HeRO Monitoring: Does It Lead to Unnecessary Testing and Treatment?

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Introduction

Evidence continues to build that HeRO monitoring improves outcomes of premature infants, including all-cause NICU mortality, (1) mortality after infection, (2) mortality at 18-22 months, (3) mortality-or-severe-cerebral-palsy at 18-22 months, (3) and NICU length of stay. (4) Yet some neonatologists find themselves hesitant to adopt HeRO monitoring for fear that it may lead to higher rates of testing and antibiotic usage. Here, we examine whether those fears are well-founded and the hesitancy justified.

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Background

The HeRO Score (aka HRC Index) is calculated every hour and identifies abnormal heart rate patterns of reduced variability and transient decelerations that are associated with cytokines (5-7) and often precede sepsis (8-18) UTI, (19) NEC, (20,21), meningitis, (19) neuro trauma, (22-25) respiratory decompensation, (26) extubation readiness, (27,28) and death. (23,25, 29-31) HeRO monitoring has been utilized as an early warning system, (32) and Moorman et al. hypothesized that it may lead to early diagnoses, earlier interventions, and improved outcomes. In the largest RCT ever published among premature neonates, 3003 VLBW patients at nine hospitals were randomized to either receive standard of care monitoring, or standard of care monitoring plus HeRO. (1)

While mortality and other outcomes described above were statistically significantly improved for those patients randomized to the HeRO-display group, Moorman et al. described non-significant trends toward increased testing and antibiotics: “Infants whose HRC monitoring results were displayed had 10% more blood cultures drawn for the suspicion of sepsis (1.8 per month compared with 1.6, $P = .05$) and 5% more days on antibiotics (15.7 compared with 15.0, $P = .31$, Table).” (1)

Mortality, however, is a competing outcome with both cultures drawn and antibiotic days, and properly accounting for the in-

crease in survival when assessing other outcomes can change the result. Indeed, we have previously reported that length of stay among this cohort was longer among the HeRO-display group when failing to account for the competing outcome of mortality, but shorter when so doing. (4)

We hypothesized that metrics of blood culture rates and antibiotic usage would favor HeRO-monitoring after adjusting for the competing outcome of mortality.

Methods

We calculated the following composite metrics for each patient: number of days alive without antibiotics, number of days alive without a blood culture, and number of days alive without a negative blood culture for suspicion of sepsis. Event days were assessed discretely—that is, if there were any antibiotics/cultures on a particular day of life, that entire day was assessed as having antibiotics/cultures. The mean values of each metric were calculated for the HeRO display group and the control group. The difference in distributions was assessed using a two-tailed t-test, with statistical significance set at $P < 0.05$. Data were queried from the SQL database (Microsoft Corporation) and analyzed using R (R Core Team). (33) Data were analyzed from birth through 120 days of life (a departure from the report of the RCT, where data were analyzed from randomization (mean 3.8 days after birth) to 120 days post randomization (1)). We performed a sensitivity analysis to determine whether analyzing the 120 days beginning at randomization changed the results.

“When comparing the number of days alive and without a negative blood culture for suspicion of sepsis, the benefit of HeRO-monitoring was significant (110.5 days versus 108.4, $P=0.048$).”

Results

Baseline demographics of the patients enrolled in the RCT have been described in previous reports and were not statistically significantly different between the two arms (1).

The results of this analysis are presented in Table 1. Patients randomized to HeRO-display had non-significant trends toward more days alive and without antibiotics in their first 120 days than controls (96.1 versus 94.5, $P=0.187$) and more days alive without a blood culture in their first 120 days (109.0 versus 107.1, $P=0.071$).

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Outcome	Control	HeRO	Delta	P
Component Outcomes				
Days alive	110.2	112.4	2.2	0.029
Days with antibiotics	15.7	16.3	0.6	0.350
Days with a blood culture	3.06	3.43	0.37	0.010
Days with a negative blood culture for suspicion of sepsis	1.74	1.96	0.22	0.014
Composite Outcomes				
Days alive and without antibiotics	94.5	96.1	1.6	0.187
Days alive and without a blood culture	107.1	109.0	1.9	0.071
Days alive and without a negative blood culture for suspicion of sepsis	108.4	110.5	2.1	0.048

Table 1. Mean days alive, days with an event, and days alive without an event for Control (standard of care cardio-respiratory monitoring) versus HeRO (standard of care cardio-respiratory monitoring plus HeRO).

Figure 1. Days alive without antibiotics

Figure 2. Days alive without blood culture

When comparing the number of days alive and without a negative blood culture for suspicion of sepsis, the benefit of HeRO-monitoring was significant (110.5 days versus 108.4, $P=0.048$). Results were similar and statistical significance was not affected when we analyzed 120 days beginning at randomization rather than birth.

In Figures 1, 2, and 3, we present curves comparing the difference between the Control and HeRO-display arms of the RCT in each of the three composite outcomes. The x-axis represents the number of days a patient was alive and without antibiotics, alive without a blood culture, or alive without a negative blood culture drawn for suspicion of sepsis, respectively, during their first 120 days of life. At a particular point along the x-axis, the y-axis represents the fraction of patients that had at least that number of days alive and without event. These plots can be interpreted much like Kaplan-Meier survival curves, with the provisos that the outcome plotted is a composite of death and/or event, and that the data are right-censored at 120 days. By definition, all trends originate at 1.0 at 0 days, separate based on differences in the measured outcome, and converge to 0.0 at 120 days.

Discussion

Concern regarding over-testing and over-utilization of antimicrobials among neonatologists has grown in recent years and may have led many to hesitate in adopting HeRO monitoring. In this

analysis, we attempt to both (a) assess over-testing and over-treatment of VLBW neonates in the context of the competing outcome of improved mortality, and (b) contextualize the relative costs of death versus over-testing/over-treatment. Toward both ends, we tested the composite outcomes of days alive and without antibiotics, days alive and without blood culture, and days alive and without unnecessary blood culture (i.e., a negative blood culture that was drawn for suspicion of sepsis).

All three metrics trended in favor of HeRO monitoring, and one of the three was statistically significant. Arguably, the statistical equivalence demonstrated by the other two metrics also favors the adoption of HeRO monitoring, as they indicate that there is no increase in death-or-testing and death-or-treatment.

Moorman et al. reported a number needed to treat of 48 patients to save a life with HeRO monitoring. (1) Here we report that HeRO-monitored patients had 0.22 more days with an unnecessary blood culture (defined as a negative blood culture drawn for suspicion of sepsis) and an estimate of 0.6 additional days of antibiotics per patient. Among VLBWs in a NICU, the price of saving one life with HeRO monitoring is 10.6 unnecessary blood cultures (48×0.22) and 29 days of antibiotics (48×0.6). Importantly, all of the additional days of antibiotics went to septic patients per Fairchild et al, (2) Table 1, where the authors reported non-septic patients had identical days of antibiotics (7.6 days for HeRO versus 7.6 for

Figure 3. Days alive without unnecessary blood culture

controls), while septic patients had 32.1 days with HeRO versus 29.0 for controls ($P=0.047$).

Furthermore, the concern that the excess testing or excess therapy will have later consequences is unwarranted because the number needed to treat of 48 is based on the all-cause mortality improvement—the net effect of HeRO monitoring on NICU mortality where any possible consequences of excess testing/treatment were built into the calculation. And among the ELBW patients with a neurodevelopmental follow-up, Schelonka et al. reported that the mortality benefit of HeRO monitoring persisted at 18-22 months³.

A possible weakness of analyzing days alive and without event (antibiotics, a blood culture, or an unnecessary blood culture) is

that it treats a day with an event as equivalent to a day deceased. Obviously, this overestimates the relative cost of antibiotics and cultures versus death.

“Nevertheless, when examining those concerns after controlling for, and in the context of, the mortality improvement associated with HeRO monitoring, hesitancy in adopting the technology is not justified.”

But this weakness is also a strength because it paints a stark contrast. It is axiomatic that a day with antibiotics or an unnecessary culture is better than death. If no parent would ever choose to exchange the death of their child to avoid an unnecessary blood culture or course of antibiotics, why would some neonatologists, who serve as advocates for their patients, choose to do so?

Conclusion

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Previous reports have indicated trends toward increased testing and treatment associated with HeRO monitoring, so clinician concern is well-founded. Nevertheless, when examining those concerns after controlling for, and in the context of, the mortality improvement associated with HeRO monitoring, hesitancy in adopting the technology is not justified.

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- Disclosure: Mr. King is Chief Executive Officer of Medical Predictive Science Corporation, where he has developed and coded real-time implementations of algorithms to predict infection in neonates based on physiological monitoring data, obtained FDA and other regulatory approvals, developed an FDA compliant quality system and sold devices to customers throughout the world. Mr. King is employed by MPSC, manufacturer of HeRO.

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