Sedation by infusion: A clinical trial in cardiac surgery patients*

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*1992 Research in Action Award

The problem of sedation and analgesia for ventilator-dependent patients was examined in this study. Twenty subjects undergoing elective coronary revascularization surgery at a major medical center were studied. They ranged in age from 49 to 83 years. A randomized, prospective research design was used to place subjects in either an experimental group or a control group. Standard postoperative analgesia with intravenous increments of morphine and midazolam in the control group was compared to treatment with a titratable sufentanil-midazolam infusion in the experimental group. In both groups, hemodynamic variables were measured at selected intervals, sodium nitroprusside consumption was measured, and time to extubation was noted. Data analysis demonstrated no statistically significant differences between the experimental and control groups. The more costly sedative-analgesic infusion appeared to be comparable to conventional treatment with incremental morphine and midazolam based on the results of this study.

Key words: Analgesia, cardiac surgery, infusion, sedation.

Introduction
The provision of adequate sedation and analgesia for critically ill ventilator-dependent patients can be problematic for everyone involved in their care. Sedative or analgesic drugs may be withheld because of hemodynamic instability or concern over prolonged depression of the central nervous and respiratory systems.

In postoperative coronary artery bypass graft (CABG) patients, sedation and analgesia may be kept to a minimum for fear of prolonging endotracheal intubation. When these drugs are withheld, residual neuromuscular blockade may render an awakening patient weak and distressed about the experience of being aware and partially paralyzed. Vasoactive drugs may be used to treat hypertension and tachycardia, some of which may be related to awareness. Smith and associates found that post-CABG myocardial ischemia peaked 2 hours postoperatively and was more frequently related to tachycardia.1 Anesthetic practice demonstrates that hypertensive and tachycardic responses to nociceptive stimuli, including endotracheal intubation, can be attenuated by sedation and analgesia.

Sedation and analgesia by intravenous titration have been practiced for some time in anesthesiology and critical care. Pharmacologic agents currently available can provide a titratable sedative analgesic infusion which causes minimal compromise in hemodynamic parameters.13 The authors
used this concept in attempting to improve outcomes, i.e., less use of vasoactive drugs and a lower incidence of postoperative tachycardia without prolonging endotracheal intubation time, for CABG patients, as has been demonstrated by several investigators with similar research designs.14

Methods

Twenty elective cardiac surgery patients over age 35 were recruited for this study. All subjects had no evidence of myocardial infarction in the previous 6 months, no signs of congestive heart failure, and all had left ventricular ejection fractions greater than 0.5. The subjects all gave written informed consent, as approved by the University of Washington Human Subjects Review Committee. Subjects were randomized to treatment and control groups.

The routine postoperative management of these patients included overnight, or longer, mechanical ventilation. All patients received sufentanil-midazolam-based general anesthetics. Sufentanil doses ranged from 5-10 μg/kg; midazolam doses varied from 0.15-0.3 mg/kg. Anesthesia was supplemented with volatile agents as necessary. Patients in the control group received a standard postoperative sedation and analgesia regimen, consisting of incremental doses of intravenous morphine in 2-mg increments and midazolam in 1-mg increments.

Patients in the experimental group received a continuous infusion of sufentanil 1 μg/mL and midazolam 0.3 mg/mL. This fixed-combination sufentanil-midazolam infusion was started at a rate of 0.1 mL/kg/hr at the time of sternal closure. The infusion was titrated by the intensive care unit (ICU) nursing staff at a range of 0.1-0.2 mL/kg/hr until 3 AM on the first postoperative day. A protocol provided for 5-mL boluses of the infusion to be given as needed for agitation and hypertension, up to a maximum infusion rate of 0.2 mL/kg/hr.

The anesthesiology and critical care staffs in this institution routinely use sodium nitroprusside (SNP) to control hypertension in post-CABG patients. SNP is titrated to maintain a mean arterial pressure (MAP) of 65-75 mmHg in a dosage range of 0.2-2 μg/kg/min. Other vasoactive drugs may be added if SNP does not adequately control MAP.

After the sufentanil-midazolam infusion was discontinued at 3 AM, 5-mL boluses of the infusion could be given every 15 minutes as needed for agitation or hypertension between 3 AM and 6 AM.

Once subjects had achieved adequate ventilatory weaning parameters, i.e., inspiratory force of at least -25 cm H2O, a forced vital capacity of 10-12 mL/kg, could sustain head lift, and were mentally alert, they were extubated. At the center where this research was conducted, extubation of stable, post-CABG patients with satisfactory weaning parameters occurred at 7 AM or shortly thereafter on the first postoperative day.

Parameters recorded were: systolic, diastolic, MAP, and heart rate at sternal closure, before leaving the operating room, in the transport elevator, and at 5, 30, and 60 minutes after admission to the ICU. These intervals were selected because the literature reviewed suggested that hypertension and tachycardia frequently occur in the immediate postanesthetic, transport, and initial ICU phases of treatment.14 The total dose of SNP administered in the ICU from admission until extubation, as well as the time from the end of surgery to extubation, were also noted.

Results

Subject demographics were similar in terms of age, sex, and body surface area (Table I). Hypothesis testing on continuously distributed variables was done by unpaired t-tests or by repeated measures analysis of variance (ANOVA), with time as the measure for hemodynamic data. A two-tailed significance level of 0.05 was used throughout. The P values reported were not significant (Table II).

| Table I | Subject demographics: Physical characteristics of research subjects with ANOVA |
|---------|-------------------|------------------|------------------|-------------------|
| Study group | Control mean (SD) | Treatment mean (SD) | P-value |
| Variable | | | |
| Age (years) | 62.6(8.6) | 64.4(6.2) | 0.66 |
| Height (cm) | 168.3(17.2) | 175.5(10.0) | 0.26 |
| Weight (kg) | 80.0(24.4) | 77.5(11.9) | 0.79 |
| Body surface area (meters squared) | 1.90(0.31) | 1.93(0.17) | 0.77 |
| Percent male | 66.7 | 90.9 | 0.18 |

Group-time interaction term, using repeated measures of ANOVA, assessed responses over time and tested for treatment effects (Table III). Subjects in both groups were hemodynamically stable (Figure 1), and no significant differences were seen between the treatment and control groups in blood pressure, heart rate, SNP consumption, and time to extubation. Each group had similar hourly SNP dosage administration ranges. Time to extubation in the treatment group averaged 53 minutes more than in the control group, a statistically insignificant value.
Table II
Analysis of physiologic data: Postoperative measures of subjects' time to extubation, sodium nitroprusside (SNP) consumption, and ANOVA

<table>
<thead>
<tr>
<th>Group</th>
<th>Control (number = 9)</th>
<th>Treatment (number = 11)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to extubation (min)</td>
<td>1051.4(144.6)</td>
<td>1104.8(156.4)</td>
<td>0.44</td>
</tr>
<tr>
<td>SNP infusion duration (min)</td>
<td>96.7(109.2)</td>
<td>253.0(256.4)</td>
<td>0.09</td>
</tr>
<tr>
<td>Mean hourly SNP infusion rate in μg/kg/min</td>
<td>0.48(0.50)</td>
<td>0.48(0.49)</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Table III
Group-time interaction term: Responses of subjects in both groups over time, testing for treatment effects

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Control</th>
<th>Treatment</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>P = 0.80</td>
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</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>P = 0.30</td>
<td></td>
<td></td>
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<tr>
<td>Mean blood pressure</td>
<td>P = 0.32</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart rate</td>
<td>P = 0.83</td>
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</table>

Discussion
Durkan noted lower SNP consumption in post-CABG patients who received a sufentanil infusion in a similar study that compared a sufentanil infusion with incremental morphine in post-CABG patients. As in this study, hemodynamic parameters were similar in the treatment and control subjects. Sladen and associates found that a continuous infusion of fentanyl and midazolam provided significantly fewer episodes of hypertension and agitation than intermittent boluses of these drugs in post-CABG patients. This improved sedation was achieved without prolonging the duration of intubation.

In this study, no significant differences were found in SNP consumption, blood pressure and heart rate control, and time to extubation in groups treated with conventional incremental intravenous sedation and analgesia versus groups treated with a continuous infusion of sedative-analgesic drugs. Both regimens provided similar control of hypertension and tachycardia; times to extubation were comparable and SNP consumption was similar in both groups.

The ICU nursing staff was able to produce similar outcomes in these patients using different drug regimens. The added costs of newer drugs—$4.75 per 50 μg of sufentanil versus $0.01 per milligram of morphine—and infusion pumps may not be necessary when intravenous increments of morphine and midazolam are successfully titrated toward desired end points.

The care of post-CABG patients in the center where this research was conducted is somewhat regimented regarding control of MAP, vasoactive drug therapy, and duration of ventilation. However, duration of endotracheal intubation and mechanical ventilation in healthier cardiac surgery patients at this center is evolving into a practice of “early extubation,” i.e., modifying anesthetic agents and dosages used in cardiac anesthesia and weaning patients from mechanical ventilation within the first few hours on the ICU.

It is notable that patients in this study who required overnight or longer mechanical ventilation had similar measured physiologic outcomes when conventional sedation and analgesia techniques were used rather than continuous infusion. Unlike other similar studies, this research demonstrates no statistically significant differences in measured physiologic parameters between the
continuous infusion and incremental injection techniques.

Suggestions for improvement in the design of this research include utilizing a visual analogue scale to evaluate analgesia. Other psychological assessment tools could be employed in future research.

Physiologic parameters which merit investigation in this population include electrocardiographic evidence of ischemia, electroencephalographic data from the compressed spectral array, plasma levels of the sedative-analgesic drugs, and plasma catecholamines. Lack of funding limited the investigators' ability to assess these parameters. Alternatives for the sedation and analgesia of ventilator-dependent patients will continue to be sources of clinical research and discussion.7-12

REFERENCES


