An Innovative Analysis of Analgesic Consumption in the Postoperative Period

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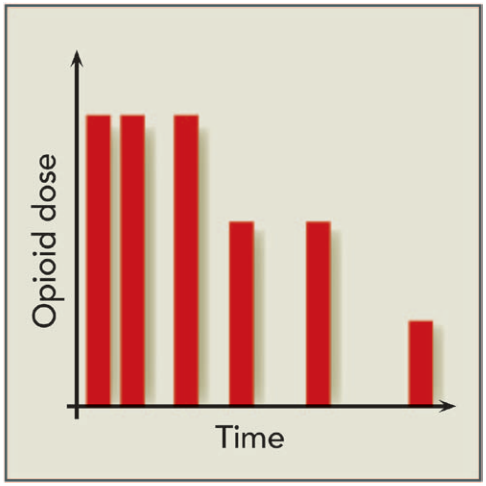
IN this issue of ANESTHESIOLOGY, Juul *et al.*[1] exhibit a statistical technique that has the potential to substantially improve the analysis of postoperative analgesic requirements. By using a retrospective sample of patients from their institution who had received a standard analgesic regimen, the authors examined the probability of repeated morphine dosing over time for up to 96 h after surgery. To accomplish this, they used repeated time-to-event modeling (RTTE). Although modeling interindividual differences in the postoperative analgesic dosing patterns using RTTE is a natural fit in the postoperative setting, this approach has not been systematically exploited. With this illustration, Juul *et al.*[1] demonstrate that the use of RTTE could improve upon commonly used statistical techniques by simultaneously addressing several of the challenges in analyzing these types of data.



"the successful application of the [repeated time-to-event modeling] approach potentially represents a substantial advancement in the analysis of postoperative analgesic requirements ..."

The analysis of postoperative analgesic consumption is highly challenging because discrete doses of an agent are administered over time in a schedule that can vary from person to person. There are many potential approaches to the analysis of these data that are based on mean/median estimates in total dosing, the presence or absence of certain regimens, time to first dosing, and several others. In a brief review of the analytical plans from 21 studies examining postoperative analgesia, Dexter[2] found substantial variability in the approach to data analysis. This variability across studies reflects the difficulties investigators face in conceptualizing postoperative analgesic data. For example, eight of the studies (38%) viewed the analgesic outcomes as dichotomous states (*i.e.*, "yes" *vs.* "no") representing whether or not a patient received any additional analgesic in the postoperative period. A greater number of studies, 13 (62%), viewed the total analgesic dose as a continuous outcome by summing the total consumption and used either a parametric (n = 10) or nonparametric (n = 3) test to examine the differences across study groups. In a recent examination of the statistical distribution of the consumption of patient-controlled analgesia (PCA), Moore *et al.*[3] concluded that cumulative doses were distinctly nonnormal (*i.e.*, not Gaussian) but were well approximated by an exponential distribution (*i.e.*, an increasingly smaller number of participants require higher doses). As Juul *et al.*[1] nicely summarize, any successful approach to analyzing postoperative analgesics must negotiate the unique nature of analgesic data in this setting.

Repeated time-to-event modeling is one such approach that simultaneously considers several aspects of the nature of postoperative analgesic dosing regimens. Karlsson *et al.*[4] credit Cox *et al.*[5] with introducing longitudinal time-to-event pharmacodynamic models in 1999. These models are an extension of traditional time-to-event (*i.e.*, survival) models and can accommodate discrete events such as the presence or absence of a PCA dose or can be modified to accommodate ordered categories, such as none, moderate, and high doses (*e.g.*, see the study by Plan *et al.*[6]). The RTTE approach has several nice features. First, by modeling the time to each repeated event (*i.e.*, PCA event 1, PCA event 2, *etc.*), the approach considers the entire range of events rather than just the time to first event. This allows a more efficient use of the data than it achieved with artificially restricting the time range or using only the time to first event as the outcome. Second, like in traditional survival analysis, the models can accommodate censored observations, which are quite common in the postoperative setting when individuals are discharged or lost to observation for any reason. Finally, the approach is estimated using mixed-effects models that use random effects to model interindividual variability

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in analgesic use. A model-based approach also allows the use of a range of predictors including time-varying covariates. The approach is nicely illustrated by Juul *et al.*[1] with elegant visual examples of the information that can be gleaned from the model predictions.

The use of RTTE is not without its own challenges. The assumptions required to properly interpret the estimates must be carefully considered and evaluated in the modeling process. Juul *et al.*[1] present some examples of this process with the use of visual evaluation, and careful consideration of the model's assumptions must always be assessed. The available statistical power of the procedure is not entirely straightforward and would require thoughtful evaluation in study planning; Juul *et al.* do not offer advice on the sample size requirements of the RTTE approach in this setting. Finally, a recent simulation study has reported that the estimates of the parameters may be quite sensitive to the estimation method used (*e.g.*, Laplace, stochastic approximation expectation–maximization) when the event rates are low,[4] as may be the case in certain types of postoperative settings. Thus, careful attention is also needed in the choice of estimation method. Taken together, the approach requires the thoughtful consideration that would be required of any sophisticated modeling procedure. However, the successful application of the RTTE approach potentially represents a substantial advancement in the analysis of postoperative analgesic requirements as has been demonstrated by Juul *et al.*

Competing Interests

The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

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