EVALUATION OF DEXMEDETOMIDINE VERSUS PROPOFOL FOR FAST TRACK ANESTHESIA IN CORONARY OPEN-HEART SURGERY: A COMPARATIVE RANDOMIZED STUDY

Heba Mohamed abdelkader¹, Hossam Salah Eldin², Ahmed Kareem mohamed³, Adham Magdy Haggag⁴, Mohamed Mohsen rashed⁵

¹Assistant lecturer, misr University for science and technology, Egypt.
²Professor of anesthesia Cairo University, Egypt.
³Assistant Professor of anesthesia Cairo University, Egypt.
⁴Lecturer of anesthesia Ain shams University, Egypt.
⁵Lecturer of anesthesia, Ain shams university, Egypt.

ABSTRACT

Objectives: Our comparative randomized study aims to compare the intraoperative effectiveness of dexmedetomidine and propofol in fast-track anesthesia in coronary open-heart surgery. Methods: We conducted this study as a randomized controlled prospective investigation at Misr University Teaching Hospital. The effect on heart rate, postoperative delirium, mean arterial blood pressure, and BIS spectral index were assessed among the two groups. Results: A total of 40 patients were included in the present study and randomized into two groups; group I (dexmedetomidine) (n= 20) and group II (propofol) (n= 20), with a mean age of 61.21 (10.50), and 61.91 (9.74). Postoperative delirium was significantly higher in group II than group I (p= 0.042). The mean arterial blood pressure seemed to be significantly lower in group I than group II after 10 minutes of drug infusion, on the bypass, after bypass by 15 minutes, and before transferring the patient to the ICU (p< 0.001). Significantly higher heart rate values were noticed in group II than group I after induction, after 10 minutes of drug infusion, after bypass by 15 minutes, and before transferring the patient to the ICU (p< 0.001). The length of ICU stay (p= 0.020) and time of extubation (p< 0.001) were also significantly longer in group II than group I. Group II showed total higher mean BIS values after induction, after 10 minutes of drug infusion, and after bypass by 15 minutes than group I (p< 0.001). Conclusion: Dexmedetomidine can lower the risk of cardiovascular complications. Keywords: dexmedetomidine; cardiovascular; anesthesiology; surgery; propofol.

I. INTRODUCTION

It is widely known that cardiac surgeries have many risks and can lead to the development of many complications and adverse events that can affect the cardiovascular and other systems, which can worsen the prognosis of any underlying medical condition and increase the chances of developing severe morbidities or even mortality. Many complications have been reported following cardiac surgeries, however, infections, acute renal failure, and postoperative delirium has been previously reported to be the main adverse events. Cranioencephalic complications are also common during cardiac surgeries and include coma, myocardial infarction, cardiac arrest or heart block, and stroke or transient ischemic attacks. Evidence shows that many events can contribute to the development of these complications, and previous research reported that operative stress can mainly contribute to the development of these complications and adverse events. Tissue manipulation during surgeries can lead to the release of many substances as adrenaline and noradrenaline, which can affect the myocardium by creating a state of imbalance between the supply and demand of oxygen and other nutrients to the myocardium that can aggravate ischemia, especially in cases where the coronary blood flow is already impaired. Fast-tracking is a term that has been widely used in cardiac surgery to refer to alleviating the healthcare and economic burdens of cardiac surgeries by reducing the hospital stay...
period, mobilization, and encouraging early extubation\(^{(7)}\). Early extubation should be planned to be done within 1-6 hours following intensive care unit (ICU) admission\(^{(8)}\).

Prolonged perioperative mechanical ventilation and increased ICU length of stay are major attributes to inducing serious perioperative complications and worsening the prognosis of the patients, in addition to being associated with elevated healthcare-related costs secondary to the prolonged ICU admission and the potential additional care\(^{(9)}\). To lower the cardiovascular complications, \(\alpha_2\) agonists have been recommended to reduce the risk in the potential surgeries\(^{(10)}\). Among the previously used \(\alpha_2\)-agonists, dexmedetomidine has been used as a selective agent that can reduce delirium and the associated respiratory depression. It has also been previously reported that the drug has many advantages as having a short half-life of eight minutes over other sedative agents that are commonly prescribed for cardiac surgeries\(^{(11)}\). Moreover, evidence also shows that it can be beneficial on myocardial oxygenation by enhancing the hemodynamic circulation and reducing the harmful effects of adrenaline release secondary to the surgical manipulation\(^{(12, 13)}\). Our comparative randomized study aims to investigate the intraoperative effects of dexmedetomidine and propofol in fast-track anesthesia in coronary open-heart surgery.

II. MATERIALS AND METHODS

Study settings and population:

This is a randomized controlled prospective study conducted at Misr University Teaching Hospital. We aimed to include 40 patients in the study and subdivided them into two groups, 20 for each group undergoing coronary artery bypass grafting (CABG) on bypass with a warm cardioplegia. Our inclusion criteria were patients that ranged from 20 to 70 years, of either sex, with no special recommendations regarding race, geographic region, or marital status, and with coronary heart surgery. Moreover, we excluded patients if they had any of the following criteria: 1) if they have an allergic reaction to either dexmedetomidine or propofol, 2) if they had any history of receiving other \(\alpha_2\) agonist medications or any psychoactive substances, 3) if their baseline and preoperative blood pressure was \(< 90\) mmHg, or if the heart rate was \(< 55\) beats per minute, 4) having a bodyweight \(> 150\) kg, 5) if they had psychological comorbidity as parkinsonism or dementia, 6) having a baseline and preoperative creatinine \(> 1.6\) mg/dL, 7) if they had any underlying cardiac condition that is affecting the systolic or diastolic dysfunction, to less than 30% and grade I, respectively.

Study procedures:

Randomization: We have randomized patients into two groups using a computer-based modality to randomly allocate these patients into either of our two groups. Our first group was named group I in which dexmedetomidine was infused at an initial bolus IV dose of 0.4 mcg/kg/hr. over 10 minutes after anesthesia was induced and then a dose of 0.2 mcg/kg/hr as the continuous infusion was administered following the initial dose. Our second group was named group II, in which propofol was administered at a rate of 2.4 mg/kg/hr.

Study protocol and ethical approval: After the institutional review board approved our protocol to conduct this study, we also sought to obtain written informed consent from all the potentially included patients. A peripheral venous cannula was inserted and all study groups received 2 mg midazolam IV as premedication, 30 minutes before anesthesia was induced in the preoperative area. We have also conducted the following monitoring: electrocardiogram, and peripheral \(O_2\) saturation, in addition to performing noninvasive blood monitoring. Face masks were also used to provide adequate \(O_2\) saturation for our patients. An arterial catheter was inserted under local anesthesia and arterial blood gasedone.

We induced anesthesia in the whole population as follows: midazolame 2.5 – 5 mg, fentanyl 3 mcg/kg, atracurium 0.5 mg/kg, and propofol 2 mg/kg then the endotracheal intubation was performed, and positive pressure ventilation was applied at a frequency of 11-13 per minute. We also aimed to maintain the end-tidal \(CO_2\) at 30-40 mmHg and monitored it using a capnograph. The bispectral index (BIS) was conducted to monitor the depth of anesthesia and a reading taken after the induction of anesthesia, these readings were considered as T1. The second reading is taken after infusion of dexmedetomidine or propofol by 30 minutes regard as T2. The third and fourth readings were taken before initiation and after weaning from cardiopulmonary bypass respectively to be T3 and T4. Central venous line inserted under complete aseptic condition. Atracurium was infused at a rate of 0.5 mg/kg/hr. Dexmedetomidine infused in group one and propofol infused in group two, both continued also after transmission of the patient to the ICU till extubation. Anesthesia maintained by sevoflurane carried in 50% oxygen and air. Sevoflurane concentration will be increased or decreased according to the depth of anesthesia.
monitored by BIS (values have to be kept between 40-60%). Analgesia (fentanyl) titrated according to change in hemodynamics (arterial blood pressure, and heart rate) if the values increased by 20% or more bolus dose of fentanyl 2mcg/kg given. Heparin will be given at a dose of 300-400 IU/kg to reach the state of activated clotting time for 480 seconds at least. Midazolam 5mg will be given as a bolus dose just before the cardiopulmonary bypass to achieve hypnosis.

Cardiopulmonary bypass (CPB): we have prepared a membrane oxygenator primed by 100 mL 20% mannitol, 2000 mL ringer’s acetate, and 5000 IU heparin. An extra 5000 IU doses of heparin were also administered whenever needed. A non-pulsatile roller pump will be used for CPB and systemic hypothermia as the standard. After the aorta was cross-clamped, warm cardioplegia was infused for all patients. During the CPB the pump flow rate was 2.4-2.8 l/min/m² and the mean perfusion pressures were between 50-60 mmHg.

After weaning from the bypass and antagonizing the effect of heparin by protamine sulfate an ACT was done to keep the value between 120-140 second and arterial blood gas done to keep the arterial oxygen tension between 150-250 mmHg and arterial carbon dioxide tension between 35-45 mmHg. BIS reading and the hemodynamics (mean blood pressure and heart rate) will be recorded after weaning from the bypass by 15 minutes in both groups T₄. The dexmedetomidine and propofol infusion continued till the patient was transported to the ICU. Criteria of extubation in the ICU included: 1) the patient is hemodynamically stable, 2) arterial blood gases within normal, 3) Glasgow coma scale is 15/15, and 4) muscle paralysis has worn off.

Measurement tools: These included the hemodynamics changes (mean blood pressure and heart rate) which were monitored by invasive blood pressure and electrocardiography (ECG) and the depth of anesthesia monitored by BIS not more than 60%. In addition to other measurements e.g. bypass time, cross-clamp time, operative time. We have also considered other measurements of pain score and delirium postoperatively in the ICU. The data were collected at the following intervals: 1) after induction of anesthesia and before starting the drug infusion, 2) 10 minutes after infusion of the drug, 3) on bypass, 4) after bypass by 15 minutes, and 5) before transportation of the patient to the ICU.

Study outcomes: Our primary outcome was the need for analgesia (fentanyl intraoperative) during the anesthesia in each group. Our secondary outcome(s) were 1) the duration of stay in the ICU in patients with propofol and patients with dexmedetomidine, 2) hemodynamics (blood pressure and heart rate) in both of the study groups, 3) The degree and depth of anesthesia in our patients as estimated using the bispectral index not more than 60% in patients with propofol and dexmedetomidine, 4) preoperative co-morbidity, bypass time, use of vasopressor, cross-clamp time, operative time, the occurrence of delirium and pain score in the ICU, and 5) time of extubation from anesthesia in patients with propofol and patients with dexmedetomidine (time from stoppage of the drug infusion to the time of extubation in the ICU).

III. STATISTICAL ANALYSIS
A study by Afanador et al. (14) demonstrated a reduction in intraoperative fentanyl requirements from 12.5 + 5.9 to 3.2 + 1.3 μg/kg in patients receiving dexmedetomidine during cardiac surgery. We assumed a more conservative approach by calculating the sample necessary to detect a potential decrease by 50% reduction in fentanyl consumption, clinically. Calculation yielded a total of 36 patients (18 patients per group) at a power of 90% and an alpha level of 0.05. Our study sample has finally reached 40 patients (20 patients per group) to compensate for possible dropouts.

We have used Fisher’s exact or the Chi-squared test for categorical variables, while the numerical ones were also tested for normality. Comparison between the two groups was achieved by using the Student's t-test or Wilcoxon Rank-Sum test according to the approached variables and parameters. Intragroup comparison is done using ANOVA with repeated measures. We also considered the difference between the two groups to be statistically significant if the p-value < 0.05.

IV. RESULTS
Postoperative delirium: A total of 40 patients were included in the present study and randomized into two groups; group I (n=20) and group II (n=20), when comparing both groups, we found that the incidence of postoperative delirium was significantly higher in group II than group I (20% versus 6.7%, p=0.042, respectively). The detailed information regarding postoperative delirium presented in Table1.
Table 1. Comparison between groups according to postoperative delirium.

<table>
<thead>
<tr>
<th></th>
<th>Group I (D) (n=20)</th>
<th>Group II (p) (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of postoperative delirium</td>
<td>1 (6.7%)</td>
<td>3 (20%)</td>
<td>0.042*</td>
</tr>
</tbody>
</table>

*statistically significant

Mean arterial blood pressure and heart rate: Regarding the mean arterial blood pressure (mmHg), we did not find any significant difference between group I and II, whether at baseline (87.06 versus 84.64, p= 0.295) or after induction (72.11 versus 75.45, p= 0.136), respectively. However, the mean arterial blood pressure seemed to be significantly lower in group I than group II after 10 minutes of drug infusion (72.01 versus 77.37, p= 0.019), on the bypass (51.11 versus 55.15, p< 0.001), after bypass by 15 minutes (53.73 versus 59.69, p< 0.001) and before transferring the patient to the ICU (75.35 versus 83.43, p< 0.001), respectively (Table 2). Regarding the estimated heart rate for both groups, there was no significant difference between group I and II at baseline (79.18 versus 80.30, p= 0.610), respectively. Significantly higher values were noticed in group II than group I after induction (92.21 versus 83.53, p= 0.039), after 10 minutes of drug infusion (84.34 versus 77.47, p= 0.018), after bypass by 15 minutes (84.47 versus 77.37, p< 0.001) and before transferring the patient to the ICU (83.02 versus 76.05, p< 0.001), respectively (Table 3).

Table 2. Comparison between groups according to mean arterial blood pressure and heart rate.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I (D) (n=20)</th>
<th>Group II (p) (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Arterial Blood Pressure (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>87.06±6.09</td>
<td>84.64±5.92</td>
<td>0.295</td>
</tr>
<tr>
<td>After induction</td>
<td>72.11±5.05</td>
<td>75.45±5.28</td>
<td>0.136</td>
</tr>
<tr>
<td>After 10min of drug infusion</td>
<td>72.01±5.04</td>
<td>77.37±5.42</td>
<td>0.019*</td>
</tr>
<tr>
<td>On by pass</td>
<td>51.11±3.58</td>
<td>55.15±3.86</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>After bypassing by 15 min.</td>
<td>53.73±3.76</td>
<td>59.69±4.18</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Heart rate (beats/minute)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>79.18±5.54</td>
<td>80.30±5.62</td>
<td>0.61</td>
</tr>
<tr>
<td>After induction</td>
<td>83.53±5.85</td>
<td>92.21±6.45</td>
<td>0.039*</td>
</tr>
<tr>
<td>After 10min of drug infusion</td>
<td>77.47±5.42</td>
<td>84.34±5.90</td>
<td>0.018*</td>
</tr>
<tr>
<td>After bypassing by 15 min.</td>
<td>77.37±5.42</td>
<td>84.74±5.93</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>Before transferring patient to ICU</td>
<td>76.05±5.32</td>
<td>83.02±5.81</td>
<td>&lt;0.001**</td>
</tr>
</tbody>
</table>

Clinical outcomes and BIS spectral index: We did not find any significant difference between groups I and II in terms of mean length of hospital stay (4.75 versus 4.44 days, p= 0.262), respectively. On the other hand, the mean fentanyl (mcg/kg) that was used in group II was significantly higher than that in group I (12.63 versus 5.56, p<
Moreover, the length of ICU stay (days) (4.49 versus 3.74, p= 0.020) and time of extubation (hours) (8.73 versus 5.97, p< 0.001) were also significantly longer in group II than group I, respectively. Regarding the difference between the two groups in terms of BIS, group II showed total higher mean BIS values after induction (56.10 versus 47.47, p< 0.001), after 10 minutes of drug infusion (54.52 versus 45.15, p< 0.001), after bypass by 15 minutes (56.26 versus 49.39, p= 0.012), before transferring the patient to the ICU(87.30, versus 79.59 p= 0.009)and no significant difference was noticed between the two groups on the bypass (13.13 versus 18.18, p= 0.162), respectively (Table 3).

Table 3. Comparison between groups according to some clinical outcomes and Bis spectral index (BIS).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group I (n=20)</th>
<th>Group II (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of postoperative hospital stay (days)</td>
<td>4.75±0.33</td>
<td>4.44±0.31</td>
<td>0.262</td>
</tr>
<tr>
<td>Fentanyl (mcg/kg)</td>
<td>5.56±0.39</td>
<td>12.63±0.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of stay in the ICU</td>
<td>3.74±0.26</td>
<td>4.49±0.31</td>
<td>0.020*</td>
</tr>
<tr>
<td>Time of extubation (hours)</td>
<td>5.97±0.42</td>
<td>8.73±0.61</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>BIS</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After induction</td>
<td>47.47±7.70</td>
<td>56.10±8.80</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>After 10min of drug infusion</td>
<td>45.15±6.60</td>
<td>54.52±5.50</td>
<td>&lt;0.001**</td>
</tr>
<tr>
<td>On by pass</td>
<td>13.13±9.90</td>
<td>18.18±9.90</td>
<td>0.162</td>
</tr>
<tr>
<td>After by pass by 15 min.</td>
<td>49.39±6.60</td>
<td>56.26±6.60</td>
<td>0.012*</td>
</tr>
<tr>
<td>Before transferring patient to ICU</td>
<td>79.59±5.50</td>
<td>87.30±3.30</td>
<td>0.009*</td>
</tr>
</tbody>
</table>

V. DISCUSSION

Dexmedetomidine is a highly selective, powerful, and specific α2-adrenoreceptor agonist. It has variable actions which depend on the location of receptors in the central and peripheral nervous systems, as well as target organs. This study compared dexmedetomidine with propofol to test the analgesic and sedative effect of dexmedetomidine and its role in fast-track anesthesia for coronary open-heart surgical settings using cardiopulmonary bypass. Our findings showed that dexmedetomidine can significantly reduce the heart rate and mean arterial pressure, as estimated in our population, compared to the other group. These actions are mainly attributable to the potential direct inhibition of the sympathetic outflow centrally, and also by decreasing the amount of the circulating catecholamines (15). Besides, the reduction in the heart rate might attribute to the vagal-like effect of the drug in these patients (16). These findings are consistent with the results of previous studies, which have also shown that dexmedetomidine can significantly reduce the blood pressure and heart rate in their populations (15, 17).

Regarding BIS, patients within the dexmedetomidine group showed statistically significantly lower values than other patients within the propofol group. We also noticed that the lowest BIS values were recorded during the bypass period. This may support the hypothesis that hypothermia decreases the metabolism of anesthetic drugs. This is consistent with the results of Mathewet al. (18) that reported that hypothermia can significantly reduce the potential BIS values by 1.12 units for each reduced one degree Celsius, as estimated in their population that
performed cardiopulmonary bypass procedures. It was also found that thermal reduction can significantly affect and reduce the potential cardiovascular physiological functions.

We also noticed that intraoperative fentanyl has been significantly reduced among patients the dexmedetomidine group than the other group. This is due to the analgesic effect of dexmedetomidine through activation of the α₂ adrenoceptors in the spinal cord and lowering the transmission of the nociceptive signaling to the higher brain centers. Moreover, dexmedetomidine inhibits the release of substance-p from the dorsal horn. This finding is supported by the previous study by Afanador et al. (14). We also found that dexmedetomidine facilitates early postoperative extubation and reduces the postoperative length of stay in the hospital and ICU. On the other hand, the previous investigation by Lewis et al. (19) found no significant differences in terms of the hospital or ICU postoperative length of stay in both groups.

Dexmedetomidine can also be used as an adjuvant drug during anesthesia helps to reduce the anesthetic requirements and facilitates early postoperative tracheal extubation and reduces ICU stays, thus reducing risks and costs. Also, dexmedetomidine has been shown to decrease the incidence of postoperative delirium. Evidence from the relevant literature explained this phenomenon by showing that the drug has a potential role in reducing the activities of the gamma-aminobutyric acid receptor(GABA), and therefore, can enhance sleeping in these patients and reduce the potential respiratory depression, in addition to the probable effective lack of the anti-opioid and anticholinergic activities (20, 21). Moreover, the previous study by Myles et al. (22) found that dexmedetomidine can significantly lead to early extubation, however, they also reported that the drug does not possibly affect the ICU length of stay irrespective of this finding. The authors have also supported their results by previous findings from similar trials that were conducted to assess the efficacy of the drug on the fast-track techniques in anesthesiology settings. For instance, the previous investigation by AFandor et al. (14) found that although using the fast-track modalities can significantly lead to an early postoperative tracheal extubation, it cannot lead to any reduction in the length of the hospital and ICU stay with no baseline changes in the policy and recommendations for providing the appropriate care for the potentially admitted patients. Therefore, it was concluded that reduce hospital and ICU length of stay is more appropriately associated with the frequency and quality of the provided postoperative care rather than the setting of the time of extubation.

Our findings might be limited by some concerns. First, although this is a randomized study, we could not properly differentiate between the two drugs so a placebo is needed. Accordingly, we encourage further investigations with proper design and randomization for further validation of the current evidence. Patients with very low ejection fraction and those having a high cardiovascular risk for developing bradycardia and hypotension during the administration of dexmedetomidine were excluded. Therefore, further investigations with larger sample signs and broad baseline demographics are needed.

Besides, for monitoring the depth of anesthesia and hypnosis, which can be confounded by many factors such as hypothermia and cerebral ischemia, only intraoperative BIS values were assessed. No baseline psychiatric and cognitive evaluation of patients was also done, which may have potentially biased the postoperative delirium statuses of our patients. Moreover, extended postoperative evaluation of these parameters was not performed in our study, and accordingly, our results might be confined to the early postoperative evaluation results only. No solid evaluation of other intraoperative medications that could have affected the cognitive status of our patients was also performed.

Lastly, we did not consider many baseline predictors such as the age of the patient because the increase in age can increase the incidence of delirium, hypertension, dyslipidemia, thyroid dysfunction diabetes mellitus, and renal diseases either acute kidney failure or end-stage kidney disease. Analgesic requirement nor sedative drugs in the postoperative period was not taken into consideration as the study did not include the postoperative period.

VI. CONCLUSION

In the present study, we investigated the potential efficacy of dexmedetomidine as a short-acting α₂ agonist on fast-track techniques in surgical cardiology settings. It can attenuate the sympathetic response to intubation, decrease the anesthetic requirement, and can also facilitate the process of early postoperative extubation. We recommend that postoperative cardiac care and early extubation are two key elements to achieve successful fast-track cardiac anesthesia.
REFERENCES