EIPH RESEARCH UNVEILS POSSIBLE 24-HOUR FUROSEMIDE DOSE

By Dr. Larry Bramlage

Two research projects on Exercise Induced Pulmonary Hemorrhage solicited by The Grayson-Jockey Club Research Foundation and funded in cooperation with The Jockey Club, the AAEP Foundation, Keeneland Association, Oak Tree Racing Association, The Stronach Group, Churchill Downs, Kentucky Downs, New York Racing Association, The Del Mar Thoroughbred Club, Oaklawn Park, and The Thoroughbred Horseman's Association have now appeared in peer-reviewed journals.

Knych HK, Wilson WD, Vale A, et al.

Bayly W, Lopez C, Sides R, et al.

In March 2015, a special call for research on exercise induced pulmonary hemorrhage was issued by The Grayson-Jockey Club Research Foundation. Emphasis was placed on strategies to control EIPH without race-day medication. Two projects were selected. The premise of the research was to look at the post-treatment effect of furosemide (Salix, or Lasix) if it had been given 24 hours before exercise with water intake limited to maintenance water levels (which are known).

One project submitted by the University of California at Davis under the direction of Dr. Heather Knych proposed to take 15 fit Thoroughbreds with no known history of bleeding and assess three treatments head-to-head against each other: saline placebo, furosemide four hours before exercise, and furosemide 24 hours before exercise with limited water access. The horses were paired in five-furlong simulated exercise sessions and assessed for bleeding via endoscopic examination using the conventional 0-4 scoring system and via broncho alveolar lavage (BAL) counting the number of red blood cells (RBC) found in the lung lavage post exercise. The horses trained conventionally at a racetrack, and the exercise sessions were separated by a two-week interval.

The results showed with 24-hour administration the pharmacologic level of furosemide is approximately 1/100th the level of circulating medication when compared to four-hour pre-exercise administration. So, more than 99% of the medication has cleared by 24 hours.

In the horses with no known bleeding history, there was one bleeder. He bled with no treatment, and he bled through both treatments, though the four-hour furosemide treatment reduced his grade of bleeding. There were three endoscopic graders, and blood in the trachea was seen in 11 of the 43 endoscopic exams; on four exams was the blood more than a grade 1 (trace), and three of those four observations were accounted for by the one horse that bled continuously.

On average, there were low levels of RBC's present in the BAL in all horses after exercise, even with no blood visible endoscopically, but the levels were less than 200(l05/ml), even with the bleeding horse included.

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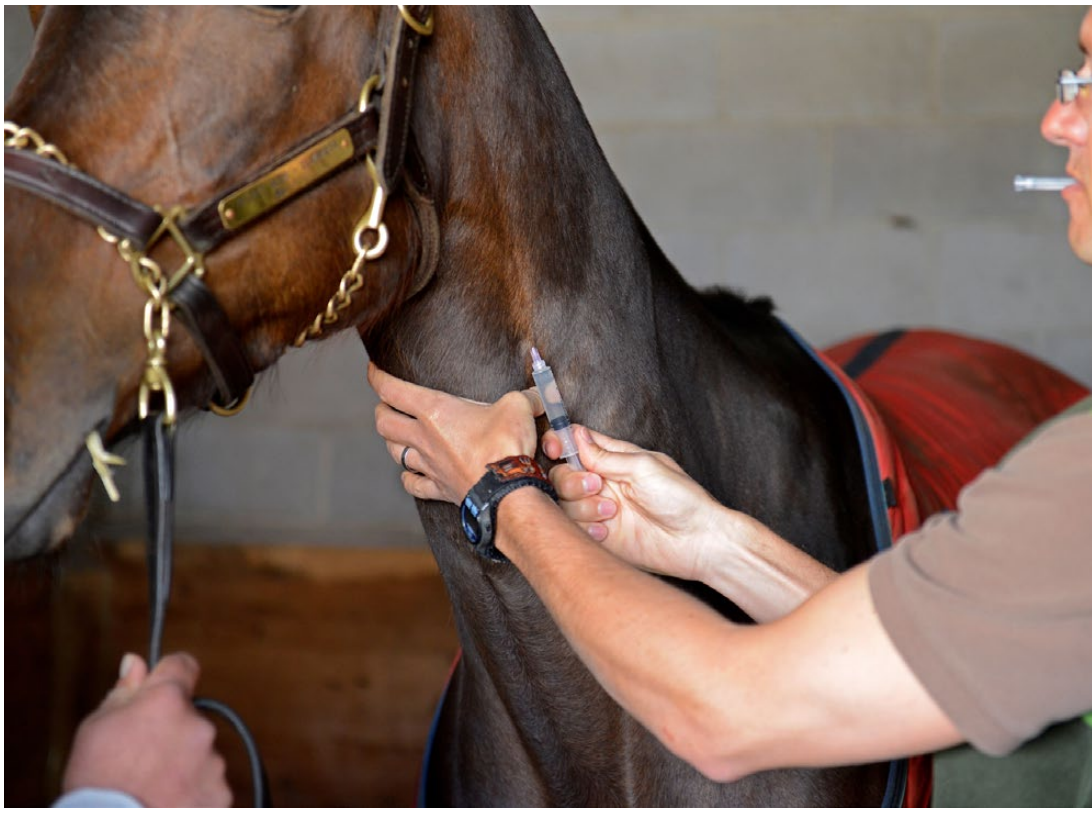

ANNE M. EBERHARDT

A racetrack veterinarian working for the Kentucky Racing Commission injects Salix into a horse on raceday

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So the conclusion from the study was that, though blood was seen on the endoscopic exam of 11 of 43 endoscopic exams, the four-hour furosemide reduced the number of times blood was observed compared to the 24-hour treatment, and the BAL results suggest the 24-hour treatment is not as effective as the four-hour treatment in attenuating the increase in RBC's associated with exercise in these horses with no known history of bleeding.

The second project done at Washington State University under the direction of Dr. Warwick Bayly took seven fit Thoroughbreds that were known to be clinical EIPH patients during racing and looked at seven different treatment protocols.

The target was to assess the efficacy of furosemide at the maximum and minimum dosage administered 24 hours prior to exercise compared to the conventional four-hour treatment prior to exercise. This required seven different maximum exercise sessions from all seven of the horses separated by two weeks of routine training. The seven treatment protocols were designed to separate all the effects of furosemide and the timing of its administration to pinpoint the differences in effect of each treatment component.

The study was a two-phase project: The first segment was to look at the components of treatment with horses performing only on a treadmill, where exercise could be controlled and the horses taken beyond their aerobic capacity (115% of VO2 Max) and exercised to fatigue where they could no longer maintain a constant speed of exercise. Each of the horses was examined with the conventional endoscopic examination and with BAL RBC assessment post-exercise. But because the horses were known "bleeders," the BAL counts compared differences in BAL numbers two days before exercise and BAL numbers post-exercise in addition to absolute RBC numbers to pinpoint further the effect

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of the treatment protocols on the "bleeding" occurring in these horses. Then with the results of these trials the horses were returned to the racetrack, trained for an additional month conventionally, and ran a simulated five-furlong race from the starting gate with all horses receiving the most promising treatment selected by the treadmill trial data and competing against each other in the races.

All seven horses underwent the seven components of the study in a double-blinded, randomized fashion: placebo (saline), conventional (low dose, 250mg, 5ml) furosemide four hours pre-exercise, controlled water access only with no medication (maintenance water access for 24 hours pre-exercise), low dose furosemide (250mg, 5ml) 24 hours pre-exercise with free access to water, high dose furosemide (500mg, 10ml) 24 hours pre-exercise with free access to water, low-dose furosemide with maintenance water access, and high-dose furosemide with maintenance water access.

In the study of horses that were known bleeders (Washington State), the findings were as follows:

Low-dose 24-hour furosemide with controlled water access shows promise as a replacement for the conventional four-hour pre-race treatment for EIPH in horses that are bleeding

No treatment produced a statistically significant difference in the endoscopic bleeding score on the treadmill because all horses bled, and the differences on the 0-4 bleeding scale were not enough to show significant changes.

However, in the BAL's assessment, where the counting range was much larger and more sensitive, the low dose (250mg) furosemide with 24-hour maintenance water was the only treatment that statistically significantly reduced the increase in the number of RBC's in the BAL fluid after exercise. So, it was the treatment that was selected for validation in the simulated races of the six horses, one race with low-dose furosemide and one race with the saline control. The horses were fit after the treadmill exercise, but they were trained an additional month on the racetrack before the simulated race. The races were among six horses going 1,100 meters (5 1/2 furlongs) from the starting gate and were separated by two weeks of training between.

The results after simulated racing produced some interesting changes in results. The difference between the BAL RBC's in the control horses and the treated horses narrowed, dropping the confidence of a treatment effect to 90% from 95%. This is below the traditional 95% significance threshold reached on the treadmill study but is still 90% certainty the low-dose furosemide with controlled water access lowered the BAL RBC's during the simulated races. But, the endoscopic EIPH scores on the racetrack actually changed in the opposite direction; i.e., the bleeding was worse, and the endoscopic bleeding scores became statistically significantly lower with the low-dose furosemide, water-restricted horses when compared to the control exercise values.

In conclusion, it looks like low-dose 24-hour furosemide with controlled water access shows great promise as a replacement treatment for our conventional four-hour pre-race treatment for EIPH in horses that are bleeding. It was less effective in horses that were not known bleeders. BH

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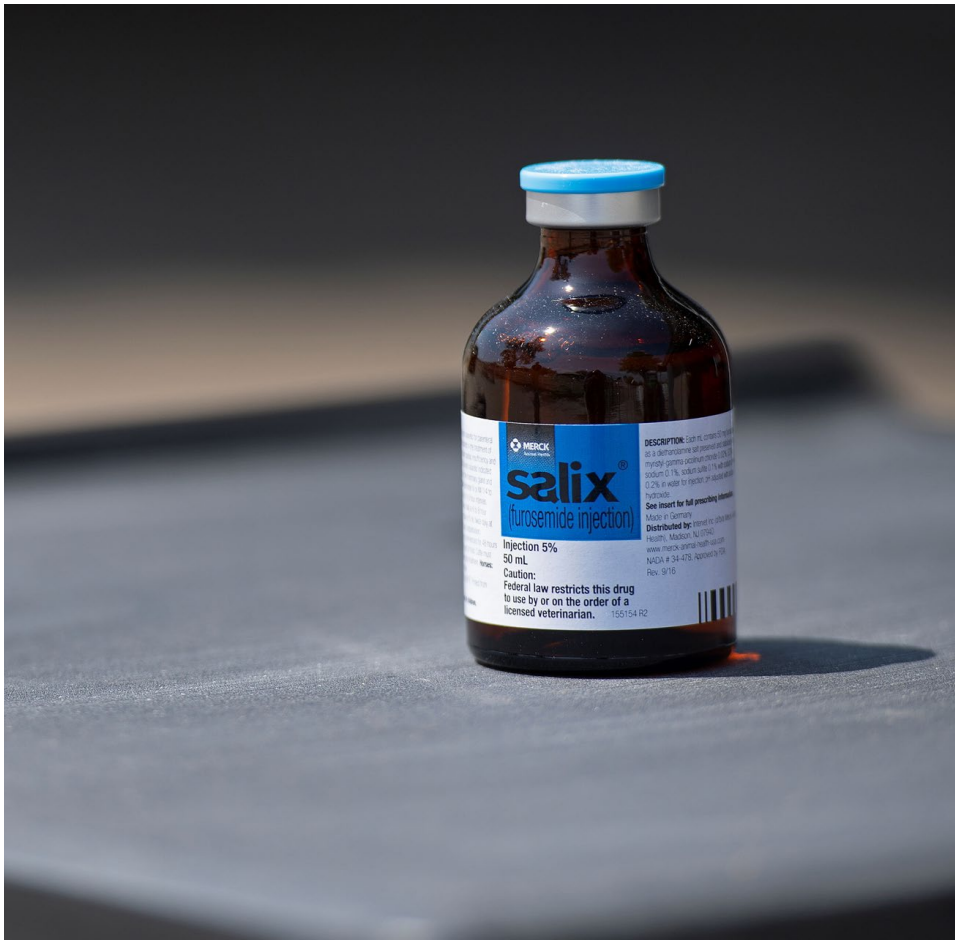
DIVING DEEPER INTO RECENTLY PUBLISHED STUDIES ON EIPH

By BloodHorse Staff



ANNE M. EBERHARDT

BloodHorse Daily sat down with Rood & Riddle and Grayson-Jockey Club Research Foundation board member Dr. Larry Bramlage to discuss his thoughts on two recently published studies that revealed low-dose 24-hour furosemide with controlled water access shows great promise as a replacement treatment for our conventional four-hour pre-race treatment for EIPH in horses that are bleeding.

You seem pretty excited about these research results. Why?

The "race day furosemide" vs. "no race day medication" debate has been waged continuously for decades, but the heat has gradually increased. I believe this is a chance to make real progress—maybe the first I have seen—and I believe the results of this research show us a viable path forward that could satisfy both sides.

What path is that?

It appears that if you pre-treat the horse with furosemide and manage the horse's hydration, you may get even better results than the way we use furosemide in racing today.

Which side are you on?

Neither. There are elements of legitimacy on both sides. The problem is not the medication furosemide. Most people believe it is an effective therapeutic medication. The problem is the administration on race day.

Can you explain the science behind the pre-treatment concept?

Some medications produce therapeutic effects that last beyond the clearance of the medication itself from the system. The familiar example of this is the effect of aspirin on the adhesion of platelets. The medication clears in a matter of hours, but the effect lasts more than a day. That is why the older of us take one baby aspirin a day to prevent transient ischemic episodes due to micro-clots. The aspirin is gone quickly, but the pharmacologic effect covers us the whole day. It appears furosemide has that attribute as well.

How so?

According to practitioners, Grayson Board Member Dr. Gary Lavin in this instance, when furosemide was first introduced it was given at varying intervals with apparent similar therapeutic effect. The four-hour pre-race time interval was chosen to facilitate regulatory monitoring. Furosemide clears the system pretty quickly, so the question was, "How long does the effect really last?"

What about the hydration management you mentioned?

It is well-known that furosemide lightens a horse's weight by eliminating water. But what was not known is exactly how much benefit to the horse comes from weight loss and how much comes from the effect of the medication on bleeding.

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How did these two things get combined for this research?

Long story! Five years ago, at the end of the racing season, a trainer from Seattle came to Dr. Warwick Bayly and told him he had two horses that were bleeders and asked if they could be of any use before he turned them out for the winter. The next week he was in Lexington, so he, Dr. Steve Reed, and I (all members of the G-JC Scientific Advisory Committee) sat down in a conference room and brainstormed about what kind of pilot project could be done that might point us in a new direction. We came up with the idea to compare conventional four-hour pre-race furosemide to furosemide given at 24-hours pre-race, but we would try to stabilize the horse's hydration status by giving them only maintenance water for 24 hours so the hydration status would be similar at performance (treadmill in this instance). We went to The Jockey Club and to Keeneland and recruited a limited pilot budget, and Dr. Bayly ran the trial to see what we could learn. This is one of those fortunate situations that happen by fate or divine intervention where we stumbled onto a formula for 24-hour administration that not only worked, but in the pilot worked better than the conventional four-hour administration of furosemide in several aspects.

It was only a pilot, but when we went to the Grayson-Jockey Club Scientific Advisory Committee and the G-JC Directors with the information, they agreed to dedicate money for a "special call" for research on the subject.

We got two great proposals that the reviewers liked very much, one from the University of California at Davis and one from Washington State University. We wanted to fund both of them, but we only had money to fund one. So the members of the Grayson-Jockey Club Research Foundation Board of Directors entered into discussions with other organizations. Fortunately, The Jockey Club, the AAEP Foundation, Keeneland Association, Oaktree Racing Association, The Stronach Group, Churchill Downs, Kentucky Downs, NYRA, The Del Mar Thoroughbred Club, Oaklawn Park, and The Thoroughbred Horseman's Association answered our plea, and together we funded both projects.

Why two projects?

Good question! There is some consternation in funding two similar projects because there is risk you would get conflicting results. But the projects were both looking at the same question from differing angles. In the interest of discovery ASAP, we funded both. One project used horses with no history of bleeding, and one project used known bleeders.

Did they get conflicting results?

Partially, but they also provided complementary information. The results are detailed in the Grayson-Jockey Club report in this issue. The California project showed us that 99% of the furosemide is gone at 24 hours. That the naive horses didn't bleed much endoscopically but were bleeding at low levels in their lungs. It also showed one horse with no history of bleeding bled through everything. Most of your readers can probably name a horse like that.

Did the treatment help?

The bleeding was relatively mild with 11 of the 43 endoscopic exams showing blood, seven of which were just a trace, "Grade 1," and three of the four examinations with more than Grade 1 bleeding were found in the one horse. The four-hour furosemide was better than the 24-hour at reducing the limited bleeding in these horses.

How about the Washington State project?

That one was much more in depth and had seven known bleeders doing seven different trial runs to separate whether it was the water restriction or the level of medication that had the most effect. Simply put, it proved that the 24-hour furosemide with controlled water access was the best and was the only treatment that was statistically proven with 95% certainty to reduce bleeding in these known bleeders. It was better than the way we treat horses now, four hours before a race. But the project also provided a lot of additional useful information. It shows furosemide could be a viable treatment that does not need to be given on race day.

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What other useful information did it provide?

Research provides different levels of information. Tradition dictates that "statistical significance" means 95% certainty that there was a cause and effect. The power of the experiment to reach 95% certainty is determined by the degree of difference in the results and the number of animals in the trial. If you are working with mice and you get a trend in the data but it doesn't reach 95% certainty, you just do more mice. But this is impractical and expensive with horses, so we often look at the data and find answers that we can use but weren't proven by the conditions of the trial because there was not enough power to prove it in the experiment or it was an incidental finding. There are things in this data in addition to the conclusions.

Can you explain that last statement a little more in depth?

You are now getting a surgeon's interpretation of a scientific experiment, but clinical decisions are generally made on the "preponderance of the evidence" to draw a conclusion, so you use the data at hand. If we waited for 95% certainty to make a decision, our patients would expire while we were waiting for the proof. The same approach is used to treat you if you go to the hospital emergency room. There is often evidence in an experiment that is true but not statistically proven.

What are some of those interpretations?

You can see the seven different trials that were run in the description in the Grayson-Jockey Club report, but this is some of the added information contained in the data:

• Restricted access to water with no furosemide was not very effective, so it is not the water restriction alone that had the effect.

• Three of the four 24-hour furosemide administration trials (low dose furosemide with free access to water, high dose furosemide with free access to water, and low dose furosemide with restricted water) produced lower RBC increases with exercise than did conventional four-hour furosemide treatment, so the residual pharmacologic effect of furosemide is real (remember the aspirin).

• High dose furosemide with restricted water was less effective than low dose furosemide with restricted access to water, so adding more furosemide is not useful. Those horses also lost the most weight due to water loss, so they may be approaching subclinical dehydration.

• Time to fatigue was one of the control items to assure race-like conditions, but restricted access to water alone shortened time to fatigue, and conventional four-hour furosemide and low dose furosemide with water restriction both produced a 10% increase in the time to fatigue compared to control. These two were similar; all the other treatments were close to control.

There is more information, but these were the most interesting items to me.

You mentioned dehydration. Doesn't furosemide always dehydrate the horse?

No. All grazing animals have the ability to store water in their G.I. tract. This enables them to spend most of the day grazing far from water. Wild horses normally go to water once a day on the high plains. This reserve of water prevents the horse from dehydrating his circulating blood volume during the day. Water is gradually absorbed throughout the day and then replenished the next drinking session. Single dose furosemide dehydrates the water reserve but does not dehydrate the blood volume.

Did the experiment measure dehydration?

Yes. Restriction of water to maintenance (roughly a gallon every four hours) reduced the horse's body weight by about 5% in 24 hours. This is slightly more than the 3.5% reduction in body weight created by the conventional low dose four-hour furosemide alone, where water was restricted for only four hours. Adding furosemide to the 24-hour water restriction at the low dose decreased body weight another 1% and at the high dose reduced it 2% over water restriction alone.

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But all of this was done on the treadmill, right?

Correct, but the second part of the experiment took the best treatment, the low dose furosemide with controlled water access and tested it in simulated races on the racetrack to validate the results. Two races breaking from the gate compared the low dose 24-hour furosemide with restricted water against a control race with a placebo.

And what happened?

The results after simulated racing produced some interesting changes. The difference between the BAL RBC's in the control horses and the treated horses narrowed, dropping the confidence of a treatment effect to 90% from 95%. This is below the traditional 95% significance threshold reached on the treadmill study but is still 90% certainty that the low dose furosemide with restricted water access lowered the BAL RBC's during the simulated races. But the endoscopic EIPH scores in the race actually changed in the opposite direction; i.e., the bleeding was worse, and the endoscopic bleeding scores now became statistically significantly lower (95% certainty) in the low dose water restricted horses when compared to the control exercise values. This again proved the low dose furosemide worked, on the track as well as the treadmill.

> *"I think we should put this in the hands of the trainers, who I believe will gradually find that the 24-hour furosemide with controlled water is better."*
>
> —DR. LARRY BRAMLAGE

If the results in the California study said the opposite, why the difference?

They were testing differing models. In non-bleeders that may not have needed help, the suggestion was the 24-hour furosemide was not as good, but in the horses that were known bleeders, the low dose 24-hour furosemide with water restriction was statistically proven to be the best treatment on the treadmill and validated during a race.

What conclusions can we draw from these findings?

It looks like some variation of the low dose 24-hour furosemide with controlled water access shows great promise as a replacement treatment for our conventional four-hour pre-race treatment for EIPH, and it could actually be better. If you take a critical look at these results, it is possible that we are currently treating EIPH with the second-best approach to the problem!

What should we do now? Should we just change the rules of racing?

No. Both projects concluded with calls for further research. I think we should put this in the hands of the trainers, who I believe will gradually find that the 24-hour furosemide with controlled water is better. The "test of time" is a great discriminator. The 24-hour low dose furosemide with restricted water intake shows enough promise of being equal to, or perhaps better than, our current approach that we should find a way to let the trainers evaluate both approaches. This would require some regulatory adjustment, but a regulatory approach that would allow both treatments would further refine the efficacy of both via the test of time.

As an example, look at tongue ties and nasal strips for improved respiratory performance. Both show research benefits, but tongue ties have stood the test of time and are almost universally accepted as beneficial. Nasal strips have not. They persist as useful in a few horses, but the general consensus is that most horses are not benefited by them. We need to subject the two approaches to EIPH to the same practical scrutiny over time. I understand from questions of regulators that the 1% residual furosemide level after 24 hours could violate current racing regulations; it would not fit horses as being on furosemide but would also not be legally without furosemide.

We would have to modify something in the rules, but I think it would be worth it. Why don't we find a way to allow both approaches and let the "test of time" work? BH