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(Accepted for publication January 13, 2011.)

Intraoperative Ketamine and Chronic Opioid Use: Less Pain, More Morphine?

To the Editor:

The recent paper by Loftus *et al.*,[1] "Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery," was of interest to me because I occasionally use the technique described. This group of patients is very complex and I congratulate the authors for undertaking this study.

There are four points that warrant clarification. First, the primary outcome of the study was based on data derived from a review of medical records (*i.e.*, mean [SD] 48-h postoperative oral morphine equivalent consumption of 500 [300] mg). However, the placebo group consumed only 309 (341) mg of this substance. Can the authors comment on this large difference and its possible relevance?

Second, the term "morphine equivalents" requires further explication. This terminology was confusing because it was applied to oral and intravenous formulations. Which formulation was used was not always immediately clear. For example, in their table 1,[1] were "median preoperative morphine equivalents" delivered orally or intravenously? The text implies that these equivalents are intravenous morphine. If this supposition is correct, then it appears to me that both groups of patients may be consuming more morphine equivalents at 6-week follow-up (data presented as mean [SD]) than they did preoperatively (data presented as median [interquartile range]). In fact, the placebo group appears to have much higher rates of morphine consumption at 6 weeks compared with their own preoperative consumption levels and the treatment group's consumption at 6-week follow-up. There is a possibility that the treatment group's 6-week follow-up consumption has also increased from the preoperative period, which is concerning. Can the authors clarify and comment on these points?

Third, the treatment group had more spinal levels operated on than did the control group. In fact, this difference reached statistical significance. However, this feature of the study was not addressed by the authors. Do the authors believe this difference was clinically significant?

Finally, with regard to these observations, specifically with respect to possible increases in morphine consumption among both groups at 6-week follow-up and the chronic nature of back pain, I believe that a more extended follow-up period is warranted. Do the authors plan to do this?

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(Accepted for publication January 5, 2011.)

In Reply:

The management of acute postsurgical pain in opiate-dependent patients is one of the most difficult clinical challenges in perioperative medicine. Although ketamine has been shown to be of value in some surgical settings for opiate-naïve patients, there is little information available pertaining to its use in opiate-dependent patients who need to undergo major and painful surgery.

Therefore, we designed our recent study[1] to determine the role, if any, of an easily implemented intraoperative ketamine protocol on postoperative recovery parameters. The study, if positive, was designed to be the beginning of an ongoing effort to define optimal treatment for surgical patients who suffer from chronic preoperative pain. As such, we appreciate the opportunity to clarify the issues raised by Dr. Seigne.

Dr. Seigne expressed concern and asked for clarification regarding the fact that the amount of opiate used in the 48-h postoperative period differed between the population reviewed in order to power the study and the actual study control group. The standard deviations for both groups are quite large. Thus, there was no statistically significant difference. Further, one would expect the groups to be different, given the intrinsic variability in the surgical population of interest.

Dr. Seigne was also concerned by the fact that the study patients, in both the treatment and placebo groups, appear to be using more pain medications at 6 weeks as compared to baseline, and that preoperative morphine use is presented as median (interquartile range) whereas postoperative use is reported as mean (SD). Preoperative morphine use is reported as median (interquartile range) because of the skewed nature of the data; this measure is a better reflection of the population. This was not the case for postoperative morphine use, however, making mean (SD) the more appropriate presentation. Results are reported in intravenous morphine equiva-

lents, as stated in the manuscript. As expected, after major and painful surgery, patients in both study groups are using more pain medicine at 6 weeks as compared with baseline. We would consider a steady decrement in opiate consumption per hour to represent an expected recovery process. Note again the 3- or 4-fold difference in opiate consumption between control and treatment groups at 6 weeks.

Dr. Seigne also wondered whether the statistical significance reached between the treatment and control groups in terms of the number of levels of surgery might have clinical relevance. We do not consider this factor to be clinically significant. We direct readers' attention to equal surgical times and blood loss.

In terms of Dr. Seigne's questions regarding longer term follow-up, this study was planned as the beginning to further studies. If we did further follow-up, we would either get the same results (better recovery in the treatment group) or there would be no difference at, say, 1 yr. At some point, we expect the latter to appear, which identifies the key question for any follow-up study, namely: What is the most relevant outcome parameter to measure in this type of study? Patient satisfaction? Functional activity level?

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(Accepted for publication January 5, 2011.)

Simple Math or Aberrant Physiology: The Complex Question of Modified Metabolic Syndrome

To the Editor:

I congratulate Glance *et al.*[1] for their work on elucidating the risk profiles of patients with modified metabolic syndrome. Their findings may change the way physician, billing, and insurance groups look at obese patients in the future. For this study, and for the interesting study methods, they must be commended. In addition, the described "complex" of obesity, diabetes mellitus, and hypertension encapsulates metabolic risk features of obstructive sleep apnea. The Perioperative Sleep Apnea Prediction score is a validated screening method that uses all three variables as a clinical prediction tool for sleep apnea.[2] Thus, the study findings could well be used to describe the perioperative outcomes associated with increased risk of sleep apnea.

One unresolved issue is whether diabetes and hypertension, two independent predictors of adverse outcome in previous outcomes studies,[3–6] unfairly skewed the analysis. Discounting the supermorbidly obese patient population, obesity has been protective for morbidity in several studies, as duly noted by the authors. On the other hand, diabetes and hypertension have both been independent predictors of organ failure and mortality. Therefore, did the current study prove the increased risk of modified metabolic syndrome or simply prove that the preoperative presence of two independent risk factors (and one protective factor) is more significant than having one protective factor? Separating these two independent risk factors from obesity is important to determine whether the described effect sizes are independent of body mass index. Although the lack of these data in no way invalidates the study results in terms of identifying higher-risk profiles of obesity, if obesity was indeed protective, as is suggested in the literature, were patients with diabetes and hypertension but no obesity at greater risk of adverse outcomes? If so, are we truly using our risk assessment tools appropriately? These are yet unresolved questions; however, Glance *et al.*[1] have provided the initial spark that could ultimately cast light on them.

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(Accepted for publication January 25, 2011.)