NATIONAL PEDIATRIC CARDIOLOGY
Quality Improvement Collaborative

Research Explained

Research Explained: The Association between Digoxin Use and Reduced Interstage Mortality

An Evaluation of Two National Databases

Background of the Study Questions and Digoxin

When the National Pediatric Cardiology Quality Improvement Collaborative (NPC-QIC) was formed in 2006, it had an initial goal to reduce interstage mortality for patients with Hypoplastic Left Heart Syndrome (HLHS) and other similar conditions. This was done by putting into place various quality improvement projects aimed at improving and standardizing care as well as evaluting the data stored in the database to examine any factors associated with interstage mortality.

During one of these evaluations there was some early evidence that the use of digoxin was associated with lower mortality during the interstage period. It was an incredibly preliminary finding but one that became worth studying in more detail. Digoxin is a very old medication, initially described in 1780 as it is an extract of the foxglove plant. It has multiple types of action on the heart including helping to control abnormal heart rhythms, regulating the nervous system of the heart and some ability to help the heart squeeze. Though its use was widespread for a long time, it fell out of favor quite some time ago when overdosing it was found to be very dangerous and it did not seem to overly affect how well kids did with a when they were taking the medication. Thus, many cardiologists stopped using it regularly for this reason.

How was the First Study Done and What it Demonstrated

Attempting to study this further, Brown and other colleagues from the NPC-QIC looked at all infants in the database to study the "digoxin effect." They needed to first eliminate patients who had a history of an abnormal heart rhythm because of the challenge in studying that group. Thus, they initially found that the interstage mortality rate was 1.7% for those patients who were on digoxin and 9.9% for those patients not on digoxin.

To look at this in a more sophisticated way, the researchers needed to control for other variables associated with interstage mortality. The reason to do this is to make sure that the lower mortality rate was actually associated with digoxin use and not because patients that were on digoxin also were

more likely to be lower risk for interstage mortality based on other known factors. Those other factors included things like how the infant was fed at discharge, what type of Norwood was performed, size of the surgical program, and genetic abnormalities, etc. When doing the best to control for these factors and others also known to affect interstage mortality, patients on digoxin were 8 times less likely to have interstage mortality than those who were not on digoxin.

How was the Second Study Done and What it Demonstrated

Bouncing off this idea, Oster and his research team performed a similar analysis but on a different group of patients. His patients with HLHS came from the Single Ventricle Reconstruction Trial. This was a study done between 2005 and 2008 (before the NPC-QIC had really gained steam) that attempted to see what type of Norwood operation was the best.

This group set up their study in a very similar way though added the element of "time" into their analysis. This means that they realized that patients were probably at higher risk of interstage mortality closer to the time of their Norwood rather than later. They also did their best to control for many of the same factors that Brown and his team did for the same reasons as above.

They found that the interstage mortality rate was 2.9% for those patients who were on digoxin and 12.3% for those patients not on digoxin, similar to Brown's findings but in a different group of patients. After controlling for the other factors, patients on digoxin were 3.5 times less likely to have interstage mortality than those who were not on digoxin. They secondarily found that there was no difference in complications between the group that was on digoxin and the group that was not, suggesting that the medication was used safely in this population.

The Limitations of Both Studies

1. The research methods that both studies utilized are considered considered retrospective (in the past). This means that you can only come to the conclusion that digoxin use is ***associated with*** the reduced mortality, but you can never really say whether digoxin use ***caused*** the reduction. Both studies did an excellent job of attempting to study this, but it is still very hard to ensure you have really isolated digoxin as the factor leading to the reduced rate
2. We will never know ***why*** patients were prescribed digoxin. Providers were allowed to choose based on their own reasons. Could this mean that there was something about those patients or providers that led to the lower rate as well?
3. We also will never know if the patients were actually taking the digoxin or when it was tarted. We just know that they were prescribed it sometime during the interstage period.

What it all Means

These are two very well designed studies done on two ***different*** patient populations that came to very similar conclusions that digoxin may be protective during the interstage period and is associated with reduced mortality. While it does not mean that we have completely answered the "digoxin question", we clearly have evidence that it ***could be*** beneficial during the interstage period and warrants further investigation going forward.

Through these results, however, we still do not know ***why*** digoxin may have a protective effect and will need to study this in the future, as well.

References:

1. Krikler DM. The foxglove, "The old woman from Shropshire" and William Withering. J Am Coll Cardiol. 1985;5:3A - 9A
2. Brown, et al. Digoxin Use is associated with Reduced Interstage Mortality in Patients with No History of Arrhythmia After Stage 1 Palliation for Single Ventricle Heart Disease. Journal of the American Heart Association. 2016;5:e002376.
3. Oster, et al. Association of Digoxin with Interstage Mortality: Results From the Pediatric Heart Network Single Ventricle Reconstruction Trial Public Use Dataset. Journal of the American Heart Association. 2016;5:e002566.