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Cognitive Outcomes after Infant Spinal Anesthesia: The Other Side of the Coin

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Few issues in pediatric anesthesia have garnered more attention from the research, clinical, and regulatory communities than the possibility that adverse neurocognitive outcomes result from the administration of general anesthetics to young children. While preclinical studies are nearly uniformly positive, data from human studies are far less consistent. Virtually all human studies conducted thus far have been retrospective, rely on a database not designed to study the outcome of interest, and exhibit profound differences with regard to the specific outcome measured.^{1,2} Criticisms of these studies are numerous, appropriate, and frequently center on two fundamental issues: confounding secondary to comorbidity and the coincidence of anesthetic exposure with a surgical procedure. In essence, do these studies truly measure the effects of anesthesia or are they simply studies of cognitive outcome among those needing surgery or the effect of the surgical procedure itself?

Several studies from the Mayo Clinic, Columbia University Medical Center, and elsewhere have attempted to control for co-morbidity.^{3–6} These studies suggest, but by no means prove, that medical comorbidity is inadequate as an explanation for the decrement in cognitive performance observed especially in those with multiple anesthetic and surgical

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exposures. If one accepts that co-morbidity can be accounted for through adjustment or matching, the major known confounder remaining is that attributed to the effects of the surgical procedure.

Like opposite sides of the same coin, the effects of anesthetic and surgical exposure are extremely difficult to separate, particularly in a retrospective study. However, in this month's issue of *Anesthesia & Analgesia*, Williams and colleagues have attempted to do just that and in so doing provide insight into one of the primary criticisms of the extant clinical literature.⁷

The Williams et al. study is the first to specifically examine whether a surgical procedure devoid of exposure to general anesthetics would produce the same cognitive effects as those procedures with general anesthetic exposure. The fundamental assumption of the study is, of course, that exposure to local anesthetics placed in the subarachnoid space would not be associated with subsequent neurodevelopmental injury. This assumption, while supported by preclinical data, has not been rigorously studied in the clinical setting and, as such, is plausible but still conjectural.^{8,9}

In their study, Williams and colleagues sought to isolate the effect of surgery from that of general anesthesia by retrospectively comparing the cognitive outcomes of a cohort of infants who had undergone a brief surgical procedure under spinal anesthesia to normative data for the population of Vermont.⁷ The authors queried the Vermont Infant Spinal Registry database, a unique database composed of children who have undergone surgery by spinal anesthesia since 1979. They found 265 children who had received a solitary exposure to spinal anesthesia for one of three surgical procedures: circumcision, pyloromyotomy, or inguinal herniorrhaphy. These children were matched by age, gender, need for a free/reduced school lunch, and year of examination to unexposed children. Borrowing from the recent study by Block et al., the primary outcome was children with very poor academic achievement (VPAA) defined as scoring below the 5th percentile on a group-administered test of achievement.¹⁰ Reading and math scores, as well as need for an individualized educational program, were evaluated as secondary outcomes. They found that children who had received a single exposure to spinal anesthetics during infancy did not differ significantly to unexposed children with regard to VPAA or need for an individualized educational program. Furthermore, standardized test scores were not negatively correlated with duration of surgery. These findings are in direct contrast to those of Block et al., who found in a similarly designed study of exposure to general anesthetics and surgery an increase in VPAA among those exposed as compared to the population at large.¹⁰ From these data Williams and colleagues concluded that the provision of a single spinal anesthetic was not associated with VPAA and that there was no link between the duration of surgery and academic achievement scores.

The obvious implications of the Williams et al. study are that the observed decrement in performance associated with surgical/anesthetic in prior studies cannot be attributed to the surgery but must result from some other factor. Whether that factor is *N*-methyl-D-aspartate receptor and/or γ -aminobutyric acid receptor active agents that comprise virtually all of our anesthetics remains to be determined. Interestingly, as the Williams et al. and Block et al.

studies together loosely resemble a retrospective version of the GAS (General Anesthesia Spinal Anesthesia) study now underway at several United States and international sites, it is tempting to ponder whether these two studies may foreshadow the results of the GAS study...or not. Indeed, while past editorials have cautioned against equating the relationship between general anesthesia and neurologic outcome as causal,² we find ourselves stressing the opposite side of that coin. While Williams and colleagues did not find significant differences between exposed and unexposed children in their study, we caution against concluding that no difference exists. Studies evaluating single anesthetic/surgical exposures as well as those utilizing group-administered tests of achievement as outcome measures have commonly not shown differences in cognitive outcome in exposed children.^{5,6,11–14} The absence of a positive control (such as a group with exposure to general anesthesia) and the observation that the upper-bound for the confidence intervals for VPPA for math and reading in this study (2.68 and 2.1, respectively) are similar to that reported from larger, positive studies,² suggest that the current study lacked the statistical power necessary to discriminate between exposed and unexposed children unless their cognitive differences were relatively large, likely larger than that reported in prior studies that evaluated children with multiple exposures to general anesthesia. As such, one must strongly caution against using the current data as justification for prematurely flipping the general/regional anesthetic coin in favor of regional techniques, the risks of which were not quantified in this study. Therefore, the critical difference between this study, Block et al.'s and other retrospective studies and the GAS study is that the GAS study is the only truly randomized controlled trial underway to evaluate the cognitive effects of general and spinal anesthesia. That study will for the most part be free of the confounding and bias that plagues this study and all others published to date.

The authors are to be commended for their contribution in assessing whether a surgical procedure may contribute to adverse cognitive outcome later in childhood. The PANDA (Columbia) and MASK (Mayo) studies, although not randomized controlled trials, will augment the insights gained from GAS. None however will report definitive outcomes for at least 2 or 3 years. In the meantime, we must content ourselves with very important but severely limited studies such as that published by Williams et al. in this issue of *Anesthesia & Analgesia*.⁷ He and his colleagues have provided us with a glimpse at the previously unseen flip side of the anesthesia-surgery coin.

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