THE USE OF DEXMEDETOMIDINE FOR POSTOPERATIVE SEDATION IN CARDIAC ICU

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ABSTRACT

Objective: This study was designed to evaluate the efficacy of dexmedetomidine as a sedative agent in cardiac surgical ICU and its benefits in regard to opioid requirements, nausea and vomiting, time of mechanical ventilation, length of ICU stay and hospital stay. **Method:**105 patients undergoing coronary artery bypass grafting or valve surgery were enrolled in this study, between June 2009 and December 2010.

Patients were divided in to two groups; group 1, control group (56 patients), received a normal saline infusion during surgery and post operative period and group2,dexmedetomidine group(49 patients), received an initial dose of 0.1 microg/kg for 10 min, followed by maintenance dose of 0.4 to 0.7 microg/kg/h of dexmedetomidine hydrochloride. All patients were observed in the ICU for pain and sedation scores, analgesic requirements, intubating time, agitation, nausea /vomiting, and length of stay.

Results: Both groups were similar for patient demographics, ASA physical status, surgical procedure, and intraoperative use of drugs and fluids.

Total morphine requirements were much less in Dex group (10.28mg/patient) than control group (53.65mg/patient) to achieve the same level of analgesia.

The Dex. group had more favorable average sedation score on the Ramsay Sedation Scale in comparison with the control group (2.51 out of 6 vs. 2.32 out of 6) with a statistically significant result (p-value=0.002). The Dex. Group achieved less pain score (3.18 out of 10 for the Dex group vs. 3.71 out of 10 for the control group).The reduction in average pain in patients receiving dexmedetomidine infusion was statistically significant (p-value=0.024).The Dex. Group had earlier tracheal extubation. The average time of mechanical ventilation in the Dex group was 7.9 hours ±2.06 hours (mean ± S.D.), compared to 13.54 hours ± 5.58 hours (mean± S.D.) in the control group (p-value <0.0001). The mean length of ICU stay in the Dex. Cohort was 21.67 hours ± 4 hours (mean ± S.D.), while it was 31.52 hours ± 20.28 hours (mean ± S.D.) in the control group. The difference between the two treatment groups in mean length of ICU stay was statistically highly significant (p=0.001). Lower incidence of nausea and vomiting was observed in the Dex. Cohort of patients (14.2 % vs. 26.7% in the control group), but the reduction in nausea and vomiting was statistically not significant (p-value=0.116).

Conclusion: Dexmedetomidine hydrochloride is effective and promising agent for sedation in cardiac ICU as it reduces the opioid requirements, shortens time of mechanical ventilation, decreases length of ICU stay and hospital stay. It decreases use of sedatives and narcotics, thereby further improving respiratory safety and decreasing postoperative nausea and vomiting.

Key words: Dexmedetomidine, sedation, analgesia, mechanical ventilation, cardiac surgery

INTRODUCTION

Postsurgical patient care in the intensive care unit should minimize stress and sympathetic nervous system responses, relieve pain and facilitate diagnostic and therapeutic procedures, and permit communication with patients without interrupting sedation-all without compromising hemodynamic or respiratory stability or prolonging time in the ICU[(1)].

Dexmedetomidine, an imidazole compound, is the pharmacologically active dextroisomer of medetomidine that displays specific and selective alpha 2-adrenoreceptor agonism.

Dexmedetomidine hydrochloride is a new sedative agent, which was approved

by the FDA in December 1999 for use in humans as a short term medication (<24 hours) for analgesia and sedation in the intensive care unit (ICU). It is a potent alpha2-adrenoceptor agonist with 8 times higher affinity for the alpha 2-adrenoceptor than clonidine.

The site of action for the sedative action of this drug is considered to be in the locus coeruleus [2].

Dexmedetomidine has shown sedative, analgesic, anxiolytic and sympatholytic effects after intravenous administration for post surgical patients in the intensive care unit. These properties can potentially be beneficial in myocardial protection, lowing narcotic usage, facilitating earlier extubation and reducing postoperative delirium after heart surgery [3]. Because dexmedetomidine use can provide sedation without respiratory depression, it can be used to assist weaning from mechanical ventilation even in patients who failed previous extubation trials [4].

In producing a state of "cooperative sedation", dexmedetomidine allows the patient to interact with healthcare providers

Dexmedetomidine 0.2to 0.7 microg/kg/h produced clinically effective sedation and significantly reduced the analgesic requirements of post surgical ventilated intensive care unit patients. There was no clinically apparent respiratory depression after cessation of assisted ventilation, in addition to maintaining a high degree of patient arousablity and anxiety reduction.

Dexmedetomidine exhibits a linear relationship between dose and plasma concentration; therefore increasing the dose should result in proportional increases in effects. The relatively short distribution half-life (t ½) of about 6 minutes results in rapid onset, and an elimination t ½ of approximately 2 hours facilitates clearance of the drug in a matter of hours. Dexmedetomidine is markedly protein bound (94%) to serum albumin and [alpha] 1-glycoprotein. It is extensively metabolized through oxidative metabolism via cytochrome P450 and direct glucoronidation in the liver, with its metabolites excreted by the kidneys [5].

Side effects include mild to moderate cardiovascular depression, with slight decrease in blood pressure and heart rate [6].

Since its release in the Royal Medical Services hospitals in Jordan in 2007, it is widely used in general and cardiac ICU as a sedative agent, but still there was no enough data about its use.

METHODS

105 patients undergoing coronary artery bypass grafting or valve surgery with cardiopulmonary bypass CPB were enrolled in this double blind study. Patients were similar in demography, ASA status (I –II), and intraoperative use of drugs and fluids.

All patients had a standard anesthetic technique; fentanyl + midazolam + propofol or etomidate for induction, high dose fentanyl + propofol + isoflurane for maintenance of anesthesia and pancuronium for muscle relaxation.

Patients were informed about the study and their consent obtained.

The total number of patients was originally 112 patients; seven patients were excluded at a later stage because they had serious surgical morbidity and/or mortality.

Then, patients were divided in to two groups; group1 or control group (56 patients), where patients received a normal saline infusion 30 min before the end of operation and thereafter, group 2 or DEX group (49 patients), where

patients received dexmedetomidine 0.1 microg/kg for 10 min followed by infusion of 0.4-0.7 microg/kg/h of DEX 30 min before the end of operation and continued in the ICU.

We applied Ramsay scale (table1) for sedation level of the patients.

Visual analogue scale(VAS),verbal rating scale(VRS) or numeric rating scale(NRS) were used to asses intensity of pain postoperatively.(figure1.)

We considered Ramsay scale of 3, and VAS /VRS/NRS of 3 as a fairly good sedation and analgesia to compare the two groups at these scores.

Patients were closely followed up in the ICU for level of sedation and analgesia, morphine consumption, agitation, nausea & vomiting, intubating time and total length of stay. A special form designed for the purpose of this study was used to collect data from every patient. Patient's pain and sedation scores were assessed hourly and an average score was calculated until patient was discharged from ICU.

Independent t-test was used to study the effect of dexmedetomidine on time of mechanical ventilation and time of stay in ICU. Chi-Square test was used to study the effect of dexmedetomidine on average pain and sedation. P-values less than 0.05 were considered significant.

RESULTS

Although the Dex. Group had less morphine required during their ICU stay than the control group (10.28 mg/21.67 hours vs. 53.65 mg/31.52 hours); average pain score was less in the Dex. Group than the control group (3.18 out of 10 vs. 3.71 out of 10). This reduction in average pain was found to be statistically significant (p-value=0.024). The Dex group had more favorable average sedation than the control group (2.51 vs. 2.32) and the p-value was found to be significant (p-value=0.021) Incidence of agitation (score 1 on Ramsay Sedation Scale) was found to be 14.28% (8 out 56 patients) in the control group, while the incidence of agitation was found in 4.08% (2 out of 49 patients) in the Dex. Group.

Boluses of midazolam (as rescue sedation) were needed in 48.21% of patients from the control group (27 out of 56 patients) in comparison to 12.24% of patients from the Dex. Group (6 out of 49 patients).The difference between the two groups in the frequency of usage of midazolam boluses was statistically significant (p-value=0.005). Morphine boluses (rescue analgesia) were needed in 51.78% of patients from the control group (29 out of 56 patients) vs. 44.89% (22 out of 49 patients) in the Dex. Group, but the average dose needed was less in the Dex. Group (0.47 mg/hour vs. 1.7 mg/hour in the control group). The difference between the two groups in the frequency of use of morphine boluses was statistically not significant (p-value=0.137).

There was no significant difference in morphine consumption during the first hour postoperatively in both groups (4.7mg in control group and 4.5mg in Dex group), while after the first hour, the differences between the two groups in morphine requirements to achieve the same pain and sedation score were obvious(table 2).

The average time of mechanical ventilation in the Dex group was 7.9 hours, compared to 13.54 hours in the control group (p-value =0.0001). The mean length of ICU stays in the Dex. Cohort was 21.67 hours ± 4 hours (mean ± S.D.), while it was 31.52 hours ± 20.28 hours (mean ± S.D.) in the control group. The difference between the two treatment groups in mean length of ICU

stay was statistically highly significant (p=0.001). The average total length of hospital stay was 2.2 days less in the Dex. group (8.4 days in the control group vs. 6.2 days in the Dex. group).

The incidence of nausea and vomiting was observed in 26.7% (15 out of 56 patients) in the control group, while it was found in 14.2% (7 out of 49 patients). The reduction in the incidence of nausea and vomiting observed in the Dex. Group was found to be statistically not significant (p-value=0.116).

Tables and Figures:

Table 1. Ramsay Sedation Scale

Score	Observation
1	Anxious, agitated, or restless
2	Cooperative, oriented, and tranquil
3	Responsive to commands
4	Asleep, but with brisk response to light glabellar tap or loud auditory stimulus
5	Asleep, sluggish response to glabellar tap or auditory stimulus
6	Asleep, no response

Table 1:

Figure 1:

Visual Analogue Scale

No pain----------worse pain possible

Numeric Rating Scale

0 1 2 3 4 5 6 7 8 9 10

Table 2:

	Control group (n=56)	Dex group (n=49)	P-value
Morphine requirements(mg)	53.65	10.28	
Usage of morphine boluses	51.78%	44.89%	0.137
Usage of midazolam boluses	48.21%	12.24%	0.005
Incidence of agitation	14.28%	4.08%	
Incidence of nausea and vomiting	26.7%	14.2 %	0.116
Intubating time (h)	13.54	7.9	0.0001
Average ICU stay(h)	31.52	21.67	0.0001
Average hospital stay(days)	8.4	6.2	

DISCUSSION

This study shows that patients receiving dexmedetomidine required less morphine (less than one fifth of the control group dose) and achieved less pain score (3.18 out of 10 for the Dex group vs. 3.71 out of 10 for the control group).The reduction in average pain in patients receiving dexmedetomidine infusion was statistically significant (p value=0.024). While in the first hour after arrival in postcardiosurgical ICU there was no significant difference in morphine consumption (4.7 mg in the control group vs. 4.5 mg in the Dex. group), analgesic requirements increased every subsequent hour. The frequency of use of morphine boluses was 51.78% in the control group (29 out of 56 patients) in comparison to 44.89% in the Dex. Group (22 out of 49 patients). The reduction in use of morphine boluses as rescue analgesia in the Dex. Group was statistically not significant (p-value=0.137). Agonism at alpha2-adrenoreceptors in the spinal cord and in the locus ceruleus produces analgesia and sedation respectively. In the presence of these effects, it is difficult to distinguish whether analgesic or sedative effects are responsible for the reduced morphine requirements [7]. Nakagawa et al suggested that alpha 2-adrenergic mechanisms are involved in the modulation of nociception at the level of spinal noradrenergic systems [8]. The opioids sparing effects by dexmedetomidine are demonstrated by several studies [9,10] and might come from the synergistic analgesic interactions with opioids, attenuation of the affective-motivational component of pain and reduction of stress [11,12].

The Dex. group had more favorable average sedation score on the Ramsay Sedation Scale in comparison with the control group (2.51 out of 6 vs. 2.32 out of 6) with a highly significant p value (p-

value=0.002). Although the average sedation score achieved in the control group was acceptable (2.32 /6 on the Ramsay Sedation Scale), there was an incidence of agitation (score 1 at Ramsay Sedation Scale) of 14.28% (8 out 56 patients) among that group, and the need for rescue midazolam and morphine boluses was also higher in the control group. Agitation and delirium in the ICU patient, while triggering a cascade of increased requirements for relief, are associated with prolonged hospitalizations [13]. Inadequate treatment of agitation initiates physiological stress response resulting in tachycardia, hypertension and hyperglycemia, all of which contribute to increased morbidity and mortality in critically ill patients.

Boluses of midazolam as rescue sedation were needed in 48.21% of patients from the control group (in 27 out of 56 patients) in comparison to 12.24% of patients from the Dex. Group (in 6 out of 49 patients). The reduction in usage of midazolam boluses as rescue sedation in the Dex. Group was statistically significant (p-value=0.005).

The Dex. Group had earlier tracheal extubation. The average time of mechanical ventilation in the Dex group was 7.9 hours ±2.06 hours (mean ± S.D.), compared to 13.54 hours ± 5.58 hours (mean± S.D.) in the control group (p-value <0.0001). Dexmedetomidine infusion continued over the extubation period. The earlier tracheal extubation in the dexmedetomidine cohort is probably due to minimal respiratory depression, reduced use of opioids and benzodiazepines.

Sedation continued over the extubation period, has been shown to reduce haemodynamic disturbances and myocardial ischemia [14].

The mean lengths of ICU stay in the Dex. cohort was 10 hours shorter than the control group (21.67 hours in the Dex. group vs. 31.52 hours in the control group). The difference between the two treatment groups in mean length of ICU stay was statistically significant (p=0.0001). Although dexmedetomidine is more expensive than traditional sedative agents, it may still be potentially cost-effective if it can reduce length of ICU stay [15].

Also the average total length of hospital stay was 2.2 days less in the Dex. group (8.4 days in the control group vs. 6.2 days in the Dex. group).

Lower incidence of nausea and vomiting was observed in the Dex. group of patients (14.2 % vs. 26.7% in the control group), but the reduction in nausea and vomiting was statistically not significant (p-value=0.116).

Nausea has been described in patients receiving dexmedetomidine [16]. This effect is overshadowed by the reduction in opioids-related nausea and vomiting, due to lowered analgesic requirements [17].

The addition of dexmedetomidine to morphine resulted in superior analgesia, significant morphine sparing and less morphine-induced nausea.

Hypotension was observed in 10.2% of patients from the Dex. Group (5 patients out of 49%), and was managed with decreasing the dose of Dexmedetomidine infusion and by administration of crystalloid intravenous fluids. Bradycardia was observed in 2% of patients from the Dex. Group (two patients out of 49) and resolved after decreasing the dose of infusion of the drug.

CONCLUSION

The use of Dexmedetomidine in cardiac surgical ICU was associated with

efficient sedation and analgesia, reduction in opioid and sedative requirements, decrease in intubating time, decrease in ICU stay and hospital stay. Its use was also associated with a reduction in incidence of nausea and vomiting, due to a reduction of opioids use. Most common side effects of Dexmedetomidine were mild hypotension and bradycardia.

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