dexmedetomidine have similar effects in maintaining hemodynamic stability and the blood gases' level. Still, Dexmedetomidine would be preferable to Morphine because it has few side-effects. Thus, our hypothesis, suggesting a reduction in CABG surgery complication with the use of Dexmedetomidine, is confirmed.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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