

9.2 A. Circumcision Pain

You have heard that newborn rodents exposed to pain have long-term alterations in pain perception, and you are wondering whether the same thing happens in human newborns. You have access to measurements of apparent newborn pain obtained as part of a randomized trial of anesthesia for newborn boys undergoing circumcision. (The pain measurements are things like change in heart rate, intensity and duration of crying, levels of stress hormones, etc.) The study found far fewer signs of pain in those randomized to anesthesia for their circumcision than in the controls (who got nothing-ouch!). These same infants, as well as uncircumcised boys from the same hospital are now to be videotaped as they receive their 4- and 6-month vaccinations; apparent pain from the injection will be rated by observers of the video recordings who will be blinded to perinatal events.

You plan to study the duration and intensity of crying after immunizations -- this will be your outcome variable. What *predictor* variable would give you the greatest strength of causal inference to address the question of whether perinatal pain in newborns *causes* an increase in future pain perceptions? Explain.

The predictor that will give the greatest strength of causal inference in *treatment assignment* in the randomized trial of anesthesia. Thus, you will compare the entire group allocated to anesthesia with the entire control group. Although the predictor of interest is pain in the newborn period, and you have measurements of that, if you use the pain measurements as your predictor variable the results could be confounded by pre-existing differences in perception of pain. Because treatment allocation is an imperfect predictor of pain in the perinatal period, your effect size estimate will be attenuated and your power will be reduced but it is worth it because this intention to treat analysis will give you much greater strength of causal inference. In fact, this study has been done, with significant results[2]!

The authors also could also could have done an instrumental variable analysis in which the result of the ITT analysis and the effect of treatment allocation on apparent pain during the procedure are combined to answer your actual research question, which was to estimate the causal effect of pain from circumcision on pain during immunizations 4 to 6 months later.

Note it is also of interest to compare the groups above to uncircumcised boys, but the strength of causal inference would be lower because factors associated with circumcision other than pain (e.g., racial or ethnic background) could be responsible for subsequent differences (confounding or selection bias).

1. Stang HJ, Snellman LW. Circumcision practice patterns in the United States. *Pediatrics*. 1998;101(6):E5.
2. Taddio A, Katz J, Ilersich AL, Koren G. Effect of neonatal circumcision on pain response during subsequent routine vaccination. *Lancet*. 1997;349(9052):599-603.