Intrathecal Dosing for Cesarean Delivery in Obese and Nonobese Patients

To the editor:

It has been proposed that the intrathecal dose of hyperbaric bupivacaine for spinal anesthesia should be reduced in morbidly obese patients undergoing cesarean delivery.[1] This recommendation is consistent with the lower volume of cerebrospinal fluid observed in patients with high body mass index,[2] but a lack of definitive evidence has been noted.[3] Previously, Ginosar *et al.* reported the ED_{50} of intrathecal bupivacaine obtained in a prospective, randomized, double-blind, and dose-finding study of healthy patients having elective cesarean delivery.[4] Using the same experimental methods, Carvalho *et al.* repeated this experiment about 5 yr later at the same institution in patients with a body mass index of 40 or greater.[5] Combining the data from the two studies on the success of the spinal block for operation, they used a quantal sigmoid Emax parametrization of the logistic model with nonlinear mixed effect model estimation using the NONMEM package (NONMEM® version V [GloboMax™, Hanover, MD]),

$$\text{Probability(success = yes)} = \frac{dose^{\gamma}}{dose_{50}^{\gamma} + dose^{\gamma}}$$

with $dose_{50}$ representing the median effective dose (ED_{50}) and γ representing the slope of the dose-response curve. They concluded from the similar ED_{50} and ED_{95} values of the two studies that obese and nonobese patients did not have significantly different dose requirements. They acknowledged their statistical methods had not compared the entire dose response of the two groups of patients. Because simultaneous analysis of families of sigmoidal curves is the preferred approach,[6] this letter argues that their data do allow such a contrast of the entire dose response. In fact, their data reveal that the morbidly obese require not a lower or similar dose, but possibly a higher dose, than the nonobese.

The sigmoid Emax model is equivalent to its restatement in a two-parameter logistic format.

$$\text{Probability(success = yes)} = \frac{1}{1 + e^{-(\gamma \log(dose) - \gamma \log(dose_{50}))}}.$$

The R software drc package (Analysis of dose-response curves) offers analysis of one or many dose-response curves in this parametrization.[7] An obesity/nonobesity covariate may be included in the model to specify models with separate intercepts and equivalent slopes (three-parameter model); equivalent intercepts and separate slopes (three-parameter model); and both separate intercepts and separate slopes (four-parameter model). Nested models are compared by likelihood ratio statistics; models with equal parameter counts are compared by Akaike and Bayesian Information Criterion. The binary counts were obtained from the figures of Ginosar *et al.*[4] (1/6, 2/6, 4/6, 3/6, 6/6, 6/6, 6/6) for doses (6,7,8,9,10,11,12) and of Carvalho *et al.*[5] (0/6, 0/6, 1/6, 1/5, 2/6, 3/6, 5/7) for doses (5,6,7,8,9,10,11). These data were reanalyzed using drc package version 2.1–2 running in R version 2.12.2 (R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria). ED_{50} and slope are reported with standard errors and 95% CI; an adjustment for binary variable overdispersion is made.

The best model for the overall data of both studies had a common slope and separate intercepts with a right shifting of dose response for the obese patients. The slope estimate was 7.7 ± 1.7 (4.3–11.1). There were statistically different ED_{50} doses for obese (9.8 ± 0.5 mg [8.8–10.7]) and for nonobese (7.6 ± 0.4 mg [6.9–8.4]) patients. Estimations of ED_{95} for obese (14.3 ± 0.9 mg [12.6–16.3]) and for nonobese (11.2 ± 0.9 mg [9.5–13.2]) had overlapping CIs. The ED_{50} estimates are very similar to those reported by Carvalho *et al.* However, the simultaneous comparison of the entirety of the two dose-response curves permits stronger statements about the overall dose response than pointwise comparisons.

This reanalysis of the two studies should not be interpreted as demonstrating a high degree of certainty about a larger ED_{95} in morbidly obese parturients having cesarean delivery. First, the study sizes (totaling 84 patients) are modest; the statistical methods of nonlinear mixed-effect models assume large sample asymptotic properties in the estimation of variances. Second, there are unstated assumptions, particularly sigmoidicity, symmetry, and homoscedasticity, in using a logistic regression model; there are many other possible dose-response models.[8] With small samples, these assumptions are untestable. Third, the upper end of the dose response (ED_{95}) is of greatest importance in anesthetic planning. The current data require extrapolation of the upper dose range. Fourth, the precision of the slope estimate is rather wide. And finally, there may have been temporal changes in patients and in anesthesia care between the two studies, leading to biased estimates. Carvalho *et al.* and this author concur in recommending that additional prospective, controlled studies are needed to more precisely identify a safe ED_{95}.

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In Reply:

We would like to thank Dr. Nathan L. Pace for his commentary and additional analysis of our study.[1] We agree that entire dose-response curve analysis does permit a more robust statistical comparison than ED_{50} and ED_{95} single-point comparisons. Dr. Pace's reanalysis found ED_{50} and ED_{95} values similar to our original calculations. We concur with the differences Dr. Pace found in the dose-response curves, noting higher dose requirements in this morbidly obese population compared with a nonobese population studied previously. Despite evidence of different dose-responses and higher ED_{50} values in morbidly obese patients, we are hesitant to firmly conclude that obese patients require larger intrathecal doses of local anesthetics compared with nonobese patients for a number of reasons:

The primary objective of our study was to determine the ED_{50} and ED_{95} in our morbidly obese population. Comparisons of ED_{50} and ED_{95} values of these morbidly obese patients with those of a nonobese population previously studied by our group were only a secondary analysis and study endpoint. In addition, using historical controls from a number of years ago presents important limitations, as we mentioned in our manuscript. Historical controls are associated with many confounders and biases that may affect group comparisons. Both studies contained small study populations (42 morbidly obese and 42 nonobese patients); therefore, a few individuals can have a greater influence on the overall population dose-response curve than preferable. In addition, although we followed a methodology similar to that of the previous study, it was not identical (*e.g.*, 5–11 mg doses administered in the obese population were compared with 6–12 mg doses in nonobese patients).

While we acknowledge Dr. Pace's analysis of a rightward shift in the dose-response curves of the morbidly obese population compared with a nonobese population, the limitations noted above remain. We therefore do not want to go as far as recommending increasing the intrathecal local anesthetic dose in the morbidly obese patients undergoing cesarean delivery. It is worth noting that no patient in our study received the calculated ED_{95} of 14.3 ± 0.9 mg, and we can therefore not comment on its safety. In contrast to expert advice, our study does suggest that the intrathecal bupivacaine dose should not be reduced for obese patients. Our findings also imply that morbidly obese patients are not well-suited to a single-shot spinal technique. More variable responses to intrathecal dosing and longer surgical times indicate that catheter-based techniques are more appropriate. Our study also highlights that initial satisfactory sensory block to pinprick following small intrathecal doses does not ensure adequate intraoperative anesthesia for the duration of the surgical procedure.

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Observations on the Study of Second Gas Effects

To the Editor:

This recent excellent study on the second gas effect was extremely interesting.[1] I would like to ask several questions to further appreciation of the findings presented. Which ventilator type, mode, inspiratory/expiratory time settings, and fresh gas flows intraoperatively (*vs.* 9 l/m during emergence) were used? Some ventilator models self-correct to end expiratory volumes, whereas others (*i.e.*, volume-controlled Narcomed II [Draeger Medical Inc., Telford, PA]) deliver fixed inspiratory volumes, which further affect expired volumes by changes in fresh gas flow as well as the additional significant N_2O egress volumes. Increasing fresh gas flow from 3 l/m to 9 l/m to fixed ventilator inspiratory volumes using 1:2 inspiratory/expiratory ratios can affect up to 200 *versus* 2,000 ml tidal *versus* minute volume changes, respectively. Although reported minute volumes are described as nonsignificantly different in N_2O *versus* air/oxygen control group *via* ml × min × kg (ml/Kg/min???) in your table 1, the calculated respective 6,605 *versus* 5,749 absolute ml/min is 15% difference (was this significant statistically?), which would be even