Fast-Track Management in Off-Pump Coronary Artery Bypass Grafting: Dexmedetomidine Provides Rapid Extubation and Effective Pain Modulation

Alicja Zientara1 Sergio Mariotti2 Sonja Matter-Ensner2 Burkhardt Seifert3 Kirk Graves1 Omer Dzemali1 Michele Genoni1

1 Department of Cardiac Surgery, Stadtspital Triemli, Zürich, Switzerland
2 Department of Anesthesiology and Intensive Care, Stadtspital Triemli, Zurich, ZH, Switzerland
3 Department of Epidemiology, Biostatistics and Prevention, University of Zurich, Zurich, Switzerland

Address for correspondence Alicja Zientara, Department of Cardiac Surgery, Stadtspital Triemli, Birmensdorferstrasse 497, Zürich 8063, Switzerland (e-mail: alicja_zientara@web.de).

Abstract

Background  Dexmedetomidine (DEX) is a highly selective α-2 agonist with many desirable effects including analgesia, improvement of hemodynamic stability, and potential myocardial and renal protection. The aim of this study was to investigate the effect of DEX on patients undergoing off-pump coronary artery bypass (OPCAB) grafting with regard to less pain medication, earlier extubation, faster transfer to normal ward, and cardiac protection.

Patients and Methods  From January 2012 to March 2015, 464 patients receiving OPCAB were included for retrospective analysis. After propensity matching (1:1), two groups (DEX vs. propofol, n = 129) could be compared. Continuous and categorical variables were reported as mean ± standard deviation or percentages, and compared with the chi-square test and the Mann–Whitney’s test, respectively.

Results  In the DEX group, less use of pain medication in the initial phase at intensive care unit was observed. During the first 2 hours, DEX patients received more niconomorphine (DEX 8 ± 3.2 mg vs. propofol 6 ± 4 mg, p < 0.001), while in the following 2 hours, the pain medication was significantly reduced (DEX 3.2 ± 2.8 mg vs. propofol 4.7 ± 3.3 mg, p < 0.001). Remifentanil was stopped considerably earlier (DEX 238 ± 209 minutes vs. propofol 353 ± 266 minutes, p < 0.001). DEX led to earlier extubation (DEX 208 ± 106 minutes vs. propofol 307 ± 230 minutes, p < 0.001) and less postoperative atrial fibrillation (AF) (p = 0.01).

Conclusion  Early postoperative DEX application supports the fast-track strategy in patients after OPCAB through enabling rapid extubation, effective pain control, and reduced occurrence of new-onset AF. We are confident to give precedence to DEX over propofol as the new routine medication during postoperative patient transfer.
Introduction

In recent years, fast-track concepts were established in cardiac surgery as a consequence of minimal invasive procedures, increasing amount of patients and the effort to reduce hospital charges. The concurrence to interventional cardiological procedures presents the need to minimize and optimize not only the operative technique but also the patients’ stay at intensive care unit (ICU) and normal ward. For this reason, the establishment of intermediate care options raised the question of faster, but still comfortable extubation and adequate sedation with pain regulation during fast-track management.

Dexmedetomidine (DEX) is a highly selective, short-acting α-2 agonist that initially has been used as an intravenous antidelirium drug on ICU and approved by Food and Drug Administration in 1999 as sedative. With a 10-fold greater α-2 to α-1 receptor selectivity than the more common clonidine, the sedative effect results from stimulation of α-2-adrenoreceptors in the central nervous system, specifically in the locus coeruleus. Many desirable effects of DEX, including analgesia, anxiolysis, improvement of hemodynamic stability, and potential myocardial and renal protection have been reported. In cardiac surgery, DEX became a convenient drug because of its shorter half-life period and good controllability. It provides safe and effective sedation in patients after coronary artery bypass grafting (CABG) and may significantly reduce the use of analgesics, β-blockers, antiemetics, epinephrine and diuretics. Although there were early concerns regarding the administration of DEX during off-pump coronary artery bypass grafting (OPCAB) grafting because of potential hypotension and difficulty of stabilization, recent studies underlined its beneficial effect of less arrhythmia, lower cardiac enzymes, and a reduction of narcotic consumption during intra- and postoperative periods.

The primary agent used for transition from operating room to ICU currently is propofol as short-acting intravenous anesthetic. Proponents of propofol endorse the agent’s anesthetic properties, its rapid offset, and its low cost. In 2014, we started to use DEX routinely for transition instead of propofol postoperatively to achieve the aforementioned beneficial effects and to establish a faster transfer concept.

The aim of this study was to retrospectively investigate the effect of DEX on patients undergoing OPCAB grafting in comparison to propofol sedation with regard to its quality as fast-track medication for earlier extubation, shorter ICU stay, comfortable pain management, and additional cardiac and renal protection.

Patients and Methods

Dendrite Database and Data Collection

The Dendrite Database (Dendrite Clinical Systems Ltd.), used for collection and analysis of information for this study, provides software, facilitating comprehensive design characteristics for cardiac procedures and their outcomes. The database is maintained by cardiomedical staff under the guidance of a statistician. There were more than 1,500 cardiac procedures that were performed at the hospital and logged into the database during the retrospective study period from January 2012 to March 2015. The data gathered from Dendrite included cardiovascular risk factors, intraoperative parameters, ICU parameters, and in-hospital follow-up. Duration of intubation, hospital stay, and ICU stay were all calculated based on specific dates and times logged in the database. Approved by the local ethics committee, the Dendrite database represents a certified source for the use of patient data for research purposes.

Patients and Parameters

Between January 2012 and March 2015, 464 patients after elective OPCAB were included for retrospective analysis of early postoperative outcome from our Dendrite database. During the retrospective study period from 2012 to 2015, both drugs, DEX and propofol, were used simultaneously with an increasing application of DEX over the years. After propensity matching (1:1) to mitigate selection bias in DEX infusion, including cardiovascular risk factors, baseline laboratory values, and operative strategy, two groups (DEX vs. propofol, \( n = 129 \) per group) could be compared (Table 1: preoperative demographics; Table 2: intraoperative data). As documented in the table, both groups consist of male patients because of a small number of women in the main group, who could not be matched by aforementioned parameters. There were no significant differences in the preoperative demographics and intraoperative data between both groups. Few patients in both groups received an additional bipolar radiofrequency pulmonary vein ablation for paroxysmal atrial fibrillation (AF). Patients with chronic AF and the need for a biatrial Maze procedure under cardiopulmonary bypass were excluded. New-onset postoperative AF was diagnosed, if AF was detected on ICU under continuous rhythm control or later on the normal ward. Routinely, an electrocardiography (ECG) was performed on the first day after the patient’s transfer to the normal ward and before removing the temporary pacemaker wires. If an irregular pulse was documented during the daily controls (three times a day), or if the patient perceived an irregular heart rhythm, then another ECG for the diagnosis and therapy adjustment was made.

Application of Dexmedetomidine and Postoperative Weaning

All patients received a standardized intraoperative administration of anesthesia consisting of sevoflurane and fentanyl (200 µg/h) according to a Bispectral index between 40 and 60. DEX patients received during chest closure an infusion of DEX, starting with a loading dose of 2 µg/kg/h for the first 30 minutes, followed by a maintenance dose of 1 µg/kg/h. Propofol patients were routinely transferred with propofol to the ICU. During the study period, the sedation and weaning assessment protocols remained unchanged at ICU. The weaning criteria of mechanical ventilation include a FiO2 under 40%, pulmonary end-expiratory pressure of 5 mbar and pulmonary support of 0–5 mbar in the spontaneously breathing patient. For the assessment of delirium, the Confusion Assessment Method for Intensive Care Unit (CAM-ICU) was used. The CAM-ICU was performed immediately...
before extubation and subsequently every 8 hours (once per shift). After transfer to normal ward, the test was performed once per day, usually in the morning.

After arrival on ICU and performance of routine ECG, chest X-ray and blood sampling, the anesthetics were reduced considering the patients’ hemodynamics and pain reaction. If there were difficulties to categorize the pain level, the nurse staff used the numeric rating scale. The first dose of intravenous nicomorphine injection (5–10 mg) was already given immediately before transfer to ICU while the patients were still sedated and asleep. After installation on ICU and reduction of remifentanil, single injections were administered depending on the patients’ need starting with a dose of 2 mg. Following administration depended on the patients’ demand. If the patient still felt uncomfortable after the initial dose, the morphine injection was repeated with 2 or 4 mg.

### Statistics
Continuous and categorical variables were reported as mean ± standard deviation (SD) or percentages, and compared with the chi-square test and the Mann–Whitney’s test, respectively. To mitigate selection bias and adjust for the missing randomization, we conducted a matched propensity analysis with 1:1 matching ratios. A logistic regression model including the parameters from Table 1 as main preoperative effects was used to estimate the propensity score. In addition, emergency procedures, number of distal anastomoses, and the use of both internal thoracic arteries were included as parameters for the matching. Propensity score matching was performed on the logit scale with a caliper of 0.2 SD of the logit of the propensity score. The statistical analysis was performed with IBM SPSS Statistics (version 22, IBM, Armonk, New York, United States).

### Results

#### Pain Modulation
In the DEX group, less use of pain medication in the initial phase at ICU could be observed. During the first 2 hours, DEX patients received significantly more intravenous nicomorphine (DEX...
8 ± 3.2 mg vs. propofol 6 ± 4 mg, p < 0.001), while in the following 2 hours, the pain medication was significantly reduced (DEX 3.2 ± 2.8 mg vs. propofol 4.7 ± 3.3 mg, p < 0.001). After 12 hours, there was no difference in both groups (DEX 5 ± 3.7 mg vs. propofol 4.9 ± 3.7 mg, p = 0.9), although remifentanil was stopped considerably earlier in the DEX group (DEX 238 ± 209 minutes vs. propofol 353 ± 266 minutes, p < 0.001) (►Fig. 1).

Intubation Time and Discontinuation of the Sedative
DEX led to significant earlier extubation (DEX 208 ± 106 minutes vs propofol 307 ± 230 minutes, p < 0.001). In comparison of discontinuation of DEX or propofol, DEX infusion was terminated significantly earlier (DEX 137 ± 95 minutes vs propofol 238 ± 208 minutes, p < 0.001) (►Fig. 2).

INCU Stay, Total Stay, Return to Intensive Care Unit
There were no significant differences in ICU stay and return to ICU. Total hospital stay was with 0.6 days significantly longer in the DEX group (►Table 3).

Clinical Parameters: New-Onset Atrial Fibrillation, Delirium, Pneumonia
There was a significant difference in the occurrence of postoperative new-onset AF, which was reduced after DEX application (p = 0.01). The occurrence was independent of previous Maze procedure. Delirium occurred only once in the DEX group and five times in the propofol group, which was statistically not significant (p = 0.10). There was no difference in the occurrence of pneumonia on the ward and on ICU between both groups (►Table 4).

Cardiac and Renal Protection
For the comparison of cardiac enzymes and creatinine, the laboratory values were documented on the first postoperative day and as peak values. Finally, there were no differences between both groups in postoperative creatine kinase (CK), CK-MB or troponin T, and creatinine (►Table 5).

Further Results
The administration of erythrocyte and thrombocyte concentrates as well as fresh-frozen plasma during operation and on ICU was without significant difference in both groups. There was no use of an intra-aortal balloon pump during or after operation. No in-hospital death occurred in either group.

Discussion
The aim of this study was to compare the effect of DEX versus propofol sedation on patients undergoing OPCAB grafting...
with regard to DEX's quality as fast-track medication. The initial idea of replacing propofol as the standard postoperative sedation during transfer from the operating room originated from a nationwide voluntary recall of select lots of propofol formulation due to possible contamination in the United States. Hospitals converted patients receiving propofol to DEX immediately after operation with interesting beneficial results that were first described retrospectively and followed in selective patients.

Table 3  No significant differences in ICU stay, total stay, or return to ICU

<table>
<thead>
<tr>
<th></th>
<th>Propofol (n = 129)</th>
<th>Dexmedetomidine (n = 129)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU stay (h)</td>
<td>27 (±22)</td>
<td>24 (±12)</td>
<td>0.45</td>
</tr>
<tr>
<td>Total stay (d)</td>
<td>9 (±5)</td>
<td>10 (±5)</td>
<td>0.04</td>
</tr>
<tr>
<td>Return to ICU (patients)</td>
<td>3 (2%)</td>
<td>8 (6%)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Abbreviation: ICU, intensive care unit.

Table 4  Postoperative new onset atrial fibrillation occurs less frequently in patients with dexmedetomidine

<table>
<thead>
<tr>
<th></th>
<th>Propofol (n = 129)</th>
<th>Dexmedetomidine (n = 129)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF (new onset)</td>
<td>23 (18%)</td>
<td>10 (8%)</td>
<td>0.01*</td>
</tr>
<tr>
<td>Delirium</td>
<td>5 (4%)</td>
<td>1 (1%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2 (2%) (ICU)</td>
<td>3 (2%) (ICU)</td>
<td>0.65</td>
</tr>
<tr>
<td></td>
<td>6 (5%) (ward)</td>
<td>8 (6%) (ward)</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Abbreviation: ICU, intensive care unit.

Fig. 2 (a, b) Intubation time and discontinuation of the sedative.

The most significant effect of DEX in our study was found in decreased intubation time while the demand for pain medication remained stable. Patients with DEX were extubated approximately 2 hours after transmission to ICU, while the extubation time of patients with propofol was around 5 hours, although the ICU weaning protocol in DEX patients did not differ from the standardized protocol after propofol. The clinically apparent difference supporting faster extubation lays in the alertness and responsiveness with DEX. This circumstance makes it easier to assess the neurological status and the intensity of pain. Because of optimized communication, the individually administered dose of nicomorphine can

Table 5  Laboratory findings: no differences in cardiac enzymes and creatinine at first postoperative day and as peak value during hospitalization

<table>
<thead>
<tr>
<th></th>
<th>Propofol (n = 129)</th>
<th>Dexmedetomidine (n = 129)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK (IU/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 d</td>
<td>602 (±883)</td>
<td>519 (±444)</td>
<td>0.45</td>
</tr>
<tr>
<td>Peak</td>
<td>713 (±1,059)</td>
<td>683 (±791)</td>
<td>0.85</td>
</tr>
<tr>
<td>CK-MB (µg/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 d</td>
<td>12 (±17)</td>
<td>13 (±13)</td>
<td>0.64</td>
</tr>
<tr>
<td>Peak</td>
<td>14 (±20)</td>
<td>15 (±15)</td>
<td>0.44</td>
</tr>
<tr>
<td>Troponin T (µmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 d</td>
<td>0.3 (±0.4)</td>
<td>0.3 (±0.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>Peak</td>
<td>1.7 (±14)</td>
<td>0.4 (±0.4)</td>
<td>0.42</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 d</td>
<td>85 (±30)</td>
<td>85 (±28)</td>
<td>0.51</td>
</tr>
<tr>
<td>Peak</td>
<td>102 (±63)</td>
<td>109 (±47)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Abbreviation: CK, creatine kinase.
be given intravenously, while remifentanil is reduced in accordance with the patient’s needs. The administration of DEX led to earlier termination of remifentanil infusion, which may underlie its positive effect regarding pain modulation. Despite significant difference in the time frame of administered remifentanil, we documented a high value for SD, which indicates to interpret this result more cautiously. It might demonstrate a low number of patients to underline the representative effect and might be explained by the retrospective study character and the individual experience of the responsible nursing staff. Nevertheless, the high SD appears in both the control and treatment groups.

In the past decade, few related publications made DEX subject of discussion as a helpful medication to optimize postoperative outcome in cardiac surgery. The most relevant differences with DEX usage can be found in the timing and application dose. In contrast to our findings, Reichert et al found no statistically significant differences when assessing the outcomes of opioid requirements and the time to extubation in the retrospective comparison of on-pump patients. Thirty-five DEX patients were compared with 35 patients receiving propofol. Unfortunately, the time frame of initiation of the DEX infusion is not mentioned clearly. The postoperative DEX dose ranged from 0.3 to 0.7 μg/kg/h, which is lower compared with our dose of 1 μg/kg/h and the additional bolus in the first 30 minutes of 2 μg/kg/h during chest closure. The abovementioned study included only on-pump patients, who were cooled till 28 or 32°C, which might influence on later extubation time as well. Nevertheless, Barletta et al found a beneficial effect with shorter intubation time and less need of pain medication in their comparison of 50 DEX patients to 50 propofol patients. Yet in the Barletta study, important differences were that DEX was administered intraoperatively after termination of cardiopulmonary bypass, which is clearly earlier than in our patients and loading doses were not used and the doses were started at 0.2 μg/kg/h. A large analysis of the effects of DEX was performed by Achuff et al in 2015 including more than 440 pediatric patients after on-pump cardiac surgery. They proved that DEX given as a bolus during chest closure provides a faster extubation, while the need of potential respiratory affecting morphine could be reduced significantly. These findings support our results and raise the question of the ideal initial dose and need of a bolus application during chest closure. According to the fast extubation and the pain control in our patients, we would recommend the application of DEX bolus during chest closure.

We found no significance in the incidence of delirium between both groups. In general, we had a low number of affected patients (4% propofol vs. 1% DEX). Shehabi et al showed as well that DEX did not reduce the incidence of delirium after various on-pump procedures. They started the DEX infusion 1 hour after admission on ICU without a loading dose and finished DEX after the removal of chest drains, or the discharge of the patient from ICU, which was definitely longer than the initial drug administration in our study. Although the occurrence of delirium failed to reach statistical significance, there was a tendency toward reduction in the duration of postoperative delirium, which might play a role regarding clinical outcome and further costs. The low occurrence of delirium in both groups in our study may be caused by patient selection. Both groups had a EuroSCORE 2 of 1 to 2%, which signifies for less comorbidities and cardiac risk factors and finally may also signify a lower risk profile developing a delirium. Moreover, the application of DEX was meant to be short and stopped after extubation, while further studies including different ICU patients report an administration of DEX for longer than 24 hours with a significant reduction of delirium. In addition, it has to be noticed that our patients were exclusively operated without the use of cardiopulmonary bypass and without partial aortic clamping with the help of heartstring proximal sealing system (Maquet Getinge Group, Rastatt, Germany), which might have an influence on better neurological outcome by supporting the aortic no-touch technique. A conceivable strategy after this experience can be a longer application of DEX in patients, who are identified for a possible postoperative delirium including older age, history of previous delirium, and further comorbidities. In our DEX patients after off-pump surgery, there was only a trend to less delirium.

Although there have been controversy about the use of DEX in off-pump patients, we did not have any hemodynamic complications regarding blood pressure management in the DEX patients. Donias and Karamanoukian mentioned concerns about the use of DEX in hypothermic patients undergoing off-pump surgery because of the potential effect of hypotension during rewarming on ICU, which might cause hemodynamic instability. In a series of 20 OPCAB surgery patients, significant reduction of mean systolic arterial pressure (12 mm Hg below baseline) within 15 minutes of initiating DEX could be documented. Unfortunately, we did not directly analyze the arterial pressure on ICU. It can be noticed that there were no clinical complications or delayed transfers to the normal ward in the DEX group compared with the control group. In contrast to the experience of Donias and Karamanoukian, isolated cases supported DEX as a particularly suitable adjuvant medication for fast-track extubation in off-pump patients. Another prospective off-pump study using DEX infusion (1 μg/kg/h for 10 minutes, 0.5 μg/kg/h continuously during operation) shortly after induction of general anesthesia did not report hemodynamic problems, but could prove faster extubation and a reduction of ICU and hospital stay in 25 patients. The influence on cardiac protection and the role of lower heart rate appeared with the more frequent use of DEX in cardiac patients. Although we had significantly less new-onset AF in DEX patients, we could not demonstrate any differences in cardiac protection between the groups represented by the cardiac parameters CK, CK-MB, myoglobin, and troponin T. Similar to our findings, a change of CK-MB and cardiac troponin T could not be documented in a prospective study of 38 on-pump patients, although the application was started during operation and continued postoperatively (0.5 mg/kg loading dose for 10 minutes and 0.5 mg/kg/h continuous infusion). Positive results were reported by Ren et al including more than
160 randomized off-pump patients. Again, the continuous DEX infusion was started already during operation following the first anastomosis grafting with 0.2 to 0.5 µg/kg/h till ICU transfer and for the first 12 postoperative hours. The blood pressure, heart rate, levels of cardiac troponin I, CK-MB, nor-epinephrine, and cortisol, and postoperative arrhythmic events were all decreased. To determine a certain dose that might demonstrate a cut of value concerning changes in cardiac laboratory parameters, Chi et al prospectively divided more than 110 off-pump patients in a high-dose group (loading dose, 1 µg/kg; maintenance dose, 0.6 µg/kg/h), low-dose group (loading dose, 0.6 µg/kg; maintenance dose, 0.3 µg/kg/h), and control group. Cardiac troponin I and CK-MB levels in patients of the high-dose group were less than those of the other two groups 48 hours after surgery. These results are convincing, especially concerning off-pump surgery. They speak for an earlier start of DEX infusion already during operation. Thus, the cardiovascular effects depend on the dosage: at lower infusion rates, the central effects of sympatholysis outweigh and result in a lowered heart rate and lowered blood pressure. At higher doses, the peripheral vasoconstrictive effect dominates leading to increased systemic vascular resistance and blood pressure, while the bradycardic effect is further enhanced. This might explain the preventive effect on the development of tachycardia leading to hemodynamic stabilization.

Another parameter of interest was the change in creatinine to monitor the renal function. The main idea of a beneficial effect lies in the centrally mediated sympatholysis of DEX, which may improve renal function during a stressful CABG operation. Leino et al investigated 66 patients for renal protection of DEX in CABG patients and found no alteration in renal function but an increase in urinary output. We could not detect any differences in creatinine as the only monitored laboratory value for renal function in both groups. Current literature points to more specific markers to investigate the renal effect of DEX and to detect renal failure. Similar to lower cardiac enzyme parameters, the start of DEX already during or at the beginning of operation might influence on renal function. The long-term effect after operation still remains unclear.

To establish this new concept, the first patients receiving DEX were low-risk off-pump cases. Subsequent to the significant outcomes in pain management and earlier extubation, the use of DEX in our clinic was extended to all cardiosurgical procedures, from minimal invasive valve surgery to complex combined procedures. The pain management protocol remained unchanged.

Propensity score matched analysis, tailored specifically for pre- and intraoperative patient and surgical parameters (i.e., use of bilateral internal thoracic arteries, number of distal anastomoses), has substantiated the usefulness of DEX as a standard protocol for improving postoperative outcome.

**Limitations and Future Plans**

The consolidation of minimal invasive cardiac procedures with new medical therapies has required necessary structural changes in hospital logistics. Outpatient services will play an increasing important role in the patient’s choice of therapy. Two pending topics remain to be mentioned. First, the reported use of DEX has the potential to lower hospital costs, not only by shorter ICU stay but also by reducing complications such as delirium and arrhythmia. To define the impact of DEX on our budget, a future calculation of costs will need to be performed. Second, the initiation of a low dose of DEX in the beginning of the operation should be discussed and measured for the purpose investigating the potential benefit for cardiac protection.

**Conclusion**

Early postoperative application of DEX supports the fast-track strategy in patients following OPCAB grafting by rapid extubation, effective pain control, reduced occurrence of new-onset AF, and a tendency to less delirium. Therefore, we are confident to give precedence to DEX over propofol as the new routine medication during immediate postoperative patient care.

**Note**

This study was presented at the annual meeting of the German Society of Thoracic and Cardiovascular Surgery, Leipzig, February 14, 2016.

**References**