JAMA Guide to Statistics and Methods

# Bayesian Analysis: Using Prior Information to Interpret the Results of Clinical Trials

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**In this issue of *JAMA***, Laptook et al[1] report the results of a clinical trial investigating the effect of hypothermia administered between 6 and 24 hours after birth on death and disability from hypoxic-ischemic encephalopathy (HIE). Hypothermia is beneficial for HIE when initiated within 6 hours of birth but administering hypothermia that soon after birth is impractical.[2] The study by Laptook et al[1] addressed the utility of inducing hypothermia 6 or more hours after birth because this is a more realistic time window given the logistics of providing this therapy. Performing this study was difficult because of the limited number of infants expected to be enrolled. To overcome this limitation, the investigators used a Bayesian analysis of the treatment effect to ensure that a clinically useful result would be obtained even if traditional approaches for defining statistical significance were impractical. The Bayesian approach allows for the integration or updating of prior information with newly obtained data to yield a final quantitative summary of the information. Laptook et al[1] considered several options for the representation of prior information—termed neutral, skeptical, and optimistic priors—generating different final summaries of the evidence.

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## Prior Information

### What Is Prior Information?

Prior information is the evidence or beliefs about something that exist prior to or independently of the data to be analyzed. The mathematical representation of prior information (eg, of beliefs regarding the likely efficacy of hypothermia for HIE 6-24 hours after birth) must summarize both the known information and the remaining uncertainty. Some prior information is quite strong, such as data from many similar patients, and might have little remaining uncertainty or it can be weak or uninformative with substantial uncertainty.

Clinicians routinely interpret the results of a new study in the context of prior work. Are the new results consistent? How can new information be synthesized with the old? Often this synthesis is done by clinicians when they consider the totality of evidence used to treat patients or interpret research studies.

Prior information may be formally incorporated in trial analysis using Bayes theorem, which provides a mechanism for synthesizing information from multiple sources.[3,4] Clear specification of the prior information used and assumptions made need to be reported in the article or appendix to allow transparency in the analysis and reporting of outcomes.

### Why Is Prior Information Important?

When large quantities of patient outcome data are available, traditional non-Bayesian (frequentist) and Bayesian approaches for quantifying observed treatment effects will yield similar results because the contribution of the observed data will outweigh that of the prior information. This is not the case for evaluating HIE treatments because very few neonates are affected. Despite a large research network, Laptook et al[1] were only able to enroll 168 eligible newborns in 8 years.

Prior information facilitates more efficient study design, allowing stronger, more definitive conclusions without requiring additional patients to be included in the study or analysis. As such, the use of prior information is particularly relevant and important for the study of rare diseases where patient resources are limited.

Prior information can take a number of forms. For example, for binary outcomes, the knowledge that an adverse outcome occurs in 15% to 40% of cases is worth the equivalent of having to enroll 30 or more patients into the trial (depending on the certainty attached to this knowledge). Another form of prior information could be beliefs held regarding the effect of a delay beyond 6 hours in instituting therapeutic hypothermia, ie, that the treatment effect at 7 hours is similar to that at 6 hours and the longer it takes to begin treatment, the less effective the treatment is likely to be.

## Limitations of Prior Information

Prior information is a form of assumption. As with any assumption, incorrect prior information can result in invalid or misleading conclusions. For instance, if prior information used the assumption that hypothermia becomes less effective with increasing postnatal age and, in fact, waiting until 12 to 24 hours was associated with the greatest benefit, the resulting inferences would likely be incompatible with the data, less accurate, or biased. If the statistical model uses prior information derived from neonates 0 to 6 hours old in evaluating the treatment effect in neonates 6 to 24 hours of age, and is based on the assumption that the patients respond similarly, the results may be biased or less accurate if the 2 age groups actually respond differently to treatment.

These assumptions can be assessed. Just as the modeling assumptions made in logistic regression can be checked through goodness-of-fit tests,[5] there are tests that can be used to verify agreement between prior and current data. More importantly, some methods for incorporating prior information can explicitly adjust to conflict between the prior and the data, decreasing the reliance on prior information when the new data appear to be inconsistent with the proposed prior information.[6]

## How Was Prior Information Used?

Laptook et al[1] incorporated prior information by allowing for the outcome to vary across time windows of 6 to 12 hours and 12 to 24 hours and prespecifying 3 separate prior distributions on the overall treatment effect (Description of Bayesian Analyses and Implementation Details section of the eAppendix in Supplement 2). The neutral prior assumes that the treatment effect diminishes completely after 6 hours, the enthusiastic prior assumes that effect does not

diminish at all after 6 hours, and the skeptical prior assumes that the treatment is detrimental after 6 hours. Primary results are presented based on the neutral prior and, as such, the authors' approach is transparent and easily interpretable. The authors found a 76% probability of benefit with the neutral prior, a 90% probability of benefit with the enthusiastic prior, and a 73% probability of benefit with the skeptical prior.[1]

An alternative to this approach might include specifying a model that relates postnatal age at the start of therapeutic hypothermia to the magnitude of the treatment effect, assuming that the effect does not increase over time. This model would explicitly account for a possible decrease in treatment benefit with increasing age at initiation, while still allowing the effect at each age to inform the effects at other ages. Additionally, this model could be heavily informed or anchored in the 0 to 6-hour range using data from previous studies.[2] With this anchor, inferences would be improved across the range of 6 to 24 hours, with a particular increase in precision for the time intervals closer to 6 hours. This may have allowed more definitive conclusions to be drawn from the same set of data.

## How Should the Trial Results Be Interpreted in Light of the Prior Information?

Laptook et al[1] used a prespecified Bayesian analysis, using prior information, to allow quantitatively rigorous conclusions to be drawn regarding the probability that therapeutic hypothermia is effective 6 to 24 hours after birth in neonates with HIE. Conclusions of the analysis were given as probabilities that benefit exists. For example, the statement that there is "a 76% probability of any reduction in death or disability, and a 64% probability of at least 2% less death or disability" are easily understood by clinicians and can be used to inform clinical care. The use of several options for prior information allows clinicians with different perspectives to have the data interpreted over a range of prior beliefs.


### ARTICLE INFORMATION

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