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Intensive Analgesia Reduces Postoperative Myocardial Ischemia? II

To the Editor:—I read with interest the recent article by Mangano and the Study of Perioperative Ischemia Research Group.[1] Their data reveal that patients who receive a continuous infusion of sufentanil after cardiac surgery have "less severe" ECG changes in the postbypass and intensive care unit time periods when compared to patients who receive intermittent intravenous injections of morphine for pain relief. From these data, the authors conclude that "the severity of ischemic episodes can be diminished following myocardial revascularization by use of prolonged intensive analgesia." Such a conclusion, while intuitively appealing, is not the only way to interpret the data.

The design of this study significantly limits any conclusions that can reasonably be drawn from its results. The two groups differ in many ways other than the degree of analgesia.

The groups received two different drugs (morphine or sufentanil). The patients in the morphine group also received significantly more midazolam. Thus, the differences in ischemia between the groups may come from a proischemic effect of morphine, not an antiischemic effect of sufentanil. The additional midazolam, alone, or in combination with the morphine, could have incited more ischemia in that group.

The intraoperative management of the groups was different. The morphine group received up to 2 mg/kg of morphine while on bypass. The sufentanil group received a bolus and infusion of sufentanil. Morphine, in these doses, has considerable hemodynamic effects. In contrast, sufentanil is well known for promoting "hemodynamic stability." Thus, differences in the intraoperative management of these two groups could be responsible for the reported results.

In the intensive care unit, the drugs were given by different protocols. In one group, the patients received intermittent injections of opioid "as needed for pain." The other group, in contrast, received a constant infusion of opioid. These different methods of drug administration could have influenced the study outcome.

The authors suggest that the less severe ischemia in the sufentanil group resulted from "intensive analgesia." However, they offer no data to show that the patients in the sufentanil group indeed had less pain than those in the morphine group. Admittedly, this is a difficult task when dealing with patients in whom the trachea is intubated, but I think the point is important.

Lastly, the investigation was in no way blinded. Nurses and physicians caring for the patients in the operating room and intensive care unit were most likely aware of the study. Even if they did not know the authors' hypothesis, they could have guessed it or derived one of their own. Either event might have produced subtle changes in the manner in which they responded to clinical events.

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In Reply:—We appreciate the comments of de Leon-Casasola and Lema. Regarding their suggestion that a larger study is needed, we agree and have so stated in the third limitation cited in the Discussion section. The intent of this study was to investigate the differential effects of the techniques on the incidence and severity of perioperative myocardial ischemia. As such, the 100 patients studied provide adequate power. To differentiate the effects on myocardial infarction and cardiac death, a much larger study is needed both because of a lower incidence

in outcome rate and because of the presence of multiple confounders. Regarding the suggestions of alternate analgesic therapy and the use of β blockers and calcium-channel blockers, no conclusion can be drawn, for the appropriate studies have not been performed. There is a rational basis for use of several of these therapies; further studies are necessary.

We appreciate Norris's comments but believe that he has misinterpreted both the design of study and the results. The study was not designed to test the difference between individual *drugs* (morphine *vs.* sufentanil) but to assess the difference between *techniques:* 1) a standard technique—intermittent, low-dose analgesia and 2) a study technique—continuous, moderate-dose analgesia. We specifically refer Norris to the study design as described in the introduction and in the Materials and Methods and Discussion sections.

Regarding Norris's second point, "The two groups differ in many ways," we disagree. As detailed in the Results section, no significant differences were found between the two groups in any of the following categories: the characteristics of the subjects (table 1), intraoperative surgical data and events (table 3), the incidence of hemodynamic abnormalities (table 4), or other data (table 5).

Norris's third point addresses the assessment of pain. Such assessment is not possible, obviously, in sedated patients in whom the trachea is intubated—our study group. Therefore, those data cannot be available in any study with a design such as ours.

Regarding Norris's fourth point, that "the investigation was in no way blinded," we disagree. All investigators who interpreted the hemodynamic event, and particularly the ischemia and outcome data, were blinded to all patients, as stated in the Materials and Methods section (page 345): "Adverse outcomes were noted by study physicians and validated separately by two investigators blinded to the patients' clinical and monitoring data . . ." The clinicians and nurses caring for the patients were not blinded to the technique; however, the dose of the study drug (sufentanil) was fixed at 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and not adjusted by the clinicians. In the control group, morphine and midazolam were given intermittently, as is the usual care. Although the potential for bias exists, and nurses or physicians could have either undertreated or overtreated these patients because they were enrolled in this study, this is highly doubtful. The amount of morphine and midazolam given these patients is very similar to the amounts given in our usual care of these patients and similar to the amounts reported in our previous studies.

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