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A Comparative Study of Dexmedetomidine and Propofol for Sedation in The Cardiothoracic Intensive Care Unit.

Azrina Md Ralib [1], Saedah Ali [2], Mohd Nikman Ahmad [3], Ziyadi Mohd Ghazali[4], Nik Abdullah Nik Mohamad [5].

Department of Anaesthesiology and Intensive Care[1,2,3,5], Cardiothoracic Unit, Department of Surgery[4], School of Medical Sciences, Universiti Sains Malaysia, Kelantan, Malaysia.

ABSTRACT

Introduction and Objectives: The intensive care unit (ICU) is an uncomfortable and stressful environment for patients. The use of adequate sedation and analgesia is important to reduce stress to patients. The aim of this study was to compare a relatively new sedative agent, dexmedetomidine to current sedative agent used, propofol in the provision of sedation and analgesia, their effects on haemodynamic and respiratory parameters and cost involved on post open heart surgery patients. **Materials and Methods:** A prospective, randomized single-blinded trial was conducted on post open heart surgery patients in the ICU of the Hospital Universiti Sains Malaysia (HUSM). Thirty two patients were randomized to dexmedetomidine or propofol groups. Analgesic requirement, haemodynamic and respiratory parameters, and extubation time were measured and compared. Mean rate of infusion to achieve adequate sedation were used to calculate the cost involved in the use of these two agents. **Results:** Patients sedated with dexmedetomidine required significantly lower dose of morphine compared to propofol [mean (sd): 12.80 (2.61) versus 15.86 (1.87) mg/kg/min, p=0.00]. Mean heart rate was also significantly lower in dexmedetomidine group compared to propofol group [mean (CI): 74.48 (70.38,78.59) versus 83.85 (79.61,88.09) per minutes, p=0.00]. However there were no significant differences in the other parameters between the two groups. Cost involved the use of dexmedetomidine was slightly higher

compared to propofol (RM 9.57 versus RM8.94 per hour). **Discussion and Conclusions**: Dexmedetomidine is comparable to propofol in the provision of sedation, and its effect on haemodynamic and respiratory parameters. However it has added advantages in the provision of analgesia, and caused a significant reduction in heart rate. This is beneficial in these patients by reducing myocardial oxygen demand, and hence subsequent ischaemia and infarction. However, further larger studies are needed to evaluate the effect of dexmedetomidine on perioperative cardiac morbidity and mortality.

INTRODUCTION

The intensive care unit (ICU) is an environment of high level of stress and discomfort for patients. The use of adequate sedation and analgesia are important in order to modulate physiological response to stress and pain, hence reducing morbidity and mortality in the ICU. Current sedative agents used in the intensive care unit include benzodiazepines e.g. midazolam, opioids e.g. morphine, and propofol. These drugs whilst providing effective sedation and analgesia, have their own limitations. Benzodiazepines are anxiolytic and amnestic, but they can also cause paradoxical agitation especially in the elderly. Opioids can provide effective analgesia, but they are not good sedative and amnestic agent. Furthermore they can cause pronounce respiratory and cardiovascular depression. Both benzodiazepines and opioids have cumulative effects, and hence their actions are prolonged in patients with liver and renal impairment, which are common in the intensive care setting[1]. Propofol, which has a very short duration of action and no cumulative effect, can cause dose-dependent respiratory depression, hypotension and hyperlipidaemia[2].

The search for an 'ideal' sedative agent continues. It should be one that is easy to administer, has a rapid onset and predictable effect, alleviates both pain and

anxiety, promotes cardiac and respiratory stability, maintains arousability during sedation, allows rapid recovery after discontinuation, lack of drug accumulation, few adverse events and interact minimally with other drugs and inexpensive[3]. Dexmedetomidine is a relatively new highly selective a_2 agonist agent (a_2 : a_1 ratio of 1600 : 1). It is a potent sedative, anxiolytic, analgesic and sympatholytic agent, currently being introduced in our intensive care setting. It acts both centrally and peripherally. At the central nervous system, it acts on the postsynaptic a_2 inhibitory receptor, resulting in sympatholytic and sedative effects. Its action at the spinal cord results in analgesic effect, whereas its action at the presynaptic membrane of the peripheral nerves and autonomic ganglia, reduces the release of catecholamines leading to sympatholytic effect[4].

In the cardiothoracic intensive care unit of Hospital Universiti Sains Malaysia (HUSM), the current standard for sedation and analgesia are propofol and morphine infusions. Propofol has a rapid onset and a very short duration of action. However it has been associated with dose-dependent respiratory depression, hypotension and hyperlipidaemia[2]. Hence, it can exert deteriorating effects in patients with limited myocardial reserve. Previous studies have concluded that dexmedetomidine has several unique properties including provision of effective sedative and analgesic effects, maintenance of patients' arousability and cooperativity, reduction of heart rate, and hence myocardial oxygen demand with minimal effects on ventilation[5]. With the advent of this new sedative agent with its unique properties, we aimed to compare it with our standard regime, in order to provide an alternative or better sedative regime to our patients.

MATERIALS AND METHODS

This study was a prospective, randomized, single-blinded trial. It had been approved by the Research and Ethics Committee, School of Medical Science,

Universiti Sains Malaysia, Kubang Kerian, Kelantan. Thirty-two post-open heart surgical patients whom were being mechanically ventilated in the Cardiothoracic Intensive Care Unit (CICU) of Hospital Universiti Sains Malaysia (HUSM) from January 2003 until July 2005 were enrolled in this study after obtaining their informed consent. Based on previous studies by Venn *et al.*[17] and Venn & Ground[11], heart rate reduction of clinical interest was 20%. A sample size of 32 (n=16 in each group) were needed to achieve a significance level of 5% and power of study of 80%. Inclusion criteria includes; male and female above 18 years of age, and written consent. Exclusion criteria of this study includes; poor left ventricular function (ejection fraction < 40% / cardiac index < 2 l/min/m^2), preexisting severe bradycardia (heart rate < 40 per minute) or heart block of any degree, chronic medical illness e.g. renal, liver or neurological impairment, any other conditions or factors that might increase risk to the patients e.g. haemodynamic instability perioperatively, body mass index > 30, and any contraindication or known or suspected allergy to propofol, dexmedetomidine, benzodiazepine or opioid.

The objectives of this study were to assess the effect of dexmedetomidine compared to propofol on haemodynamic and respiratory parameters**,** to assess their efficacy in the provision of sedation and analgesia, and to compare the cost involved in the use of these two drugs. Patients were randomized into two study arms, dexmedetomidine and propofol group. Intraoperatively, patients were induced with fentanyl, midazolam and pancuronium. Anaesthesia was maintained with isoflurane as inhalational agent and pancuronium as muscle relaxant. The infusion was started in the operation theatre at the start of skin closure, once the patient was haemodynamically stabilized with minimal amount of inotropes.

The infusion rate was titrated to achieve bispectral index score (BIS) of 65 to 85 to maintain adequate sedation[6]. Morphine infusion of 0.01 mg/kg/hour was started in the ICU, for both groups. If the blood pressure and heart rate increased more than

20% from the baseline despite on adequate sedation, rescue morphine 1 mg bolus was given. Patients were ventilated in the CICU. Weaning criteria includes; alert, conscious, no neurological deficit, cooperative, comfortable, normothermia, cardiovascular stability; MAP > 70 mmHg with minimal inotropic support, stable heart rate and rhythm, PaO_2 > 75mmHg, FiO_2 < 40%, PEEP < 5 cmH2O, and no excessive bleeding from surgical drain. The study drug was stopped during weaning, prior to extubation. Extubation was undertaken when spontaneous respiration with pressure support < 10cmH2O, V_T > 6ml/kg and respiratory rate > 10 but < 20 per minute.

The outcomes of this study include haemodynamic parameters (heart rate, systolic and diastolic blood pressure), respiratory parameters (PF ratio (PaO_2/$Fi0_2$), and pCO_2 level), metabolic parameters (serum lactate, and pH), bispectral index score (BIS), total morphine requirement, and extubation time. Cost was calculated from the mean rate of infusion of study drug required to achieve adequate sedation.

All data analysis and data entry were done using Social Science and Statistical Packaged (SPSS) version 10.0 software licensed to Universiti Sains Malaysia. Results were presented as mean (standard deviation), unless otherwise stated. Statistical analyses were performed using independent t-test or Mann-Whitney U test for numerical data and Chi-Square test for categorical data. Haemodynamic and respiratory data were compared using analysis of variance (ANOVA) for repeated measures. Statistical significance was considered at p value less than 0.05.

RESULTS

A total of 36 patients were included in the study. Four patients were excluded from the study after randomization; two due to severe bleeding affecting haemodynamic parameters, one due to development of significant arrhythmia unrelated to the

study drug, and one due to severe hypotension secondary to cardiogenic shock post cardiopulmonary bypass. There were no significant differences in the demographic and sedative characteristics between the two groups (Table 1).

Mean heart rate in propofol group was 83.85 (79.61, 88.09) and in dexmedetomidine group was 74.48 (70.38, 78.59). From repeated measures ANOVA, mean heart rate in dexmedetomidine group was significantly lower than in the propofol group ($p = 0.00$) (Figure 1). There were no significant differences in mean systolic blood pressure, diastolic pressure, PaO2/FiO2 ratio, PaCO2, pH, serum lactate and bispectral index score (BIS) between the two groups.

Morphine requirement (mg/kg/hour) during study drug infusion in dexmedetomidine group was significantly lower than in propofol group (Mean (CI): 74.48 (70.38, 78.59) versus 83.85 (79.61, 88.09) (Table 2). There was no significant different in extubation time after discontinuation of study drug infusion in the two groups. The cost involved in sedating an average 70 kg man in dexmedetomidine group was slightly higher compared to propofol group (RM 9.57 versus RM 8.94 per hour).

DISCUSSION

This study only involved post open heart surgical patients whom were being mechanically ventilated in the cardiothoracic ICU (CICU). This was mainly due to the homogeneity of this group of patients in terms of underlying diseases and type of anaesthesia and surgery. The result hence could only be extrapolated to this population of patients. It could not be generalized to the general ICU settings. Administrations of loading dose were omitted in both groups. Rapid infusion of loading dose of dexmedetomidine has been associated with a biphasic response, transient hypertension followed by severe hypotension[7,8]. Activation of peripheral α_2-adrenoreceptors in blood vessels mediates vascular smooth muscle contraction, transiently increasing vascular resistance. This is followed by activation of

postsynaptic receptors in the central nervous system, which then induces centrally mediated sympatholysis, lowering blood pressure[7]. Large bolus of propofol used as in induction of anaesthesia has also been associated with the occurrence of significant hypotension and bradycardia[9,10]. To avoid the occurrence of these responses, large rapid bolus of loading doses were omitted in both groups. Both study drugs were instituted in the operation theatre at the start of sternal closure. Average time from sternal closure to patients arrival in CICU were about 1 hour. This was sufficient for adequate plasma level and depth of sedation when patients reached CICU.

There were no statistically significant differences in mean age, weight, height and gender between dexmedetomidine and propofol groups. The ethnic group distribution showed that majority of patients were Malay, which contributed to 81.25% (26) of the total patients as compared to 18.75% (6) Chinese. This was due to the higher percentage of Malay population in the study area. However, there were no statistically significant differences in the ethnic distribution between the two groups. The use of intraoperative fentanyl and the duration of sedation were not significantly different between the two groups. Hence, these effects can be eliminated when analyzing the results of this study.

Patients sedated with dexmedetomidine had significantly lower heart rate compared to patients sedated with propofol [mean(CI): 74.48 (70.38,78.59) versus 83.85 (79.61,88.09)]. The significant difference between the two groups was similar to a study by Venn & Ground[11]. However Herr *et al.*[7] did not show any significant difference in heart rate between these two groups. Reduction in heart rate is expected from the known pharmacology of dexmedetomidine, an α_2 adrenoceptor agonist[12]. It may be due to two pathways: a vagomimetic effect and blockade of cardioaccelerator nerve[13]. Other studies in healthy volunteers and in ICU patients, also showed a significant reduction in heart rate when compared to placebo[14,15,16,17].

This reduction in heart rate can theoretically reduce myocardial oxygen demand, and hence subsequent ischaemia and infarction. This is of major importance in critically ill patients, especially during periods of stress e.g. endotracheal suctioning, physiotherapy, and mobilization. Stress is considered to be a major risk factor in myocardial ischaemia after surgery. Although no study has been conducted on dexmedetomidine on the incidence of ischemia, two other α_2 adrenoceptor agonists; mivazerol and clonidine have been shown to reduce ischaemia[18,19,20]. American College of Cardiology/American Heart Association (ACC/AHA) guideline has conferred the use of α_2-adrenoceptor agonist as a grade IIb recommendation in the 2002 guideline update on perioperative cardiovascular evaluation for non-cardiac surgery. Since the use of b-blocker had been proven to significantly reduce perioperative cardiac morbidity and mortality, a_2-agonists were recommended in patients whom b-blockers are contraindicated[21].

There were no significant differences in mean systolic blood pressure and diastolic blood pressure between dexmedetomidine and propofol, similar to a study by Venn & Ground[11]. Herr *et al.*[7] showed a slight decreased in mean blood pressure in dexmedetomidine patients compared to propofol patients. However this finding was not clinically important. Other studies that demonstrated the safety of dexmedetomidine have shown that there were no significant differences in blood pressure when compared to placebo groups[17,22].

Mean PF ratios (PaO_2/FiO_2 ratios) were not significantly different between dexmedetomidine and propofol groups. Similarly, Venn & Ground[11] did not show any significant difference in mean PaO_2/FiO_2 ratios between dexmedetomidine and

propofol. However, when compared to placebo, Venn *et al.*[23] showed a significantly higher mean PaO_2/FiO_2 ratio in dexmedetomidine group. Previous studies have shown that there were no clinically important adverse effects on ventilation[7,23,24]. This finding was similar as in this study. Mean $PaCO_2$ levels were not significantly different between the two groups. Dexmedetomidine has been shown to be safe when continued post extubation with no effect on ventilation[17]. Mean serum lactate and pH were also not significantly different between dexmedetomidine and propofol groups. These may be due to stable haemodynamic and respiratory parameters associated with the use of these two agents. Similarly, Venn & Grounds[11] did not show any difference in mean pH and base excess between the two groups.

Bispectral index score was used to maintain adequate sedation between the two groups. Triltisch *et al.*[22] used BIS as a guidance of sedation when comparing dexmedetomidine and placebo for sedation in the ICU. They found that BIS-guided sedation seems to be suitable during administration of dexmedetomidine, similar to other sedation regimes in surgical ICU settings. Mean BIS values between the two groups were not significantly different, indicating equivalent levels of sedation. Most other studies commonly used Ramsay sedation scale as an assessment of sedation. In this study, Ramsay sedation score was initially used in the sedation scale of these patients along with BIS. However there was a lot of interrater variability in scoring these patients. Furthermore, the use of Ramsay sedation scale necessitates the use of acoustic and tactile stimulation. These manipulations can cause undesired arousal and agitation leading to patients discomfort and a possible increase in sedative and analgesic drug requirements[22]. Due to these reasons, this parameter was excluded from the study and only bispectral index score was used. Previous studies have shown that there were good correlations between BIS and Ramsay sedation scale[25,26].

Patients sedated with dexmedetomidine needed lower dose of morphine compared to propofol [mean (sd): 12.80 (2.61) vs 15.86 (1.87) mg/kg/min]. This was consistent to the finding of previous studies on ICU patients, which demonstrated that dexmedetomidine reduced the use of concurrent analgesia[7,11,17,22]. Studies on healthy volunteers have also demonstrated its analgesic effect[27,28,29]. Mechanism of analgesia effect is postulated to be due to its binding to a_2-adrenoreceptors in the intermediolateral cell column and the substantia gelatinosa of the dorsal horn of the spinal cord[8]. Supraspinal and peripheral sites of analgesic action have also been reported[12]. This analgesic property of dexmedetomidine is one of its unique features. Ebert[3] described one of the properties of ideal sedative agent is to alleviate both pain and anxiety. Other commonly used sedative agents such as midazolam and propofol have no analgesic effect, necessitating the use of concurrent analgesia in postoperative patients. However, the potency of its analgesic effect was low compared to other analgesic drugs. Dexmedetomidine could not be use as a sole agent in major operation e.g. CABG. Concurrent use of other analgesic drugs is still needed, however to much less extent compared with the use of other sedative agents.

Times to extubation were not significantly different between dexmedetomidine and propofol groups. This may be due to rapid distribution half life ($t_{½}$ α) of both drugs, dexmedetomidine; 6 minutes and propofol; 1.8 to 4 minutes[8,30]. This finding was similar to previous studies[7,11]. Both propofol and dexmedetomidine did not exhibit accumulation effect even after prolonged infusion[31,32,33]. The elimination half life ($t_{½}$ b) of dexmedetomidine was longer compared to propofol (2 hours versus 21 to 69 minutes)[8,30]. However, dexmedetomidine has been shown to be safe when continued post extubation with no effect on ventilation[17]. This may not affect the decision for extubation in patients sedated with dexmedetomidine. Hence,

extubation times did not differ between the two groups despite longer elimination half life ($t_{½}$ b) of dexmedetomidine.

To calculate the cost involved in the use of these sedative agents, mean rate of infusion used to achieve adequate sedation was used. Cost involved in sedating an average 70 kg man was calculated in each group. Cost involved in the use of dexmedetomidine was slightly higher than propofol (RM 9.57 versus RM 8.94 per hour). On an average of 12 hours of sedation, the cost involved in dexmedetomidine was only RM 7.56 higher than propofol [(RM 9.57 – RM 8.94) x 12 hours]. However, the use of morphine was lower in dexmedetomidine group compared to propofol. Taken these factors into account, the cost involved in the use of dexmedetomidine was almost similar to propofol.

This study showed that dexmedetomidine was comparable to propofol in the provision of sedation in post open heart surgical patients with preserved left ventricular function and similar co-morbidities. However it has added advantage in the provision of analgesia, as shown by lower morphine requirement with the use of dexmedetomidine. Haemodynamic, respiratory and metabolic effects of both drugs were comparable. A significant property of dexmedetomidine shown in this study was reduction in heart rate. This is beneficial in these patients by reducing myocardial oxygen demand, and hence subsequent ischaemia and infarction. However, further large randomized trials are needed to evaluate the effect of this newest selective a_2-agonist, dexmedetomidine on perioperative cardiac morbidity and mortality.

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TABLES

Table 1: Demographic and Sedative Characteristics

Variables	Dexmedetomidine		Propofol		p value
	Mean	(SD)	Mean	(SD)	
Age (years)	52.44	12.90	55.38	12.26	0.51[a]
Weight (kg)	66.44	11.50	59.81	8.92	0.08[a]
Height (cm)	162.50	9.70	160.94	7.83	0.62[a]
Duration of sedation (hour)	12.47	4.10	11.88	3.65	0.67[a]
Intraoperative fentanyl (mg)	903.10	157.55	862.50	173.69	0.49[a]
	Frequency	(%)	Frequency	(%)	
Gender Male Female	 9 7	 56.3% 43.7%	 11 5	 68.8% 31.3%	0.45[b]
Race Malay Chinese	12 4	75.0% 25.0%	14 2	87.5% 12.5%	0.37[b]

Note: All variables were approximately normally distributed.

[a] Independent T test

[b] Pearson Chi-Square test

Table 2: Morphine requirement (µg/kg/hour)

Variable	Morphine		p value
(mg/kg/hour)	Mean	(SD)	
Propofol	15.86	1.87	0.00[a]
Dexmedetomidine	12.80	2.61	

Note: Variable was approximately normally distributed

[a] Independent T test

FIGURE

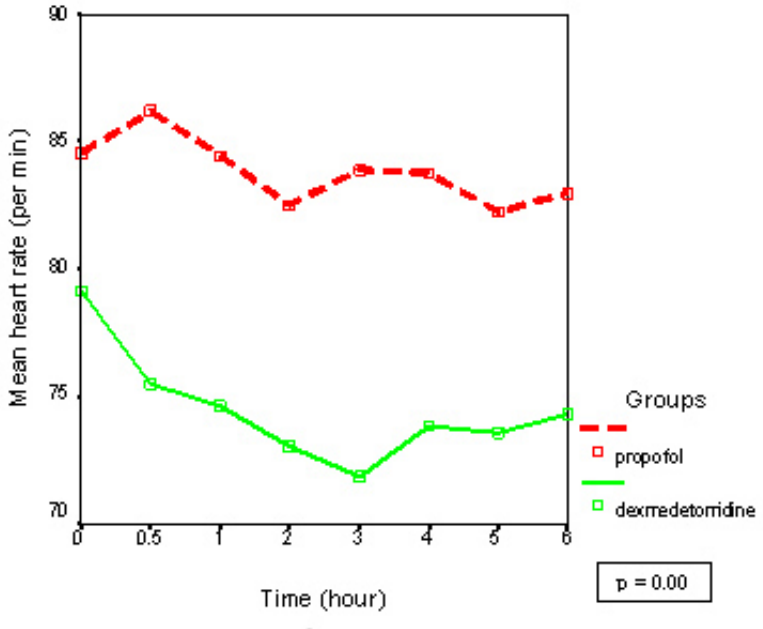

Figure 1: Mean heart rate

Posting Mail Address:
Department of Anaesthesiology and Intensive Care,
Kuliyyah of Medicine,
Jalan Hospital Campus,

25100 Kuantan, Pahang Darul Makmur.
Telephone Number: 019-9120803
Email Address: drazrina@gmail.com