Comparing dexmedetomidine and propofol for sedation and hemodynamic stability in cardio-thoracic intensive care unit for patients following off-pump coronary artery bypass graft surgery

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ABSTRACT

Background: Most patients in intensive care unit (ICU) require both sedation and analgesia to encourage natural sleep, facilitate assisted ventilation and modulate physiologic response to stress. The ideal sedative after Coronary artery bypass grafting (CABG) should have rapid onset, immediate resolution of both pain and anxiety, promote cardiac and respiratory stability, maintain a reusability during sedation, allow rapid recovery after discontinuation, and attenuate the cardiovascular, neuroendocrine, and inflammatory response. All these properties may improve outcome in cardiac patients after CABG.

Methods: Setting-cardiac ICU. A prospective, randomised, single blind study including 60 patients divided into 2 groups. Data collection tools-study proforma and Ramsay sedation scale (RSS). Data analysed using science and statistical packaged (SPSS) version 20, independent sample ‘t’ test, chi-square test, analysis of variance (ANOVA) and p value ≤0.05 was considered statistically significant.

Results: Sedation levels and length of stay of patients on ventilator were comparable in both groups, however, analgesic requirement was significantly less in dexmedetomidine group. Dexmedetomidine group showed significantly lower heart rates compared to propofol group.

Conclusions: Dexmedetomidine and propofol are safe sedative agents during mechanical ventilation in ICU for patients undergoing off pump coronary artery bypass (OPCAB). There is more than 50% reduction in analgesic requirement and a significant reduction in heart rate in dexmedetomidine sedated patients.

Keywords: Sedation, Analgesia, Hemodynamic, Intensive care unit, Off pump coronary artery bypass

INTRODUCTION

The goal of sedation in the intensive care unit (ICU) is to keep patients comfortable, calm, and without pain. The ideal sedative after CABG should have rapid onset, immediate resolution of both pain and anxiety, promote cardiac and respiratory stability, maintain arousability during sedation, allow rapid recovery after discontinuation, and attenuate the cardiovascular, neuroendocrine, and inflammatory response. All these properties may improve outcome in cardiac patients after CABG.

Dexmedetomidine is a highly specific α2-adrenoreceptor agonist that received Food and Drug Administration approval in 1999 as an ICU sedative. The sedative effect of dexmedetomidine results from stimulation of α2-adrenoreceptors in the central nervous system (specifically in the locus coeruleus). The patient is effectively sedated, yet easily awakened to answer questions, take neurologic tests, and respond to visitors and staff, while calm and comfortable. As soon as the awakening stimulus is removed, the patient returns to a sleep-like sedated condition.
Propofol is commonly used in the ICU for short-term sedation of the ventilated postsurgical patients. Propofol alone has no analgesic property; opioids are given to control pain. Propofol has moderate vasodilatory effects, it may cause clinically significant hypotension in patients who have unstable vital signs or limited myocardial reserve. It may also cause some respiratory depression, an effect that can be amplified in the presence of opioids. It must be stopped whenever the patient must be assessed for neurologic function.

In OPCAB, the surgical approach most commonly performed is with full sternotomy. The focused involvement of the anaesthesiologist is more important in OPCAB than during on-pump CABG. Fast-track management for CABG has received considerable attention. Although the fast-track clinical pathway encompasses a variety of perioperative management strategies, early extubation is the one that has received perhaps the greatest attention.

This study aimed to compare a relatively new sedative agent dexmedetomidine to a current sedative agent propofol following off pump coronary artery bypass graft surgery in the intensive care unit with following variables: analgesic requirement, sedation, length of stay of patients on ventilator and hemodynamic parameters.

**METHODS**

This was a prospective, experimental, randomised single blind study. It was conducted in cardio-thoracic intensive care unit of Lisie hospital, Kochi, Kerala. Approval from the institutional ethical committee was obtained. Duration of the study was April-September 2012.

Study population was adult patients less than 70 years of age undergoing CABG surgery during the study period in Lisie hospital. Written informed consent was obtained from all patients for participation in study.

**Inclusion criteria**

Inclusion criteria included adult patient less than 70 years who are posted for CABG, Elective CABG patients.

**Exclusion criteria**

Exclusion criteria excluded patient refusal. History of previous CABG surgery or heart valve surgery. Patients with ejection fraction less than 45%. Patients with severe bradycardia or heart block. Patients with renal, liver or neurological impairment. Patients who needed intra-aortic balloon pump and have overt congestive heart failure. Any contraindication or known or suspected allergy to propofol, dexmedetomidine, opioids or paracetamol.

**Randomization and blinding**

60 patients based on the inclusion and exclusion criteria were selected and allocated a serial number from 1 to 60. By using a computer-generated random number list the participants were allocated to either group D or group P.

Group D: Patients who received dexmedetomidine infusion. Group P: Patients who received propofol infusion.

We elected not to mask the study drug from the observer because the physical appearance of propofol (formulated in a white lipid emulsion) is different from dexmedetomidine (clear liquid) and any leakage of solution would unmask the study drug. Other reason of not masking the study drug was the individual dosing range decided for adjusting the sedation levels. Hence, our study was a single blind study, with patient being blinded of the study group.

In the operation theatre, at sternal closure for patients randomized to group D dexmedetomidine infusion was started at 0.2 µg/kg/hr and for patients randomized to group P, propofol infusion was started at 0.5 mg/kg/hr.

Time of starting the study drug infusion was considered as ‘0’ hour and baseline hemodynamic parameters were noted.

After shifting to ICU, patients were mechanically ventilated with synchronized intermittent mandatory ventilation (SIMV) and pressure support mode. ECG, blood pressure (mean blood pressure), heart rate, CVP and SpO2 were monitored continuously. Blood gases and blood glucose levels were measured upon admission to ICU, 2 hourly for 4 hours and then 4th hourly till extubation.

Sedation was monitored in both groups by using Ramsay sedation score.

During the mechanical ventilation period in both groups RSS was maintained between 3 and 4. If RSS fell below the target levels then study drug infusions were titrated in the range for group D (dexmedetomidine 0.2-0.5 µg/kg/hr) and for group P (propofol 0.5-1 mg/kg/hr).

Injection paracetamol 1 gm sixth hourly was administered to all patients during the study period, first dose being given as soon as the patient comes to the ICU. If the mean blood pressure and heart rate increased more than 20% from the baseline despite on adequate sedation, rescue injection fentanyl 0.5-1µg/kg bolus for pain was administered. The total dose of rescue fentanyl administered in ICU in both groups was recorded till 12 hours.

Time to become responsive was noted. It was defined as time interval between sternal closure and when the patient became responsive, hemodynamically stable without shivering, had no significant bleeding, warmed to a temperature above 36°C, FiO2≤0.4 and SpO2≥95%. Length of stay of patients on ventilator was noted, which was defined as time interval between sternal closure and when the patient was considered ready to extubate. Patient...
was considered ready for extubation, if awake or arousable, neurologically intact, cooperative and comfortable, \(\text{FiO}_2\leq0.4\), peak\(\leq5\) cm H\(_2\)O, pressure support \(\leq10\) cm H\(_2\)O, minute ventilation>4L and \(<5\) L/min, tidal volume >5 ml/kg, and spontaneous respiratory rate \(<25/\text{min}\). ABG was done one hour after extubation. When the patient was considered ready to extubate, we stopped the study drug infusion in both groups.

In our institute, most of the patients underwent CABG with total arterial revascularisation (TAR) so as per our institutional protocol mean blood pressure was maintained around 80 mm Hg. As per our institutional protocol, hypotension was defined as the mean BP less than 60 mmHg and managed with optimal preloading, postural adjustments (head low), vasopressor adjustment (noradrenaline) and atrial pacing. Hypertension was defined as mean blood pressure above 100 mm Hg. This hypertensive response was managed with adequate sedation, pain relief, postural adjustments (head up) and titrating the dose of venodilator like nitro-glycerine. If heart rate is \(<60\) beats/minute, we considered it as bradycardia and managed with atrial pacing if it was associated with hypotension. If heart rate \(>100\) beats/minute, we considered it as tachycardia. Causes for tachycardia like hypovolemia, pain was excluded.

RSS, mean blood pressure and heart rate were continuously monitored but noted half hourly till extubation and then hourly till 12 hours. If any adverse event occurred in between was noted separately. If any patient required mechanical ventilation more than 12 hours was excluded from the study. ECG was continuously monitored. CVP was always maintained between 8-12 mmHg and \(\text{SpO}_2\) was maintained \(>96\%\).

**Statistical analysis**

Data was analysed using social science and statistical packaged (SPSS) version 20. We used independent sample ’t’ test for comparing demographic data (age, weight and height), time to become responsive, length of stay of patients on ventilator, rescue fentanyl requirement. Gender distribution is categorical data for which we used chi-square test. For comparing Ramsay sedation score and hemodynamic parameters (HR and MBP) analysis of variance (ANOVA) for repeated measures was used.

All data were reported as mean±standard deviation (S.D.).

Significance level achieved in our study was 5 at 95% confidence intervals.

(*) p value \(\leq0.05\) was considered statistically significant.

**Sample size determination**

Based on the previous work done by Grounds, Triltsch, Hell VJ et al suggested that reduction in analgesic requirement in dexmedetomidine group of clinical interest was 50%.\(^5,9,10\). Using ’G power’ software version 3.1.5 for calculating sample size, \(n=20\) in each group was sufficient to have a power of study more than 95% at a significance level of 5% (type I error) and less than 5% of type II error.

We took the sample size of 30 in each group to avoid reduction in sample size due to exclusion of patients who would have been ventilated for prolonged duration (>12 hours).

**RESULTS**

The results were analysed as follows:

Age, weight and height distribution were compared using independent sample ’t’ test. They were statistically similar in both groups as shown in Table 1. Gender distribution being a categorical data we used chi-square test and it was statistically similar. Hence, demographically both groups were comparable.

**Table 1: Rescue analgesic requirement-independent sample ’t’ test.**

<table>
<thead>
<tr>
<th>Analgesic requirement</th>
<th>Group D Mean±SD</th>
<th>Group P Mean±SD</th>
<th>(P)</th>
<th>Power</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rescue fentanyl req. (µg)</td>
<td>78.33±31.30</td>
<td>170.00±48.42</td>
<td>&lt;0.001*</td>
<td>1.00</td>
</tr>
</tbody>
</table>

Analgesic requirement-there was a statistically significant difference in both groups in rescue fentanyl requirement. Using ANOVA for repeated measures for comparing HR showed a statistically significant difference, however, MBP and Ramsay sedation scores did not show any significant difference over 12 hours. There was no statistically significant difference in two groups in terms of time to become responsive and length of stay of patients on ventilator (\(p>0.05\)).

**Analgesia**

![Graph showing error bar for rescue fentanyl requirement.](image-url)
Sedation

Ramsay sedation scores of both groups were recorded every half hourly till extubation and then hourly till 12 hours.

Table 2: Ramsay sedation score.

<table>
<thead>
<tr>
<th>Levels</th>
<th>Score</th>
<th>Observation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Awake levels</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Anxious, agitated or restless.</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Cooperative, oriented and tranquil</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Responsive to commands only.</td>
<td></td>
</tr>
<tr>
<td>Asleep levels</td>
<td>4</td>
<td>Asleep but with brisk response to light glabellar tap or loud auditory stimulus.</td>
</tr>
<tr>
<td>5</td>
<td>Asleep, sluggish response to glabellar tap or auditory stimulus</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Asleep no response.</td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Ramsay sedation score (ANOVA-muti variate test for between groups).

<table>
<thead>
<tr>
<th>RSS</th>
<th>Wilk’s Lambda value</th>
<th>F</th>
<th>Hypothesis df</th>
<th>Error df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.73</td>
<td>1.22</td>
<td>14.00</td>
<td></td>
<td>45.00</td>
<td>0.29</td>
</tr>
</tbody>
</table>

Table 4: Length of stay of patients on ventilator-independent sample ‘t’ test.

<table>
<thead>
<tr>
<th>Independent sample ‘t’ test</th>
<th>Mean length of stay of patients on ventilator (hours)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group D Mean±SD</td>
<td>7.78±0.28</td>
<td>0.34</td>
</tr>
<tr>
<td>Group P Mean±SD</td>
<td>7.71±0.25</td>
<td></td>
</tr>
</tbody>
</table>

Hemodynamics

Table 5: Heart rate (ANOVA-multi variate test for between groups).

<table>
<thead>
<tr>
<th>HR</th>
<th>Wilk’s Lambda value</th>
<th>F</th>
<th>Hypothesis df</th>
<th>Error df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.28</td>
<td>4.91</td>
<td>20.00</td>
<td></td>
<td>39</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>HR: Heart rate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 6: Mean blood pressure (ANOVA-multi variate test for between groups).

<table>
<thead>
<tr>
<th>MBP</th>
<th>Wilk’s Lambda value</th>
<th>F</th>
<th>Hypothesis df</th>
<th>Error df</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.71</td>
<td>0.81</td>
<td>20.00</td>
<td></td>
<td>39</td>
<td>0.69</td>
</tr>
<tr>
<td>MBP: Mean blood pressure.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 7: Incidence of adverse events.

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>Group D</th>
<th>Group P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reintubation</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Exclusion of patient from study due to prolonged ventilation (&gt;12 hours).</td>
<td>Nil</td>
<td>Nil</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
<td>Nil</td>
<td>Nil</td>
</tr>
</tbody>
</table>

Figure 2: Heart rate versus time.

DISCUSSION

Patients admitted to intensive care units are under high level of stress and discomfort. The use of adequate sedation and analgesia is important in order to modulate physiological response to stress and pain, hence reducing morbidity and mortality in the ICU. All CABG patients have homogeneity in terms of underlying diseases and type of anaesthesia and surgery, so post CABG patients were selected for this study.

Dexmedetomidine has been used in the intensive care for its sedative, anxiolytic and analgesic properties and not producing respiratory depression due to its non-opioid mechanism of analgesia.5,12 Dexmedetomidine induced sedation is very different from that induced by the general anaesthetic propofol. Unfortunately, there are no validated tools that evaluate sedation resulting from α2-adrenoceptor stimulation.13 All current tools, including the Ramsay system and BIS, were designed to estimate the depth of sleep or loss of consciousness and they do not measure the level of calmness and comfort.14 Dexmedetomidine patients are comfortable but arousable and cooperative.15 They may fall asleep because they are relaxed; in fact, the mechanism appears to promote a natural sleep.16 This allows neurologic assessment and communication with the patient without interruption of the calming effects of sedation. Disadvantage of dexmedetomidine is the inadvertent cardiovascular effects after bolus dose and lack of amnesia.2,17

Propofol is a short-acting, intravenous sedative-hypnotic agent initially marketed as an anaesthetic, and now widely
used for the sedation of patients in the intensive care unit (ICU). Advantage of using propofol as a comparison to dexmedetomidine is that it has been regularly used in ICU’s for post-operative sedation. Second benefit is that most of the clinicians are used to dosing regimens of propofol and thirdly, propofol is having short context sensitive half time even with long infusion period. Disadvantages of using it are the hemodynamic changes caused by it, secondly, patients sedated with propofol are considered by the observer to be “sedated” because they are unresponsive and lastly it may exacerbate delirium. Next best alternative for comparison with dexmedetomidine is midazolam. But it may also exacerbate agitation, delirium and prolonged drowsiness.

Mean rescue fentanyl requirement during sedation in dexmedetomidine group was 78.33±31.30 µg where as in propofol group it was 170.00±48.42 µg with p<0.001. This indicates that the rescue fentanyl requirement in dexmedetomidine group was reduced over 50% compared to propofol group. These finding are consistent with previous studies done in cardiothoracic ICU by Azrina et al. These results are also consistent with studies done in other ICU’s like Samia, Venn and Triltsch et al which showed that dexmedetomidine reduces the use of concurrent analgesia. Studies on healthy volunteers have also demonstrated dexmedetomidine’s analgesic effect. With analgesic requirement as a variable using ‘G Power’ software version 3.1.5, the calculated power of study with sample size of 30 per group was 1.00 at 5% significance level. In our study, as part of a multimodal analgesia, in both groups’ injection paracetamol 1 gm sixth hourly during study period as an adjunct was given. Use of paracetamol as an adjunct is supported by previous study of Khalil et al.

Sedation levels using RSS were comparable in both groups in our study. The results are in accordance with previous studies like Herr, Samia and Venn et al. The tool used in our study for assessing sedation was RSS because most of the reference studies used it and there is no cost involved. Disadvantage of using RSS for scoring sedation is that there is a lot of interrater variability, also it necessitates the use of acoustic and tactile stimulation which can cause undesired arousal and agitation leading to patients discomfort which may necessitate increase in sedative and analgesic drug dose. Alternative to RSS is BIS for scoring sedation. Advantage of BIS over RSS is that it is more objective method without acoustic and tactile stimulation. Only disadvantage being cost involved in using it. Studies have shown that there is good correlation between BIS and Ramsay sedation scale. In our study, lack of significant difference in sedation levels in both groups would be a result of small sample size for which we recommend a study with larger sample size.

We used dexmedetomidine infusion range of 0.2-0.5 µg/kg/hr and propofol of 0.5-1.0 mg/kg/hr. Compared to Herr and Snellen et al who also had post cardiac patients, our dose range is lower. This lower dose caused lesser hemodynamic changes in our patients. Previous study by Samia et al also recommend this range of infusion in both groups for adequacy of sedation in mechanically ventilated ICU patients. Hence, we recommend this dose range of both drugs for sedation in OPCAB patients who are mechanically ventilated.

In our study, intraoperatively for maintenance of anaesthesia fentanyl (10-20 µg/kg), sevoflurane as an inhalational agent and vecuronium as muscle relaxant were used, this made fast tracking with reduction in duration of ventilation possible. Previous studies by Cheng, Myles et al and Hawkes et al supports the fact that fast tracking reduces the duration of ventilation with no significant increase in morbidity and mortality. In these studies, the average length of stay of patients on ventilator was around 8 hours. The context sensitive half-life and terminal half-life of propofol and dexmedetomidine is less than 4 hours. This was the reason we kept the study period of 12 hours.

In our study, the mean time to become responsive was comparable. This signifies that the intraoperative use of fentanyl, sevoflurane and muscle relaxant in both groups were comparable. The mean length of stay of patients on ventilator in both groups was comparable. This finding is in accordance with previous study by Herr et al. Mean (SD) length of stay of patients on ventilator in dexmedetomidine group was 7.78±0.28 hrs and in propofol group it was 7.71±0.25 hrs. Hence, the average length of stay of patients on ventilator was less than 8 hours in both groups with no incidence of reintubation and none of the patient was excluded from the study groups because of prolonged ventilation period (>12 hours). On comparing with previous studies of Cheng, Myles and Hawkes et al on early extubation, our study satisfies the requirement of fast tracking the post OPCAB patients in ICU in both groups.

Rapid infusion of loading dose of dexmedetomidine has been associated with a biphasic response, transient hypertension followed by severe hypotension. Also, large bolus of propofol used as in induction of anaesthesia has also been associated with the occurrence of significant hypotension and bradycardia. Study by Herr et al has also shown that the adverse event of hypotension occurred mostly within 10 minutes of loading dose of dexmedetomidine. This was the reason we omitted loading doses in both groups and maintenance infusions were started in operation theatre at sternal closure. Time required for patient to reach ICU from sternal closure was around 1 hour. According to Yahya and Azrina et al one hour was sufficient time for achieving adequate plasma levels and adequate sedation levels in both groups.

In our study, hemodynamic variables compared were heart rates and mean blood pressures. Mean blood pressure was comparable in both groups. Mean MBP in dexmedetomidine group was 85.57±1.90 (SD) mmHg and in propofol group was 85.82±2.07 (SD) mmHg. On
comparing HR using ANOVA test for repeated measures in both groups we got a statistically significant difference. Mean HR in dexmedetomidine group being (69.45±1.66 (SD) beats/min lower than mean HR in propofol group [78.87±3.30 (SD) beats/min]. This indicated that heart rate was significantly lower in dexmedetomidine group compared to propofol group. These findings are consistent with previous studies like Venn, Samia and Rabib et al.9,11,21 One patient of each group had bradycardia but did not require intervention. The numerous other inadvertent cardiovascular events like hypotension, hypertension and tachycardia seen in previous studies with loading dose infusion of dexmedetomidine were not seen in this study.20
In our study, CVP and SpO2 were well maintained in all patients throughout the study period.

This reduction in heart rate is expected from the known pharmacology of dexmedetomidine, an α2 adrenergic agonist.6 Stress is considered to be a major risk factor in myocardial ischaemia after surgery. The significantly lower heart rates seen with dexmedetomidine in comparison with patients receiving propofol may lower the risk of ischaemic events during the stressful ICU period.7 This makes major difference in critically ill patients, especially during periods of stress e.g., endotracheal suctioning, physiotherapy, and mobilization. It is proven that the perioperative use of α2 agonists like clonidine, reduces the incidence of perioperative myocardial ischemia.31 There were no adverse events in both groups.

CONCLUSION

To conclude, dexmedetomidine and propofol are safe sedative agents during mechanical ventilation in ICU for patients undergoing OPCAB. There is more than 50% reduction in analgesic requirement and a significant reduction in heart rate in dexmedetomidine sedated patients. Fast tracking of OPCAB patients with early extubation was successfully possible with both drugs.

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