**DR. TOM MCLEAN:** So here are the objectives. After this presentation, I'd like you to be familiar with the epidemiology, the pathogenesis, the natural history of infantile hemangiomas, the indications for the mechanisms of action of propranolol for infantile hemangiomas, dosing, monitoring, potential side effects, and also some practical tips, and also when to refer. And if I get to speaking too quickly, which I sometimes do, please raise your hand or slow me down. Or if I say something that doesn't make sense, just get my attention.

**SPEAKER 1:** Could you speak a little louder?

**DR. TOM MCLEAN:** Speak a little louder? Thank you. That's very helpful. I'll try to raise this up a little bit. Is that better? Great, thank you. Thanks. So I'm going to start off by showing you some pictures of hemangiomas that you really should not see anymore in 2015 and beyond. These are in the pre-propranolol era. And as you can see, a big, beard distribution hemangioma. This is the same child several months later. You can see some ulceration setting in, and she looks uncomfortable. Here she is many years later, obviously with residual cosmetic defects.

Here's another one. It's a newborn. You can't really see much. That's a picture of a picture. But just a few weeks later, you can see, again, a large facial hemangioma here. And then here she is a couple years later also with a poor cosmetic outcome.

And then here's a patient that was treated pre-propranolol. And the mother was anxious to have something done. It's hard for parents to be patient sometimes, and she sought surgery in another state. And as you can see in follow-up, the outcome is not particularly good.

Now all that changed-- I'm going to come back to the story of propranolol in just a minute. But before I do, I want to just give you one slide on vascular anomalies-- the classification. The font is probably a little small, and sorry about that. But it's there in your handout. I won't go over all the details. But the key points are this; congenital hemangiomas, which are actually quite uncommon, are present at birth, as opposed to infantile hemangiomas, which are usually not present at birth. They may or may not have a little tiny speck, or spot, or a red something. But typically the history is we didn't see anything at birth, but during the first few weeks of life, all of a sudden this thing started to grow.

And then in addition to vascular neoplasms, vascular malformations are divided into slow flow and fast flow. I'll mention this briefly, but for the most part, those do not respond to propranolol. I'm going to really focus today on infantile hemangiomas.

So they are in fact considered, if you consider it a tumor, the most common benign tumor of infancy affecting 5% to 10% of the population. They're more common in Caucasians than African-Americans and Hispanics. Three to one ratio at female to male ratio, for reasons that we don't understand. And they're associated with prematurity, low birth weight, multiple gestations, and advanced maternal age. And they are typically located in the head and neck, although about a quarter on the trunk, and 15% are on the extremities.

The natural history, as I mentioned, they typically appear in the first few weeks of life, and then they grow. And they typically grow, grow, grow for the first 9 to 12 months of life, and then they kind of plateau. And then they start to slowly regress over many years. And the rule of thumb that I remember is 10% per year. So by the age of five, about 50% will have had complete resolution. By the age of 7, 70%, and by the age of 9, 90% will have had complete resolution.

So it can take a long time. And again, it often is hard for parents to be patient. But left untreated, most hemangiomas do well-- not the big ones that I've shown you there. In fact, at least 90% of hemangiomas require no therapy at all. However, they can cause scarring, atrophy, redundant skin, discolored skin.

So what are some other treatments for hemangiomas? These are all-- steroids, of course, is for long-time mainstay. We also used interferon alpha for a while, vincristine, cyclophsphamide, which is why a pediatric hematologist oncologist is talking about hemangiomas, because they used to come to us for some of these cytotoxic chemotherapies and other therapies; steroids, laser therapy, intralesional steroids, and surgery. The problem with all of these is that they don't really work, and they're toxic. The beauty of propranolol is that it works most of the time, and it's very well tolerated.

So what are the indications? Which patients need treatment? And really it's a judgment call, but for the most part, these are some general guidelines; anything that's rapidly proliferating or causing a functional deficit, alteration, pain, or significant disfigurement, which is a judgment call in many cases; anything interfering with breathing, vision, or eating, or swallowing; high output heart failure, which can happen particularly if they have big liver lesions; and in Kasabach-Merrit Syndrome, which is one of those things you might see on boards and never see in real life, but that's characterized by thrombocytopenia and a microangiopathic anemia; and then diffuse hemangiomatosis or lymphangiomatosis.

Who should not be treated with propranolol? In general, it should not be administered for small lesions in harmless locations, i.e. lesions that have an excellent prognosis with supportive care only. Particularly if there in the extremities and they're small, I would typically leave those alone. And then older children tend to respond less favorably than younger children. The oldest reported responder is 10 years of age. So again, who to treat, who not to treat, in many cases, it's a judgment call.

Let's talk a little bit about propranolol. It's a nonselective beta-adrenergic receptor antagonist. It was invented, not discovered, but invented in 19-- it was published in 1964 by Sir James Black, who went on to win the Nobel Prize, in large part because of this. It results, as you all know-- beta blockers result in a decreased heart rate and decreased blood pressure. It has a number of-- brand names include the Inderal, Hemangeol, and others. And I'm going to come back to Hemangeol a little bit later.

It has a long list of indications. On the left are FDA-labeled indications, and on the right are non-FDA-labeled indications. Pediatricians, of course, we use a lot of drugs that are not FDA approved for children. But propranolol is now FDA approved for the use of infantile hemangiomas in children. It was approved about 13 months ago in March of 2014. And one of the themes that I want to tell you, one of the take home messages that I would like you to take back to your practices this week, is that you, too can use propranolol for infantile hemangiomas in your practice. It's safe, and I hope to be able to convince you of that-- safe and effective.

So how did this come about? How did anybody figure this out? This is a picture of the second patient. The first patient I don't have pictures of. This is published in the *New England Journal of Medicine* in June 2008. And when you read the article-- the first patient had a hemangioma on the tip of the nose. I think it was-- I can't remember if it was a male or female. But they started propranolol for cardiac reasons. And lo and behold, the hemangioma started to shrink and go away. Here is patient number 2-- also started on propranolol for cardiac reasons. And what a dramatic response after just one week. You can see that the child is starting to open her eye-- right eye. And then after age six months, and then nine months, dramatic resolution compared to those earlier photographs that I told you.

It was after this patient that the investigators in France-- by the way, this is in France. The light bulb went off, and they said, huh, maybe it wasn't just a coincidence. So they treated nine other patients, and they wrote it up. This is a summary of the first 11 patients. They were treated with 2 milligrams per kilogram per day of propranolol. All 11 had color changed noticeable within 24 hours. I mean you see this overnight. You can see the lesions starting to soften up and lightening in color. And all 11 had continued subjective responses, and five had objective responses by ultrasound.

They published it, and it kind of took the hemangioma world by storm. Because for decades, we've been using all these other therapies; prednisone, and interferon, and vincristine and laser, just with very minimal success and a lot of toxicity. And all of a sudden we have a treatment that works and is nontoxic. But we had to show, in fact, that it was nontoxic And I'm going to come to that in a minute.

So in fact, that was the very first study in 2008. The only other study you need to know about, I'm going to come to. There have been a lot of studies in between. The number of studies, as you can imagine, over the last seven years has really just escalated dramatically. But the most recent one, I'm going to come to.

Ironically, in that same summer, 2008, we treated our first patient here at Wake Forest with propranolol, also started by the cardiologist for a cardiac reason. Because this child had large liver lesions. It's not a great picture, but she had high output heart failure. We started propranolol, and sure enough, she got better. And at the same time, just a couple of months later, we realized hey, this is a fortuitous thing. So then we started treating children here. And I've treated-- my colleagues and I have treated probably over 100 patients now over the last seven years. I'm going to show you some examples of those pictures.

Let's go back a little bit to propranolol. This is just one slide on how we think it might work. There's actually-- this is a lot of research summed up into one slide. There is some evidence that it causes vasoconstriction, so the vessels start to constrict. There's also good evidence that it decreases expression of some growth factors that are important for blood vessel formation. So it inhibits angiogenesis, which is the formation of blood vessels. And then finally, there's some evidence that it triggers direct apoptosis of capillary endothelial cells. We don't really know, but what we do know is that it works.

Here's a patient, one of the early patients that I treated. She was a daughter of a missionary couple from Central America. She came back-- had this large lesion on her lip. It was interfering with breastfeeding, and it was ulcerated if you look closely. And after just a couple of months of propranolol, she's had a dramatic response-- is feeling well again.

Who are some patients at risk for heart disease? There's something called-- well, anybody who has diffuse or large hemangiomas are at risk for high output heart failure. And there's also something called PHACE syndrome. P-H-A-C-E, which stands for posterior fossa, hemangioma, arterial lesions, cardiac abnormalities, specifically aortic coarctation, and eye abnormalities. And in those patients, because of the lesions and the other problems, they're at risk. So those are the kind of patients that I would definitely recommend referral-- the large ones, the complicated ones, any patient that you think might have PHACE syndrome.

This is in fact the first and only patient I've ever personally treated with PHACE syndrome, and we've just started treating her in the last few weeks. That was-- on the top left, you can see day 1, which was baseline. And just overnight with one day-- on day 2 of propranolol, you can already see that she's starting to open that left eye. And then there's day 17 and day 44. Parents are thrilled. I'm thrilled.

There is some literature suggesting that you have to be careful with PHACE syndrome, because sometimes they have, and this baby in fact has, some arterial narrowing. So if you give up an agent that lowers the blood pressure, in theory at least-- at increased risk for stroke. But the largest series of PHACE syndrome patients treated is 34. The majority of them did quite well and had good responses to propranolol.

Before you start propranolol, I suggest-- and this is sort of a consensus conference that was published in 2013-- obviously a carefully h & p with vital signs including the blood pressure. And that's one reason why a lot of other sub-specialists or physicians don't want to treat with propranolol. For example, a lot of these patients come from dermatology, or ophthalmology, or plastic surgery, and those folks, I don't even think-- I mean I don't know if you're in the audience or not-- but they don't like to check blood pressures. It's hard enough for pediatricians, right, to check blood pressures on babies-- but I guess where a good nurse comes in handy. And obviously you want an accurate weight as well. And I also find baseline photographs very helpful.

Other tests, depending on each case, you can consider. At the very beginning, we were doing a lot of these things. And we were even admitting children to the hospital to start propranolol, because it was so unknown. But now, I rarely admit. The most recent child I admitted was that child with PHACE syndrome, but that's the first one in two or three years at least. But if you're worried about heart disease, think about a heart workup, liver ultrasound if they have diffuse lesions or you hear a bruit or something, or heart problems. Think about labs, although I don't routinely get them.

And then for beard distribution lesions, think about an ENT consultation, because they can sometimes have airway involvement. And if a child eats normally, you don't need to monitor blood glucose. Although in theory, that's a risk of propranolol. It's really only a risk, I think, for the really small babies, the premature babies who don't have much reserve. Here's another picture of a nice response-- a coliform type lesion on the back of the ear.

So another slide about propranolol-- the peak absorption is one to three hours. It comes as two different solutions. I recommend always using the 20 milligram per 5 mL solution. It comes as one that's 40 milligrams per 5 mL's, but that's-- I would just say, just use the 20 per 5. It comes as caplets and tablets as well, and extended release capsules. It's a very commonly prescribed drug in the adult world and in the cardiology world. But for this indication, I recommend 20 milligrams per milliliter.

How do you dose it? The goal dose is 2 milligrams per kilogram per day, divided into three doses. However, three milligrams per kilogram per day is also acceptable, and that's based on the next-- the article I'm going to show you that was just published last month in the *New England Journal of Medicine*. Some of you may have seen it. But most of the experience so far has been with 2 milligrams per kilogram per day. And I'm still sticking with that for now, because it seems to work so well with so few side effects.

And the way I like to do it is I calculate the goal dose based on the patient's current weight, and I start at half that dose. And I give it for three days, and if they're doing well, then I tell the people to go up to 75% dose for three days. And if they're doing well, go up to full dose. I have them come back in a week or two to check for side effects, see if they have any questions, and then I start spacing out their visits.

Twice a day dosing is also acceptable. That's how they did it in the study I'm going to show you, and sometimes it's more convenient. Although, we had a patient come in last week who said, we don't like the twice a day. We want to go to three times a day. And we've had just the opposite as well. Twice a day is so much easier than 3 times a day. So you can divide the total daily dose two or three times.

This is an example-- I won't get through it. It's there in your hand out. But this is exactly how to do it. If you have a child that weighs 6 kilograms, this is how I would recommend dosing the propranolol. I talked about some of this already. Make sure you get a blood pressure when they come back and vital signs. If it's low, then you obviously wouldn't push the dose up. I recommend that they administer it during the daytime hours at the time of a feed. Because, again, the peak absorption is one to three hours. In theory, that's the time when their blood sugar could drop down. So even if it's just a few swallows of milk or formula, that should be enough. Prolonged fasting should be avoided. And if the child is sick and not taking good oral intake, just tell the parent to hold the dose until their intake is normal again.

This is a handout which is busy, but I put it on there because parent education is so important. We give a sheet to every parent who starts this with instructions. And the most important part is here's how much to give your child-- blank milliliters three times a day, then blank milliliters three times a day. And I hand write it in, and I go over it with them. And I also provide them with syringes, and I show them on the syringe. And I let them play with the syringe, and make sure you get it exactly right. I can't communicate-- I can't overemphasize how important communication is. We all know about medication errors and things. And I think parents appreciate just having this at home.

Here's another nice responder-- lesion in the scalp. This is the study that just came out. It was published in February, so two months ago-- *New England Journal of Medicine*-- a randomized controlled trial of oral propranolol in infantile hemangiomas. This was done by the group in France that was the original group that discovered it. Although, the trial was actually all over Europe and some centers in the US.

And I think I've boiled it down to just two or three slides. It was a multi-center, double blind, adaptive, phase 2-3 randomized controlled trial to assess the safety and efficacy. And they targeted infants between the age of 1 and 5 months who had proliferating infantile hemangiomas who required systemic therapy. And again, that was a judgment call. And they have five treatment arms. And one arm was placebo, and the other four arms were 1 milligram per kilogram per day for three months or six months, and then three milligrams per kilogram per day-- three months or six months.

The interim analysis of the first 188 patients showed that 60% had complete or nearly complete resolution by six months versus 4% of the placebo. So they said, OK, we know it's better than placebo. Let's focus on giving it. Now what dose should we give and for how long? And they decided on-- there's some complicated statistics too, which I don't really understand. But they decided on 3 milligrams per kilogram per day for six months, and they treated a total of 456 patients. That's a graph showing the dramatic difference between placebo, and I won't spend much time on that.

But here's the bottom line. 88% of propranolol treated infants showed improvement after five weeks of treatment versus 5% who received placebo. So clearly it works. 10% required retreatment during follow up. And for that reason, I typically treat-- actually we did this even before-- I typically treat until their first birthday, until about the age of 12 months. Because that, if you remember, is the time when those things start to stop growing anyway and then start to slowly regress. So typically around the first birthday is when I taper off the propranolol.

Side effects were typically mild and did not significantly differ from placebo treated infants, and adverse reactions led to discontinuation in less than 2% of patients. This is from the package insert. You can see that sleep disorders was the most common side effect, followed by bronchitis, peripheral coldness, agitation, diarrhea, and a few others, some of which were not any different than placebo.

Potentially serious side effects are rare. This is from a large review published in 2013. Bradycardia, hypotension, which are the two things that we think about with beta blockers, and then hypoglycemia all occurred at a less than 1% rate. And none of those patients died or had any serious complications.

So Hemangeol, based on this study and based on the FDA review of the study-- propranolol has been rebranded as Hemangeol. It was approved, as I mentioned, last year. The recommended full dose is 3 milligrams per kilogram per day. Again, I am still sticking with 2 right now. I haven't changed my practice to go up to 3, but 3 is actually what the FDA says is safe to use. And FDA also says you can divide it twice a day rather than 3 times a day, which I think probably is a very reasonable thing to do.

The cost however, as you might imagine, for a rebranded drug is quite expensive. In fact, I did the math. It's 25 times more expensive than the generic drug. So I personally can't think of a reason to prescribe the-- I forgot to say it by the way-- but at the beginning I don't have any conflicts of interest. I honestly can't think of a reason to prescribe-- they have a list of reasons-- things like a patient assistant program we sweetened it with something. I don't know-- a couple reasons. It really didn't even add up to me, certainly not to make 25 times more of a cost difference. But it is approved.

So what about follow up and stopping therapy at Wake Forest? We typically see the child as I said, again, a week or two after starting to check for side effects, answer any questions, things like that. And then I space their visits out to once a month. And then, again, we treat them until about their first birthday. And then when it's time to stop, we typically-- you probably could just stop it cold turkey-- but what we do is we go from t-i-d to b-i-d for one week, and then we go to once a day for one week, and then we stop. And it's fun, because all the parents are happy. The children are well. As an oncologist, this is like a great thing for me. I just love it. Everybody leaves my clinic happy-- almost everybody.

I'll sum up a few little things. What about topical propranolol? I get asked about that a lot. And the dermatologists really enjoy-- I don't know if any dermatologists are here, but they really like to use it-- topical propranolol or timolol. There have been four studies. They're all small, and I can summarize it by saying that topical propranolol or timolol is in fact a safe and effective option for small superficial hemangiomas that have not ulcerated and are not on the mucosal surfaces.

Now the paradox is that if they're really small, and they're not ulcerated or on mucosal, they probably don't need treatment. But it does work. It's safe. If you have a small one on the face or some other part of the body, it's OK. And you can prescribe this, too. You can prescribe a timolol that's a gel forming solution that forms a little gel. You can also use the ophthalmic solution, which is little more liquidy and runny. But they do work for superficial. If there's any depth to that lesion, I would recommend systemic propranolol, because you really need to treat that lesion from the inside out. That's kind of why laser therapy doesn't work, because laser doesn't penetrate very well. But some of these things can be quite deep.

This is the only patient-- well, is it the only-- maybe the only patient I've prescribed topical timolol for. Because I didn't actually even want to treat this patient, but the momma wanted to. I said, OK, we'll treat her. And she had a nice response to her propranolol, and then she got some peripheral coldness-- little bit of sinus. She was acting fine, but we decided to stop the propranolol and then we switched over. And as you can see in the third photograph, it had very little effect. You can see a little depth to that lesion. Her long term prognosis is excellent. She's going to be fine cosmetically and every other way. But I don't have a lot of experience with the topical, but you can try it. It's very safe.

Now just to summarize a bunch of other research-- there have been several other small randomized trials that show-- before propranolol, there's only one trial that looked at pulse dye laser versus propranolol, and it showed no difference. They were equal in terms of long-term outcome. In fact, in some cases, the laser patients did worse when they looked at skin color and changes like that.

And then some other studies have been done looking at propranolol versus some of these other things. And in fact, in each of these studies, oral propranolol has been shown to be better than observation, pulse dye laser, cryosurgery, prednisone, or prednisone with propranolol-- and when I say better in that context, I mean less toxic-- and then topical or intralesional propranolol. So in fact, systemic propranolol works better than topical propranolol.

Here's another picture of a nice responder. There's another nice responder in a fairly harmless location. But you got to be careful in some of these chin/neck lesions that could involve the airway. I'm going to show you a few examples of some poor responders. This little girl, you could say she had a little bit of a response, but it's a big earlobe lesion that really didn't respond as well as we hoped it would.

Here's one-- and for some reason, these deep wounds on the forehead and at the bridge of the nose don't respond as well. That's an OK response, but it's not great. Same for this one. This is a disappointing response. But again, long term, her prognosis is excellent.

And here's one that probably is not a hemangioma. It's also cutaneous, and I think it's probably more of an AV malformation that really, in my opinion, didn't respond at all. This one is probably not a hemangioma either. This is a child's lower lip. This is probably a lymphatic lesion-- mixed vascular lymphatic lesion. And he ultimately went on to have surgery.

This is a child who has a large lesion on her leg as in the perineal region with some perirectal, perianal fissures and bleeding. And she has not responded. Although, this is also not a typical infantile hemangioma. Nor is this. This is a child with an unknown diagnosis who has these strange skin lesions all over his body. And we decided to try propranolol, because we didn't have anything else to offer. The mother is happy. She thinks it's better. I'm not convinced, but if mom's happy, I'm happy. It's nontoxic. It's not hurting him.

This is a child that was referred to me by the ENT service. If you look closely on the bottom left of her floor of her mouth. She's got a vascular lesion. We tried propranolol, but it didn't work. I am willing to try propranolol for these vascular lesions, not because I have evidence that it works, but because sometimes surgery-- or there are no better options.

Now here are some good responses. This little girl had a great response. It's a shame that that posterior neck lesion got as big as it did. Here's a nice one from the scalp. Again, these are only after a few weeks of therapy. This one's a pretty good response. And this is one of my favorites. This is one of my early on's favorites. This little girl just did beautifully, and had no problems.

So how and when to refer patients-- the bottom line is just trust your judgment. Any patients that you would like to be evaluated in our clinic, we are happy to see them any time. And we can usually see them on very short notice. So please call me, or call one of us through the PAL line. Or you can e-mail me. You can call me on the phone. I've helped some of you do things over the phone. And once you do two or three or four cases and get comfortable doing it, I promise you, it will get easier, and easier, and easier.

And so in conclusion, propranolol is a safe, effective therapy for infantile hemangiomas. You can treat most patients in your practice with propranolol. I'd like to acknowledge Hernan Sabio, who provided some of the early photographs, Diane Samelak, who's a nurse practitioner who works with me with these patients, and also the patients, and their parents who gave me permission to take their photographs and use them in this presentation. So with that I will stop, and thank you very much for your attention.