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# EFFECTS OF DEXMEDOTOMIDINE IN THE CORONARY ARTERY BYPASS GRAFT (CABG) PATIENT: A PILOT STUDY

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**Key words:** Dexmedetomidine, coronary artery bypass , propofol, intubation, pain

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It will be hard to catch me at the office number as I am usually in the O.R. E-mail is probably best. Thank you.

## EFFECTS OF DEXMEDETOMIDINE(DEX) IN THE CORONARY ARTERY BYPASS GRAFT (CABG) PATIENT: A PILOT STUDY

**Introduction:** Postoperatively, CABG patients remain intubated requiring sedation and pain management. Propofol is a commonly used sedative but requires concomitant analgesic use. Dexmedetomidine (DEX) is an alpha-2 agonist providing both sedative and analgesic properties. The purpose of this study was to compare Propofol to DEX infusions to determine differences in amount of post-op pain medication used, intubation time, and Cardiothoracic Unit (CTU) time.

**Methods:** Data was collected via an IRB approved retrospective chart analysis on 100 consecutive CABG patients presenting to the study institution.

**Results:** Of the 90 charts meeting inclusion criteria, n=32 received DEX and n=58 Propofol. Data analysis by t-test for independent groups showed that the DEX group had significantly shorter total intubation (362 minutes [SD±236] vs. 493 [SD±374], p=.044). Though the DEX group used less pain medication post-op, (14.5mg morphine equivalents [SD±11.5] vs. 17.5mg [SD±11.9]) and had shorter mean total CTU time (1442 [minutes SD±471]) vs. 1621 [SD±555]), differences were not statistically significant ( $p > .05$ ).

**Conclusion:** DEX has potential to benefit the CABG population. In this sample, use of DEX appeared to be related to shorter total intubation time. DEX use may also be related to decreased total CTU time and pain medication usage. Prospective randomized studies are needed.

## Introduction

In the adult cardiac surgical population, there are many advantages to early extubation. Decreased length of stay in the cardiothoracic unit, less need for pain medication, decreased cardiac and respiratory morbidity, increased cardiac performance, and lower rates of nosocomial pneumonia are all potential benefits of an early extubation program.<sup>1</sup> Literature documents that patients receiving DEX-based sedation protocols compared to propofol sedation protocols in the intensive care unit (ICU) post-op require less narcotics and are extubated much earlier.<sup>2</sup> Herr, et al (2003) conducted a study investigating a group of 295 adults at 25 different medical centers undergoing coronary artery bypass graft (CABG) operations and compared the DEX-based sedation to propofol based sedation in the ICU post-op. Two of the most significant findings were that the DEX-sedated group required significantly less morphine and were extubated much earlier.<sup>2</sup> Our study differed from this landmark study in several ways. Parsonnet scores in our study were identified and included in data collection to eliminate patients with multiple comorbidities. The Parsonnet score is a method of uniform stratification of risk for evaluating the results of surgery in acquired adult heart disease. It has been identified as the best available predictor of coronary artery surgery mortality.<sup>3</sup> Exclusion and inclusion factors utilized for our study were different. Herr, et al (2003) enrolled adult patients scheduled for a CABG and exclusion factors included: women pregnant or lactating, patients with neurological conditions, unstable or uncontrolled diabetes, gross obesity, ejection fraction of < 30%, drug overdose, and any other condition or factor that the investigator felt might increase risk to the patient or interfere with obtaining study data. In our study, exclusion factors included: intubated > 48 hours post CABG, length of stay > 48 hours in the cardiothoracic unit, ASA score > 3, propofol infusion > 50 mcg/kg/minute, DEX infusion > 0.7mcg/kg/hour, age < 50 or > 70 years old, and

Parsonnet score > 44. The Parsonnet score was utilized to reduce subjective investigator opinion in eliminating patients with co-morbidities. Also, in the larger study, subjects were evaluated from 25 different locations involving 26 different investigators, whereas our study identified a patient population in one medical center with only three evaluators.

Other studies have been conducted investigating the use of DEX and found that it decreased pain and the need for narcotic administration in several different surgical populations, but very few studies were identified focusing on the CABG population which is a group whom traditionally receives a high narcotic regimen.<sup>4,5,6,7</sup>

DEX is a relatively new  $\alpha_2$ -adrenergic agent that was approved in 1999 by the Food and Drug Administration as an ICU sedative. DEX provides both sedation and analgesia, decreasing the necessity of using concomitant pain medications both intra-op and post-op. The sedative effects result from  $\alpha_2$  stimulation in the central nervous system, specifically the locus coeruleus. DEX also provides analgesia and amnesia which produces a patient effectively sedated yet easily awakened while calm and comfortable in a sleep-like state.<sup>2</sup> Research conducted on the  $\alpha_2$  prototype, clonidine, has been shown to have beneficial effects as an anesthetic adjuvant, provide intra-op hemodynamic stability, and reduce the requirements of narcotic analgesics and volatile anesthetics.<sup>5</sup> Clonidine has an affinity for  $\alpha_2$ -adrenoreceptors over  $\alpha_1$ -adrenoreceptors 220:1. DEX also has an affinity for  $\alpha_2$ -adrenoreceptors over  $\alpha_1$ -adrenoreceptors 1620:1. This makes DEX eight times more selective and potent than Clonidine without the unwanted cardiovascular effects that are produced by  $\alpha_1$  receptor activation. The half-life of DEX is also only 2-3 hours compared to clonidine's half-life of 6-10 hours. DEX is a pre and post synaptic  $\alpha_2$  adrenergic activator which inhibits the release of norepinephrine (NE) and also decreases brain noradrenergic activity producing sedation. DEX

inhibits sympathetic activity decreasing blood pressure and heart rate which provides hemodynamic stability. Alpha<sub>2</sub> agonists also exhibit analgesic properties considered to work at multiple sites but primarily by inhibiting the release of excitatory neurotransmitters from afferent nerves conveying nociceptive signals in the spinal cord.<sup>8</sup> The analgesic effects of DEX appear to be mediated via both spinal and supraspinal mechanisms, although peripheral antinociception via release of an enkephalin-like substance has also been postulated. A close relationship between opioids mu and alpha<sub>2</sub> adrenergic actions in the modulation of pain pathways has also recently been suggested.<sup>9</sup>

Propofol is an intravenous (IV) sedative-hypnotic agent introduced commercially in 1989. It is indicated for general anesthesia in the adult population as well as maintenance of general anesthesia and ICU sedation for intubated, mechanically ventilated adults. Propofol is a commonly used agent in cardiothoracic units, but it provides no analgesic activity. Post-op CABG patients receiving propofol require supplemental narcotic administration for pain relief. As shown in a study by Herr and Sum-Ping, propofol patients require four times the amount of morphine in the ICU compared to patients who received DEX.<sup>10</sup> By showing that DEX provides analgesia to these patients, there may be less need for other pain medications, such as morphine.

The purpose of our study was to compare propofol to DEX infusions to determine if there would be differences in: 1) the amount of post-op pain medication administered; 2) length of time to extubation in the cardiothoracic unit; 3) length of time to discharge from the cardiothoracic unit; 4) patients subjective perception of pain. Hypotheses formulated were: 1) the use of DEX in this patient population would reduce the amount of opioids utilized post-op to manage pain; 2) extubation times in CABG patients would decrease with the utilization of DEX; 3) CABG patients who receive DEX would have a shorter stay in the cardiothoracic unit

compared to those who received propofol for sedation; and 4) Patients receiving Dex would have lower pain perception.

### **Materials and Methods**

This study involved an institutional review board-approved, retrospective review of 100 charts for patients that underwent a CABG procedure at the study institution. The subjects reviewed were to be sorted into two groups: either DEX or propofol. Inclusion criteria were: CABG operation, age 50-70 years old, and Parsonnet score < 44. Exclusion criteria were: intubated > 48 hours post CABG, length of stay > 48 hours in a cardiothoracic unit, ASA score > 3, propofol infusion > 50 mcg/kg/minute, and DEX infusion > 0.7mcg/kg/hour. A Parsonnet value of < 44 was utilized because it indicates a predicted risk of < 33% mortality. Patients intubated > 48 hours, in the CTU > 48 hours, or assigned an ASA score > 3, were eliminated because these confounding factors would indicate higher risk of morbidity and mortality and multiple disease processes. Patients with propofol drips > 50 mcq/kg/min or DEX > 0.7 mcg/kg/hr were eliminated because these values are greater than the range indicated for sedation.

After IRB approval, data was pulled and collected in monthly units in order to avoid the necessity of coding and to protect confidentiality. One hundred consecutive charts were reviewed for patients admitted between April 2003 and December 2004. Specific demographic data collected included: ASA score, age, weight in kilograms (kg), ethnicity, gender, and parsonnet score. Independent and dependent variables collected included: intubation time in the cardiothoracic unit, length of stay in the cardiothoracic unit, DEX or propofol utilization, the rate of infusion of DEX or propofol, the duration of infusion of DEX or propofol, total morphine equivalents administered, and the assessment of post-op pain.

The measurement of the variables involved in this research study were evaluated based on

time and the standard numeric rating scale. Intubation time was measured in minutes. The measurement tool for intubation time was based on the minutes manifested from admission to the CTU immediately post-op until extubation subsequent to physicians' orders. Length of stay in the CTU was measured as minutes from admission to the CTU until transfer to another ward per physicians' orders. Pain was measured by the numeric rating scale (NRS). The NRS utilizes a numeric range (typically 0 to 10 or 0 to 100) to quantify pain intensity that can be administered in oral or written form, and is the most common and efficiently used method of assessing pain levels according to the Veterans Health Administration.<sup>11</sup> The NRS has been found to be valid and reliable, and to be sensitive to changes in acute, cancer, and chronic pain. Studies by Paice & Cohen<sup>12</sup> and Holdgate et al<sup>13</sup> support the usage of this tool to measure the assessment of acute, cancer, or chronic nonmalignant pain and in varied clinical settings. It has been well established that this type of measurement tool belongs to public domain. This measurement tool for pain has been utilized by many health care professionals and has documented reliability and validity.

Post-op pain medication administered consisted of morphine IV q 1 hour PRN and/or tylox 1-2 tablets oral q 4-6 hours PRN once extubated. The Tylox dose was converted to a morphine equivalent dose in order to have one unit of measurement to compare the analgesic requirements of each group. Tylox is a medication consisting of 5 milligrams (mg) oxycodone and 500 mg acetaminophen per tablet. The multiplication factor for converting the dose of oral oxycodone to a dose of morphine in mg was determined in accordance with the Physician Desk Reference.<sup>9</sup> Oral oxycodone can be converted to an equivalent parenteral dose of morphine by using a division factor of 3. For example, a dose of 6 mg of oral oxycodone is equivalent to 2 mg of morphine IV push.<sup>14</sup> An average of morphine equivalents in mg/hour used postoperatively was obtained for each patient, as well as total mg. Pain perception and treatment was recorded from



each chart for the entire length of stay in the cardiothoracic unit. All statistical procedures for the study were conducted using SPSS version 12.01 (SPSS, Chicago, Ill). Data were analyzed using independent t-tests for continuous data and Chi-Square test of Independence for nominal data. Differences were considered statistically significant at a p value of 0.05 or less.

## Results

One hundred charts were reviewed. Ten charts were eliminated: 2 for receiving both medications, 5 for receiving neither of the medications, and 3 because they exceeded the age criteria, leaving 90 charts for analysis.

The DEX group (n=32) included patients who received DEX infusions  $\leq 0.7$  mcq/kg/hr and the propofol group (n=58) included patients who received propofol infusions  $\leq 50$  mg/kg/min. There were no significant differences between the groups regarding age or Parsonnet scores. The weight in kg for the DEX group was significantly less than the propofol group (85 [SD  $\pm$  15]) vs. (91 [SD  $\pm$  14]),  $p = 0.04$ . (Table 1).

The total intubation time in minutes for the DEX group was significantly less than the propofol group. The mean times in minutes were 362 (SD  $\pm$  236) for the DEX group 493 (SD  $\pm$  374) for the propofol group ( $p = .04$ ).

Although the differences were not significant, the DEX group had shorter lengths of stay in the cardiothoracic unit than the propofol group (1442 [SD  $\pm$  471]) vs.(1621 [SD  $\pm$  555]),  $p = .12$ , power = 0.34, as well as less total mg of morphine equivalents in the DEX group (14.5mg [SD  $\pm$  11.5] ) vs. (17.5mg [SD  $\pm$  11.9]),  $p = .25$ , power = 0.21. (Table 1).

We were unable to make any analysis for pain scores among the DEX and propofol groups. In the review, the evaluators found that pain scores had not been recorded consistently in the charts and were, therefore not able to be utilized for comparison. It was understood by the

evaluators that pain perception was to be recorded every hour as well as any intervention provided and then a follow up pain rating one hour after the intervention. In reviewing the charts, it was found that this information was omitted > 50% of the time. The lack of consistency in reporting of this variable made it impossible for us to evaluate the perception of pain or the subjects' response to the opioids administered.

### **Discussion**

In this study, the authors showed significantly shorter intubation minutes in the DEX group compared to the propofol group. This suggests that using the drug DEX in this patient population for post-op sedation allows for earlier extubation which may decrease cardiac and respiratory morbidity, increase cardiac performance, and lead to lower rates of nosocomial pneumonia.<sup>1</sup> Herr, et al (2003) found that DEX-sedated groups required significantly less morphine and were extubated much earlier in a large study at multiple institutions.<sup>2</sup> Our findings were obtained on a particular patient population in one medical center. The findings support the evidence that DEX can provide analgesia while preventing respiratory depression.

In the surgical population of post-op CABG patients, the traditional regimen is to provide pain relief and hemodynamic stability that frequently requires infusions of propofol for sedation with narcotic supplementation for analgesia. This combination results in respiratory depression and mechanical ventilation that must be continued until the patient is stable enough to be weaned off the propofol infusion. The downside to this regimen is possible prolonged intubation time with mechanical ventilation. This can lead to pneumonia, ventilator dependence, respiratory morbidity, and decreased cardiac performance. With the use of DEX instead of propofol, patients are able to be extubated earlier which may prevent these side effects.

The authors were unable to show a significant decrease in the amount of morphine

administered or in the length of stay in a CTU. This suggests that infusions of DEX in the post-op CABG population did not decrease the amount of narcotics administered or the length of stay in a CTU. However, this may be due a lack of power within the study. Prior to data collection, power analysis was conducted with beta (power) set at 0.8, alpha (significance) at 0.05, and an effect size to detect a difference of 0.566 standard deviations between groups. A sample size of 100 patients (50 patients per group) was found to be required to detect a significant difference between the two groups. Operating on rule of thumb, it was also known that if we were unable to obtain 50 subjects for each group, the number of each group could be increased up to a 3:1 ratio to increase power. Once we determined that we were only able to obtain 32 records for the DEX group, we increased the control group (propofol) to 58, staying within the 3:1 ratio. Despite attempting to control for this limitation, the two differences were found not statistically significant due to low power. However, this study shows that the DEX group of patients had a shorter length of stay in the CTU than the propofol group and that less total mg of morphine equivalents were required in the DEX group.

There is evidence that DEX offers sedation and pain relief reducing the need for subsequent narcotic administration. Studies have shown that the addition of DEX to a post-op pain relief regimen has decreased the amount of morphine administered, as well as fentanyl.<sup>4,15,16</sup> Studies have also shown that the amount of hemodynamic variability has been decreased with the use of DEX infusions which is particularly desirable in the recovering post-op CABG patient.<sup>6</sup>

The authors' hypothesis was framed by prior studies that have shown DEX reduces the requirement of morphine by more than 50%, DEX has shown a clear analgesic effect on ischemic pain, large doses of DEX caused very effective long-lasting antinocioception, and the amount of hemodynamic variability was decreased with a peri-operative infusion of DEX in

CABG patients as well as catecholamine levels.<sup>4,5,17,7</sup> In the current study design, the group of DEX patients were extubated significantly earlier than the propofol group and differences were found in the length of stay in the CTU and the amount of morphine equivalents administered.

The most beneficial effect of substituting DEX for propofol is the avoidance of respiratory depression. This is particularly valuable for the post-op CABG populations who often have underlying chronic lung disease as well as cardiac disease. Ventilary reserve is also impaired by the surgical incision and reliance on mechanical ventilation immediately post-op. After anesthesia, DEX has been shown to provide sedation and analgesia without respiratory depression.<sup>18</sup> In a retrospective study on post-op surgical patients requiring intensive care, Venn et al (2000) established that the DEX group had significantly higher PaO<sub>2</sub> levels, there were no adverse respiratory events in either group, and cardiovascular stability was demonstrated with significant reductions in rate-pressure product during sedation and over the extubation period. They also showed that DEX reduces the hemodynamic response to intubation and extubation as well as attenuating the stress response to surgery, and sedation can occur with DEX over the extubation period without concerns of respiratory depression. This benefit appeared to be confirmed by the current study which showed that patients receiving DEX infusions were able to be extubated earlier without any evidence of respiratory or cardiovascular events.

There is evidence that DEX sedated patients require significantly less morphine. A difference in the amount of morphine equivalents was observed between the DEX group and the propofol group. This difference was not found to be significant and further studies will be required to show whether DEX truly decreases the amount of morphine needed in this patient population.

Although there was limited research found on CABG patients receiving DEX, there is also evidence to support the fact that patients may spend less time in a CTU. Although not

statistically significant, the DEX group in this study was found to have shorter length of stay in a CTU. Again, further studies are required to determine if DEX significantly reduces length of stay in a CTU.

There are limitations to this study. With a retrospective design, we were unable to control for provider preference. Many subjects were eliminated due to strict inclusion/exclusion factors limiting our sample size. Titration of the propofol and DEX infusions was unable to be controlled, and pain scores were not documented consistently in the patient charts.

In conclusion, this study has shown that CABG patients post-op receiving DEX have shorter total intubation times. Although not significant, satisfactory analgesia may also be achieved by utilizing DEX infusions reducing the requirement for narcotic administration as well as the length of stay in a CTU. A possible beneficial effect of infusions of DEX on post-op CABG patients necessitates further prospective, double-blind studies.

The opinions and assertions contained herein are the private views of the author(s) and are not to be construed as the official policy or position of the U.S. Government, the Department of Defense, or the Department of the Air Force.

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Table 1.

VARIABLE	<u>GROUP</u>		p
	Propofol (N=58)	DEX (N=32)	
	Mean (SD)	Mean (SD)	
Age (years)	59.4 (5.1)	61.5 (5.0)	.06
Weight (kg)	91.4 (14.3)	84.8 (15.2)	.04
Parsonnet Score	8.0 (5.7)	10.0 (8.0)	.17
Total mg Morphine	17.5 (11.9)	14.5 (11.5)	.25
Total time intubated	493 (374)	362 (236)	.04
Total time in cardiothoracic unit	1621 (555)	1442 (471)	.12