

DR BISHR HAYDAR (Orcid ID : 0000-0003-2709-189X)

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TITLE PAGE

Title: Judging Causal Associations in Observational Research on Caudal Anesthesia and Hypospadias Repair

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Author:

Bishr Haydar

Department of Anesthesiology

Section of Pediatric Anesthesia

University of Michigan, Ann Arbor, United States of America

Corresponding Author:

Dr. B Haydar

Department of Anesthesiology

Section of Pediatric Anesthesia

University of Michigan

4-911 Mott Hospital

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1540 E Hospital Dr, SPC 4245  
Ann Arbor, Michigan 48109-4245  
United States of America  
Email: [bhaydar@med.umich.edu](mailto:bhaydar@med.umich.edu)

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Conflict of Interest: I am a co-investigator on Dr. Polaner's multicenter prospective randomized controlled trial on this subject.

Correspondence: Main Text:

To the editor,

I was pleased to see Dr. Polaner et al.'s editorial<sup>1</sup> accompanying Dr. Taicher et al.'s study<sup>2</sup>. Using a classic paper on bias in observational research<sup>3</sup> as a guide, Dr. Polaner's conclusions can be pushed further. Dr. Taicher's study may lack internal validity due to unequal administration of caudal anesthesia (selection bias, as they described<sup>2</sup>) and the possible confounding described by Dr. Polaner. When contrasting results from these retrospective studies, selection bias will vary by local practice. These and other limitations of observational research can be enumerated by Hill's criteria for judging causal associations in observational research<sup>3</sup>. While the temporal sequence between caudal anesthesia and fistula is appropriate and occasionally the effect size is large, as in Dr. Taicher's study, the other Hill's criteria cast

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serious doubt as to whether this association signifies causation. Namely, the association between fistula and caudal anesthesia is inconsistent between studies, is not specific, is biologically implausible, is inconsistent with other known effects of neuraxial anesthesia, has no meaningful analogy to other conditions and there are no randomized controlled trials supporting this relationship. It may therefore be prudent to dismiss Dr. Taicher's findings as likely spurious, due in large part to their stated selection bias. This association may merely represent an indirect effect due to confounding, where caudal anesthesia reflects higher surgical complexity and is an "innocent bystander", though this is far from clear.

Additional data and analysis from Dr. Taicher's group might provide some clarity. Analysis of their caudal administration by surgical experience, hypospadias severity and surgical duration may identify trends in their reported selection bias. The existing regression should be studied for collinearity which may have falsely inflated the odds ratio. In addition, a new multivariate regression using distal hypospadias patients alone, potentially with surgical duration and cumulative surgeon experience as continuous rather than binary variables may better address potential confounding. While this new regression will undoubtedly be underpowered, comparing the odds ratios between regressions may suggest what is driving these results. Our study's multivariate regression showed a trend toward a negative association between caudal anesthesia and fistula<sup>4</sup> in distal hypospadias while others showed harm or a trend towards harm<sup>2</sup>. These analyses should help, as would a more plausible mechanism with specific and supportive evidence.

Disclosure: Dr. Haydar is a co-investigator on Dr. Polaner's multicenter prospective randomized controlled trial on this subject.

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