
Anesthesia and Cognitive Performance in Children: No Evidence for a Causal Relationship. Are The Conclusions Justified By The Data?

Response to Bartels et al., 2009

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We have read with great interest the paper authored by Bartels et. al. (2009) and appreciate the opportunity to comment. We recognize and applaud the efforts of the authors to provide additional insight into what we believe to be among the most pressing issues facing the anesthetic care of children around the world. As was discussed extensively in our recent publication (Wilder et al., 2009), we share the authors concern that any association between early exposure to anesthetic agents and the subsequent development of learning disabilities is potentially related to comorbidity rather than anesthetic exposure per se. Nonetheless, we believe the author's conclusion that '...there is no evidence for a causal relationship between anesthesia administration and later learning-related outcomes in this sample' should be qualified due to limitations of the study design and the data.

As pointed out by the authors, in our study (Wilder et al., 2009) we failed to demonstrate an increased risk for learning disability among those with a single exposure to anesthesia prior to their fourth birthday. An effect was observed primarily in children undergoing repeated anesthetics and when total duration of exposure to anesthesia was evaluated as the potential risk factor. In the study by Bartels the authors provide no information as to the number or duration of anesthetic exposure for any of the groups. The majority of exposed children in our study had a single exposure and the absence of effect among these children obscured the clear effect seen in the much smaller group that received multiple exposures. Consequently, it is not surprising that the Bartels study was negative. If an analysis of those in the Bartels cohort that received multiple anesthetics were possi-

ble, the authors may have observed an effect similar to the effect observed by Wilder.

The use of a twin study allows one to reduce or eliminate the effects of genetics on the outcome of interest but does not, as stated by the authors, 'provide a direct test of whether the environmental exposure was associated with outcome'; in this case, to isolate anesthesia as 'the' environmental exposure that is or may be responsible. Clearly a child that is injured and requires surgery and anesthesia may be genetically identical to his or her sibling but have physical and psychological ramifications from that injury that may predispose them to learning disabilities later in life. The child with an injury or other health problem clearly will have environmental (parenting, school, sibling, peer) influences that may contribute to the risk of learning disability separate from the potential effects of anesthetic exposure. Although it has been demonstrated that many common surgical indications in children may have a genetic component, most common procedures such as myringotomy and tonsillectomy are likely not genetically determined but rather genetically influenced. Alternatively, if as stated by the authors, there is a genetic component to the most common surgical procedures performed in children (myringotomy and tonsillectomy), then within the group discordant for these procedures, those not exposed (not undergoing the procedure) may in fact be at greater risk for subsequent learning disability as they may have persistent hearing loss or untreated obstructive sleep apnea; both of which

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may be associated with problems in learning and behavior. Thus the twin study design, like every other study design, has its weaknesses as applied to this question.

The twin registry on which the study is based was established by response to mailed questionnaires. The authors do not report the response rate for any of the several questionnaires upon which the data is dependent, a potential source of bias. It is also difficult to discern from the manuscript how many discordant twin pairs were identified and how many of these had information available for the endpoints of interest (EA and CP). In Table 2, there are 4 columns of data but the column headings are repeated; presumably the first 2 columns are for males and the second 2 columns are for females. If that is the case, then for exposure to anesthesia under the age of 3 there should be a total of 130 discordant twin pairs (71 male, 59 female). However, in Table 3 it appears that EA is only available for 110 of these discordant pairs (61 M, 49 F) and CP information is only available for 56 discordant pairs (29 M, 27 F). This would indicate that CP is missing for more than 50% of the discordant pairs. For the concordant pairs (whose data are summarized in Table 4 and the figures) there is no information provided that allows the reader to determine how many of the pairs had data available for EA or CP. The small number of discordant twin pairs used in the analysis, due to missing data and the relatively few patients who required anesthesia in this cohort, limit the power of this study to detect differences or generate definitive conclusions.

Finally, the use of group administered tests of achievement clearly limits the ability to discriminate those with learning disability from those without. In the study by Wilder all children defined as having a learning disability received that label based on the results of individually administered tests of achievement, a more robust method of evaluating achievement.

Clearly, the use of twin studies has great potential to add to the growing body of knowledge surrounding the issue of anesthetic neurotoxicity in children. This is a difficult issue to study, as it is impossible to perform a controlled trial randomizing children to receive anesthesia (without surgery) or not. The study by Bartels and her colleagues represents an important contribution. Like our study (and every other study), there are important limitations to the methods employed, and we suggest caution in the interpretation of these results, a caution that we tried to communicate in our own work.

References

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