BBGuy Essentials 058CE:
Transfusion and Blood Clots with Ruchika Goel
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Joe Chaffin: Hi, everyone. It is my honor to welcome you once again to Blood Bank Guy Essentials, the podcast designed to help *you* learn the essentials of transfusion medicine. This is episode 58CE, and my name is Joe Chaffin. I'm really excited about today's episode, because today we're going to discuss how red blood cell transfusion appears to be a really significant risk factor for postoperative blood clots. But it's just not nearly as well appreciated as it should be. And we're going to try to define that for you. More on that in just a second.

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So, I think everyone would acknowledge that way too many patients get blood clots, or their fancy name, "venous thromboemboli" (or "VTE"), after surgery. It happens way too often. VTE includes both deep venous thromboses and pulmonary emboli, and they are thought to cause or contribute to just a ridiculous number of deaths every year. I mean, the numbers are breathtaking: 100,000 to 200,000 deaths every year. That's astonishing! Now, for years, we have actually known pretty clearly that surgery itself is a risk factor. It appears to induce inflammation and by itself will probably foster formation of blood clots. But aside from looking at some things like hypercoagulation disorders (of course that occurs), or platelet disorders, we really haven't thought that much about how much red blood cells contribute to postoperative blood clots.

Well my guest today is someone who has thought about that. Her name is Dr. Ruchika Goel. Ruchika is part of the Hematology/Oncology faculty at the Simmons Cancer Institute at Southern Illinois University. She's Associate Medical Director of the Mississippi Valley Regional Blood Center, and she's an Adjunct Assistant Professor of Pathology in the Division of Transfusion Medicine at Johns Hopkins.

Ruchika is the primary author on a paper that's really making a stir. That paper was published in the September 2018 *JAMA Surgery*. The paper was called "Association of Perioperative Red Blood Cell Transfusions with Venous Thromboembolism in a North American Registry." This was the first study to primarily address the role of perioperative red blood cell transfusions in developing postoperative venous thromboemboli, including those DVT's and PE's. This paper has really created quite a stir, as I've mentioned before. It was

actually e-published earlier in 2018, and since it came out in e-publication form, it's been awarded the AABB-Fenwal award, and it's resulted in a "Young Investigator Award" for Dr. Goel from the Academy of Laboratory Medicine Physicians and Scientists.

Further, when you look at "Altmetric," which is a research tracking company, the paper is in the 99th percentile of all papers they've EVER tracked for impact! The bottom line is that this paper is a big deal, and the findings are really, really important. We are super-lucky to have Ruchika with us to discuss it. So let us get to it! Here's my interview with Ruchika Goel on red blood cell transfusion and venous thromboembolism.

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Joe: Hi, Ruchika! Welcome to the Blood Bank Guy Essentials Podcast.

Ruchika: Hi Joe, very good morning. It's absolutely a pleasure and honor to be here.

Joe: Well, thank you for taking the time to be with me. I'm guessing that your dance card is pretty full right now, Ruchika, because you have been involved in several really interesting and high profile projects recently. And one of those is what we're going to talk about today. It's an article that you published with an "all-star" group of Transfusion Medicine specialists and other specialists in *JAMA Surgery*.

This article was published in June of 2018. It was e-published, actually, and by the time this interview comes out, it may actually be formally published [NOTE: The article was formally published in September 2018 in *JAMA Surgery*]. I'll just say the name of the paper and we'll start talking about it in a moment. The paper's called, "Association of Perioperative Red Blood Cell Transfusions with Venous Thromboembolism in a North American Registry." Lot of words, but we'll break those down in a minute. But Ruchika, I'm wondering... I mentioned your dance card is probably pretty full because of all the attention this article is getting. Can you talk a little bit about what kind of an impact this made when this article landed?

Ruchika: Sure, Joe. It's really been a very gratifying and humbling experience. To me, a transfusion research getting so much attention, it's truly a very gratifying feeling. Yes, the paper has been extremely popular. There's been many thousands of downloads within the first week of being released. It's been scored as one of the top 99th percentile of attention output. So, we're just happy. There's been a lot of people who've written to us for having several questions answered about it, and planning future studies that could be based on this. So, it's just something we hope is setting the stage for future research, and just getting transfusion research out there, and more recognized. Truly, so very happy about it.

And I would just like to take a chance to, as you mentioned, it's been a wonderful team of collaborators and researchers on this. And truly, specifically my thanks to Aaron Tobian, who's been my mentor and now a dear friend and colleague from Johns Hopkins, and just an absolutely phenomenal experience working with him and the rest of the team. Looking forward to more good stuff.

Joe: Wow. I think your future might be fairly bright, my friend. So again, congratulations. It's really wonderful, and I would like to get into the details of this paper. But before we do, I wonder if we could just set the stage a little bit. And first, let's just make sure everyone listening to this podcast know what we're talking about. As I said, it's the "Association of Perioperative Red Blood Cell Transfusions with Venous Thromboembolism in a North American Registry." So let's just start from the beginning a little bit, and let's make sure everyone understands what we mean when we say the term, "venous thromboembolism." What does that entail, Ruchika?

Ruchika: Sure. So when we say "venous thromboembolism," it's talking about two entities that are included. It means deep venous thrombosis; so that is having clots formed in the deep venous system and they typically start in the lower extremity and can travel up. So when the clot dislodges, it can actually travel to the lungs and cause symptoms because of blockage. That's called a pulmonary embolism. So, VTE is construed of DVT and PE.

Joe: So VTE is the combination of both? It entails both deep venous thrombosis and pulmonary embolism, correct?

Ruchika: That's right. And it may or may not be mutually exclusive. One can have, at the same time, DVT as well as pulmonary embolism. So if the DVT dislodges, it could have a pulmonary embolic phenomenon, or one could just have a clot in one of the extremities and be that way.

Joe: So, your paper was dealing with these things happening, both DVT's and PE's (if we can shorten that so we don't have to say "deep venous thrombosis" all the time)... So both DVT's and PE's happening in the perioperative timeframe, the time before and after surgery, is that a big deal? Is that an issue in healthcare?

Ruchika: So, absolutely Joe. Venous thromboembolism is currently recognized as one of the most important public health burdens, and it is directly or indirectly responsible for as many as 100,000 to 200,000 deaths annually. So, that's about 5-10% of all hospital deaths. So, it's definitely a big deal, but what makes it even more important is that about more than 50% of all these hospital-acquired venous thromboembolisms, or VTE, are considered preventable. So, there's a scope to find out anything that's putting any risk factor that we could identify. Anything that's causing an additional predisposition, which is a modifiable risk factor. So, there's a scope for intervention. There's a scope for prevention, which is huge.

Joe: And traditionally, I know that we've... As we've thought about this in the past, Ruchika... Goodness, I went to medical school five million years ago, and it was certainly... We were talking about preventing postoperative, primarily, but certainly perioperative, venous thromboembolism back then. But I remember speaking about things like, you know, issues with the platelets or issues with other stuff. Issues with the patient just sitting there and not moving too much, and things like that. You guys were analyzing the effect of red cells. So I wonder if you'd just take us through a little bit, how we've traditionally thought about these things occurring, and what led you guys to think that maybe red cells could be an issue?

Ruchika: Sure, absolutely. So Joe, exactly as you said, and this is right even today, if you were to look at a biomedical textbook teaching, it will teach that coagulation and thrombosis, they are primarily an interplay of endothelial cells, platelets, and coagulation factors. Nowhere in the pathway are red blood cells included. And the most common traditional teaching is the "Virchow's triad," which includes three categories of factors that contribute to thrombosis, being number 1, hypercoagulability; second being stasis (so blood flow stasis or any hemodynamic changes which is causing stasis); and the third factor being endothelial injury or dysfunction of any cause.

So, it's been an interplay of these things which is proposed to cause thrombosis. But there is new molecular, as well as clinical evidence, that is coming up. This may not be all and there is more to the story. And that's one of the angles that's caught a lot of attention in recent times, has being the role of red blood cells.

Joe: Okay. I'd love it if you summarized what... I mean, before you guys got to doing this, I'm assuming that there were some things in the literature as you said, molecular and clinical evidence, that suggested red cells had a role. Could you take us through a little bit of what the state of the science was before you guys did your study?

Ruchika: Yeah, certainly. So, there's been both, as I mentioned, molecular as well as some translational evidence, and some clinical evidence, showing that red blood cells are not just innocent bystanders. They are not just passively flowing through the blood vessel while there is actively a clot generating.

The evidence centers around two things, two broad pathways, one being that red blood cells are actually impacting the platelet aggregation. And, this effect has been shown in vivo as well as in clinical, animal models as well. So, in showing that the red blood cell is truly affecting platelet aggregation being one thing. And the second is, as has been a path that has been discussed before, about the immunomodulatory or inflammatory effects of red blood cell transfusions. So, we are talking here about the native red cells as well as transfused red cells. So, there's different studies which are looking at the impact, number one, of the native red cells as well. They are involved. And second, the additional impact of transfused red cells which again, brings in the hypothesis about, that is there an inherent prothrombogenic properties of red blood cells which could be from their immunomodulatory action?

So, as you would know, a lot of the immunomodulatory roles of red blood cells has been a highly debated thing. There are multiple mechanistic pathways outlined, but none have so far been zeroed down upon or none that's been proven. So, a lot of this still remains in a state of validation or truly still as "proposed" pathways. But to us, that just gave thinking that these are biologically plausible. It gave us enough grounds to see if we can explore this question from a clinical setting.

Joe: That's awesome. Well, I dare say that perhaps part of the reason that this paper is having such an impact is that I suspect, and I'd love your perspective on this, Ruchika... I suspect that our clinical colleagues... Our clinical colleagues, particularly in surgery, those that transfuse before, during, and after surgery, perhaps are still in the mode of not really recognizing that red cells could have an

impact. Is that your perspective as well, that surgeons, anesthesiologists, may not appreciate as much as perhaps that they should? That the red cells might play a part?

Ruchika: I think so, Joe. This is still... I agree with you that one of the reasons this study is creating a stir, and similarly some recent publications in Blood, including a spotlight commentary specifically addressing the role of red blood cells in thrombotic outcomes, these are relatively new concepts, and the importance is, a lot of these things can be practice-changing. Because every time a surgeon is transfusing, or every time an anesthesiologist is transfusing, if there is a very important clinical outcome that it could be just putting one additional impact at, we can't say that this is overly attributable, right? The attributable risk would be relatively smaller. But it's just in the overall picture, could that be the one thing that puts the patient over the edge and then they just reach that threshold for developing a clot? So, it's almost a combination of factors, but I do think that this is catching attention because of some of the recent evidence that has come out.

Joe: Got it, okay. I guess that takes us to a point where I think we can have you define, perhaps, what your hypothesis was, you and your very large group of brilliant folks that were doing this study. So, what were you... As you went into this study, what is it that you were trying to define? What is it that you were trying to prove?

Ruchika: I think first of all, we wanted to see, exactly as you mentioned, Joe, that what are the different time points during surgery that one could get into the perioperative period, as we would say, that one could get a transfusion? So we separated them as... One outcome was ANY perioperative transfusion. So, that would mean, "preoperative" or we could define the category as "intraoperative." So, from the start of the surgery to at least 72 hours post-surgery. So, it could be all things that could be attributable to something related to the surgery.

So, that would be defined as a perioperative period, and we wanted to see if the transfusions around this period are related to venous thromboembolic event within thirty days post surgery. The majority of surgical outcomes, having thirty days postoperative, is a standard criteria. So we decided to go ahead with that, and one thing I want to emphasize here is that, we are using NEW venous thromboembolic events. The things that are included are, if someone had either a new event, or, if they had a chronic VTE, then it was only included as an outcome here if there was a definite progression. So for all the events, there was a radiographic confirmation. So, we did need to have an actual modality to confirm that. Like a duplicate angiogram or a radiologic modality confirming that. And, the second requirement was that these thromboembolic events were needing to qualify enough that they warranted an intervention. So, if it was considered severe enough that, yes, it needed some form of anticoagulation therapy or some surgical intervention. Something. Only then were these events were included.

And we wanted to see the association between getting the red cell transfusion and any new event. And then the second step, we wanted to see if there was a dose-response relationship. That the more the number of transfusion events are, does it correlate to higher odds of getting the venous thromboembolism?

Joe: Okay, and did you guys include every transfusion individually, or... I noticed you used the word "event," I wanted to make sure that was clear. Was there a way to distinguish number of UNITS or were you looking at number of times the patient was transfused?

Ruchika: Thank you so much for bringing that, Joe. That's definitely a very important distinction. We are not commenting here on individual units transfused for the dose-response relationship. It was each time in the registry, a distinct transfusion EVENT was coded intraoperatively or preoperatively, so that distinction is very important. It cannot do, at least in the adult's database, we cannot do a ccs's and per kilo or total volume transfusion distinction that way; it's a "transfusion event."

Joe: Got it, okay. So what you're trying to do is a fairly big concept, obviously and I would think that in order to do something like that, you would need a pretty big source of data. So I wonder if you would take us through, where did you go to try to find all this data? I imagine you could find this information for one hospital, two hospitals, whatever, but that may not be all that particularly helpful, so where did you guys go to try to find a bigger data set?

Ruchika: So for this study, we have utilized the American College of Surgeons database, it's called a "National Surgical Quality Improvement Program." It's a mouthful there. I will be referring to that as the "NSQIP" [NOTE: Say it "NIS-quip'} database henceforth. It's a multi-center registry with contributions from over 500 teaching and non-teaching institutes across North America. There's actually a pediatric version of the registry as well, it's called is American College of Surgeons "Peds NSQIP" and that has data from over 60 participating children's hospitals.

So the NSQIP, besides being a multi-center registry, one unique design is that it's a prospective registry. So basically, the patient is followed prospectively from the time of admission, and any surgical intervention or any outcomes henceforth are coded in real time. So there is, just to give a little example, there is qualified database coordinators who are recruited specifically for entering data into the NSQIP from the participating hospitals. And this NSQIP is the leading nationally validated outcomes-based program to study basically surgical outcomes. The accuracy and the reproducibility has been previously extensively demonstrated in previous, prior studies.

So it's a huge resource. We think that it has not been utilized that well for studying transfusion outcomes. We are talking about surgery and anesthesia. Certainly, transfusions are an integral part, so we wanted to give it a try to study this outcome using this registry. And as you mentioned, Joe, it's indeed a rich resource. From one year itself, we could study 3/4 of a million patients undergoing surgery across the country.

Joe: Wow. That's fantastic. And it is a US database, Ruchika? Or does it include Canada as well? I'm actually not sure about that.

Ruchika: Yeah, sure. It has Canada and United States, so it's North America.

Joe: Okay, so North America. I imagine, with that kind of a huge resource, you were able to pull a whole lot of information. As I look at your paper, one of the things

that jumps out at me, Ruchika... let me see if I can ask this properly... Obviously, just analyzing transfusions and venous thromboembolism is probably not going to be enough to answer the question, because so many other things are potentially involved. I guess, I always find that when studies like this come out, I will hear things like, "well, but, how can they tell that something else wasn't contributing?" So, I wonder if you'd take just a moment now to talk about the potential confounding factors, and how you guys analyzed and avoided those.

Ruchika: Sure, that's a very important question. Definitely, as you mentioned, the first critique, a very valid critique that comes up for any peer review. We tried to address the confounding, as you brought up, by two ways. One is, we did multi variable logistic regression. So we came up with a list of all potential predictors or additional risk factors for venous thromboembolism, and see if we could do an adjustment in the logistic regression model. Definitely, as you mentioned, having the big numbers gave the study this powered enough that we could have a pretty big model which we could adjust for, and still study a statistically valid outcome. So we adjusted for age in this analysis, for gender, race, body mass index (because higher BMI in itself is a known predictor or factor for venous thromboembolism). We did look at the total length of stay, and then we did an adjustment for, what was their functional status before undergoing the surgery? And the complexity of surgery. For these, we used two surrogate markers. We used the RVUs for the surgery as a surrogate marker for the complexity of the surgery. It's not a perfect marker, but it's been used before with a good degree of specificity. It is a fairly valid surrogate marker. There's no way for having an exact mathematical correlation to that. And the second thing is, to look at the severity of the underlying illness, because sicker patients are, in general, predisposed to developing clots more, especially in the postoperative period. So the functional status with which the patient underwent the surgery, for which a validated marker is the American Society of Anesthesia Severity of Class, the "ASA class," we adjusted for that using five different criteria, ranging from no underlying dysfunction to being in a moribund state, like really very sick patients. So we adjusted these factors in our multi variable model.

So the second way we adjusted the confounding here was using a statistical technique of "propensity score matching." What we've essentially done is that we tried to create a smaller database out of our 750,000. The database had patients who developed clots, and those who had received transfusion and did not, and we did a 1:1 matching for all the confounding variables that I just mentioned. So propensity score matching is very well validated, an accepted technique for overcoming our bias from observational data. And it's trying to replicate, creating a 1:1 matching, to as much degree as possible. So that brought us down, just to give you an example, when you try to do 1:1 matching for all variables, it's obviously hard. And that brought us down from 750,000 to approximately 47,000 subjects who had transfusions, versus approximately 47,000 subjects who did NOT have transfusions. And then, they had all these factors matched 1:1. So we could truly say, "okay, is it just the transfusion? Or is it any of these other factors which is really making the contribution?"

So, we used the term "observable variables." Whatever variable that was available, and we could truly adjust for them, they were accounted for. Even after adjustment for these, even after using propensity score matching as a sensitivity

analysis, our results stay robust. This was also presented, which truly made the study, the results, it provides an additional marker of the validity of the results.

Joe: Absolutely. That is impressive work, and I have to say, it "swims in the deep end of the statistical pool." I'm a dog paddler, Ruchika, I don't go too far into that. So I admire people that can speak intelligently about that, and you just did. Thank you very much for that. Again, I bring that up just because that is one objection that people often have about studies that come to big conclusions like this.

So, if you would, Ruchika. Let's get into the actual data itself, and talk about what you guys found, and talk about how you went about it. So, in terms of the study participants, you've already mentioned some of these people that were in your study and people that were not. Could you talk a little bit about the data that you gathered from this massive database?

Ruchika: Certainly. So as I mentioned, we had over 750,000 total subjects which we included. All of these subjects underwent elective surgical procedures. Of these, we first found out how many of them had received any red cell transfusion, which was about 6.3% of subjects received any transfusion, which could be preoperative, or intra- or postoperative. And we then separated these out. About 1% of all participating subjects received preoperative red cell transfusion. So for whatever reason, to correct preoperative hematocrit or whatever indication might have been, they received preoperative transfusions. About 5.8% of the subjects received a transfusion during the surgery, so from the beginning of the surgery to 72 hours postoperative. So these were the two broad categories we created.

Then we looked at how many of these subjects developed a venous thromboembolism. The main outcome, which was postoperative VTE, that was seen in about 0.8% of the total participants. About 6,300 subjects had VTE. Which we stratified as deep venous thrombosis, or pulmonary embolism. So, DVT was seen in about 0.6% of subjects, and PE, which is definitely a less common outcome, that was seen in about 0.33% of our subjects. So about 2500 subjects had pulmonary embolism.

And then, we did the analysis by stratifying by different type, various transfusion windows. "Perioperative" was split as preoperative or intra-op (or, a combination of either/or). And then, the outcome was stratified as all VTE, and then we individually looked at the risk for DVT or PE separately. And then did a multivariable regression there.

Joe: Ruchika, before we get further into that data, this is just a little side bar (I hope I don't shock you too much with this question). I'm curious as to whether this has come across your radar. One of the things that I find very interesting in this, and this data, just so I'm clear, this data was from people who were transfused in 2014, correct?

Ruchika: That's right.

Joe: Okay. So in 2014, you have data from 750,000 subjects undergoing elective surgery. And again, for clarity, this is kind of across all surgical subspecialties, right? This wasn't just general surgery, this was across subspecialties?

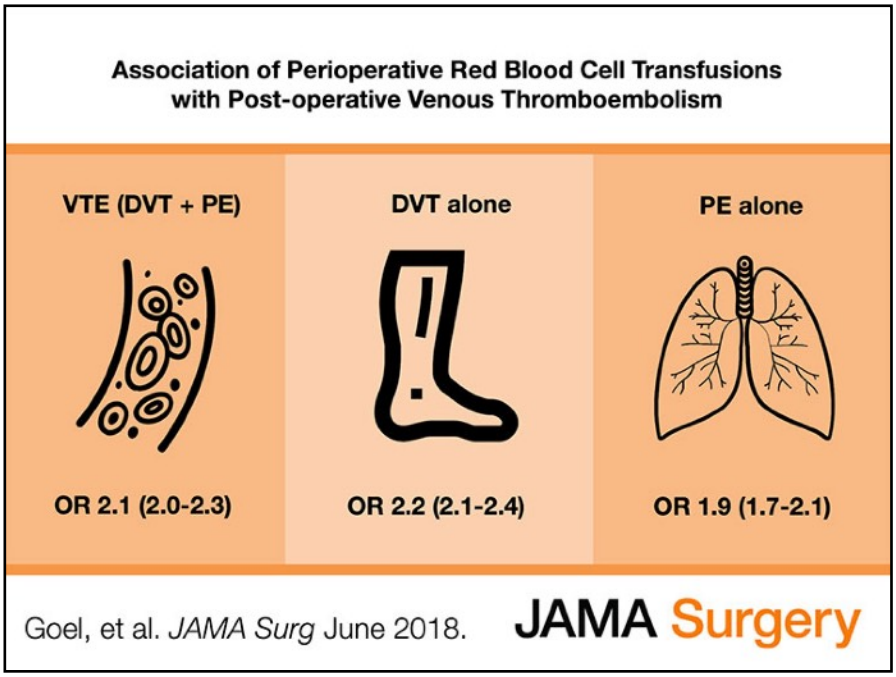
Ruchika: That's right. We have many surgical specialties. The most common contribution of patients, about half of the patients, were from general surgery patients. But we have neurosurgery patients, orthopedic surgeries, cardiothoracic surgeries, vascular, gynecologic surgeries, and neurological surgeries which were included in this.

Joe: Okay. That's awesome (and I promise you, I'm getting to my question! I just wanted to make sure I laid the groundwork there). So with that, with the 750,000 patients getting elective surgery across multiple different surgical subspecialties, and we see about 6.3% of them getting red cell transfusions, here's my question. We have talked for a long time about how transfusions are going down, and how transfusion is being done more wisely in the "age of patient blood management." This is not in your paper, but I'm wondering if you have any impression of this. Is that 6.3%, is that a number that should mean something to us? In other words, and I know you didn't do this, but if you looked at say, 2010, or 2005, do you suspect we'd see a significantly higher number of patients that were transfused? Or are you aware of that data?

Ruchika: That's an excellent question. Actually, objectively, this is one of the things we are working on right now, to see the trends in the surgical procedures and transfusion. But they recently published some national data looking at how the transfusion trends are changing. To answer your question, personally, I definitely think that we would have seen, back in 2005 or 2006 if you were to compare, much higher transfusion rates. So nationally from 2011 onwards, there's been a significant inflection point where we are seeing the peak of the "patient blood management revolution," as I like to call it, and decrease in transfusion. So, I can't quote objectively with numbers as of now, looking at what the surgical trends are. Like I said, this is one of the things we are working on right now. I would anticipate it's lower. I can also add, as a commenter just verified this, some of the comments that Aaron and I have been receiving from some researchers from Europe, they have commented on that, yes, because of the patient blood management, they are surprised by 6.3%. They are surprised by 1% preoperative and they are surprised by 6.3% being low. I think that's good news, and that patient blood management is really making an impact. But we'll have objective numbers for you soon, hopefully.

Joe: Yes. Okay. That's awesome. And, folks, I should have mentioned this in the beginning, but if you'll visit the show page for this episode, [NOTE: BBGuy.org/058], I will not only, of course, have the link to this wonderful article that Ruchika and colleagues published, but I'll also have the link... Ruchika just mentioned that she was involved in publication of a summary of transfusion of different components in recent years. Ruchika, forgive me for not remembering the exact specifics of that, but I know that you and Aaron were involved in that as well. I'll have that link also, so that people can see a little bit of the context against which all of this is occurring. So, Ruchika, thank you for going with me on that little excursion. Let's get back to your study, and specifically, what you guys found. Just to set the stage, you looked at 750,000 patients, you saw in the range of 6.3% total transfusions. You're breaking them down into people that had venous thromboemboli in the pre-op period and in the intra-op period and the post-op period. So what did you find? What did you find in terms of the risks of transfusion in those settings?

Ruchika: So, after, if you were to look at the unadjusted odds ratios, if we did not account for any other factors, we were seeing that any red cell transfusion and postoperative risk, it was very high odds. We had about 5 to 6 times odds of developing a venous thromboembolism within thirty days. After adjusting for the list of factors we just discussed, all of them adding them in the model, as completely expected, the adjusted odds go down. So as a nice summary number, for receiving perioperative red cell transfusion, venous thromboembolism, there's twice higher odds of developing venous thromboembolism. And again, when stratified by DVT or PE, there is similar numbers. So just to approximately say, twice higher odds of developing venous thromboembolism on adjusted analyses with any perioperative red cell transfusion. This was kind of like, I would say, the gist of the study.



Ruchika: And if we look at the dose-response relationship, it goes higher. With having one transfusion event, it was 2 times higher odds. With two transfusion events, approximately 3 times higher odds. With three or more transfusion events, it was going to 4 or more times higher odds of developing a venous thromboembolic event. Again, when stratifying by DVT or PE, very similar results are seen.

Joe: Wow. Those are kind of staggering numbers, Ruchika. Did that surprise you guys? Were you surprised to see that big an impact?

Ruchika: Honestly, it is real scary, so to say. And definitely surprising. The dose-response relationship was absolutely an eye opener. We were thinking that it would be higher, but it definitely is higher. Because the number of transfusion events intraoperatively do not go very much more than three or more, we did have to lump all of them together in one category. But still, to go to 4 times higher odds of developing venous thromboembolism, on adjusted analyses, after accounting for all potential confounders you could measure for. There's always some unmeasurable covariates that you cannot account for. But this relationship, I

think, yeah. It's a little bit [inaudible]. And I would say these results are somewhat scary.

Joe: They very much are. Boy, I'm right there with you. I found this both sobering and somewhat stunning. We'll talk about it at the end, Ruchika, about some of the things that this maybe has led you and your personal practice when you're consulting with folks about perioperative transfusions that may be somewhat borderline in their indication. So we'll get to that all in just a second. But before we do, you've mentioned some of the limitations of what you guys found. So I wonder if again before we hit the "how do we use this data," what are things that you guys put in the article in terms of the limitations of what you found and perhaps what needs to be done next?

Ruchika: Thank you so much, Joe, for bringing up the question because I think without very due acknowledgment to the limitations, we'd be overstepping the boundary. So I think it's very early on during my teaching when I was getting my formal biostatistical and epidemiological training in UNC Chapel Hill. I remember discretely the lectures were ... It was always this thing that just "remember the scope of the data." Do not step beyond and just due acknowledgement of the limitations is very important.

So, first and foremost I would start off with that. Knowing that, first of all I want to mention that these data are hypothesis-generating. By no means do these data suggest causality. We are at the best, able to propose an "association." We are at the best able to propose that yes we are suggesting an association. We have used valid, robust, statistical techniques to suggest the association, and we have done sensitivity analyses. We have analyzed our data in looking at different ways in every possible way to critique it. We have done subgroup analysis. So as far as talking about a statistical association, and as far as talking about a biological plausibility of this question, we are very... feel strongly that these data are robust and they stand strong.

However, there's recognized limitations. So, first and foremost, the exact intraoperative event that prompted a transfusion (these are supposed to be likely associated with some form of a bleeding event), so the exact indication is not known. We don't know the exact intraoperative hematocrit that prompted a transfusion. So, these are things that are ... The list that I'm making, suggesting here are things that in an ideally, well-designed prospective study, these are things that need to be accounted for and studied. So that was not available.

We did not have a idea, which is I personally feel one of the major limitations, is that what the POST-transfusion hematocrit was. So, we did not know that when these patients get transfused, how high did they get transfused to? To be able to truly establish a correlation between [inaudible] there is this threshold if you're transfusing above this number. This is where the risk or odds of developing an adverse outcome go significantly higher. I think that would make the study much more stronger.

The other limitation is that we, as I mentioned, we have used surrogate markers for assessing the severity of illness. There are multiple indices. There are the case mix Index, cause and severity index, APR-DRG Severity Indices. So every index has its own limitation, and at the best these indices can serve as surrogate

markers. To have a real-time correlation of what the patient's severity is, or what the exact event at that point which prompted this particular intervention and the outcome, that's not available, which would make the study more robust.

But I would acknowledge this as a limitation currently of pretty much EVERY study, observational, prospective, or to have a really composite, validated index of severity, it's hard. The other thing is if we would very much have liked to have a family history of illness, and whether these patients were on VTE prophylaxis or not. Those would be two clinical markers, and we could have adjusted them in the analysis. That would have been very helpful. However, we do hope that with our using the propensity score matching, we are trying to adjust for measured, unmeasured covariates to the best degree as much as possible.

Joe: Got it. I think that's a great summary of the potential limitations of what you're seeing there. Nonetheless, despite those limitations, what you guys have published, I think is very eye-opening, and should be eye-opening to everyone involved in perioperative transfusion, from surgeons to the anesthesiologists, to those of us that work in Transfusion Medicine. So I wonder if, given those limitations, given what you've found, I'll just throw the question to you: In your opinion, at this point, how should what your findings are either change or not change protocols for transfusions in the perioperative period?

Ruchika: That's a great question, Joe, because I think all conclusions have to be made within the scope of our study findings. I would say that our study is demonstrating that there MAY be additional risks to blood transfusion which are not currently well-recognized in the community. While additional research is needed to confirm these results, at least from what we have, the findings of this study, they do reinforce that we need to follow rigorous perioperative patient blood management best practices. Every drop of blood that we're transfusing, there should be a clear indication for that, to the degree possible, an evidence base supporting it. It should only be used when truly necessary.

The other thing is the preoperative input, which is a correction of preoperative anemia whenever it's possible. If you have the luxury of time, and can use a non-transfusion alternative, with the eventual goal being to you can avoid an intraoperative transfusion, that should be paid attention to.

I think it zeros down truly on the patient-centric approach. That the goal of all this is keeping the patient and the patient's best interest in mind, and going from there. Any time you're doing patient blood management, any time you're really thinking, "What else could I do? Could I do cell salvage? Could I use antifibrinolytic agents? Could I use a better, less invasive surgical technique? Could this be done laparoscopically? Would a robotic technique be better? Could I use a better hemostatic cautery?" Anything that causing less blood loss and does just putting the patient less at risk for receiving transfusion. I think it's like not just one ... Just exactly as patient blood management is, it's not just one thing. It's like a conglomerate of various steps throughout the patient care, throughout the hospital stay that comes into account. So, I think every little input would matter, and while we don't have definite evidence supporting this relationship, we cannot suggest causality (and that's something we really hope

we can do in the future), at least the practice-changing part is something that should not hurt the patient, we hope. So it can only help.

Joe: Boy, completely agree. I think you guys stated that, in fact, very well in your conclusions in your paper, Ruchika. Because there's a lot that you could say about this study if you wanted to, perhaps, "jump the gun." So I really appreciate your perspective on this, and I should have known that that's the perspective I was going to get speaking with a physician who also has a master's in public health. So I should have know that. That you were going to be very reasoned in your discussion, which I think is absolutely appropriate. But it does ... I think this information has to be sobering for everyone involved in the transfusion, as I said, of patients in the perioperative period.

For those of you listening, I did an interview with Dr. Aryeh Shander, who Ruchika a little bit mentioned earlier. That's at BBGuy.org/052 where he was talking about preoperative anemia and preoperative anemia management. Ruchika mentioned that just a moment ago, and earlier in the interview as well. I would really recommend that episode to you to hear a little bit more about that process. If this scares you, one of the things that Dr. Shander was talking about is how to potentially avoid those scenarios of unrecognized preoperative anemia, in particular. So that's just a little commercial. Ruchika, forgive me for throwing that in.

Ruchika: Absolutely. It ties in beautifully. I think the work Dr. Shander's done, work from Dr. Steve Frank. These are such big, huge mentors and for me so inspirational to look at their work. They've set the ground for some of us I would say budding enthusiastic researchers to really follow suit and really follow the example they've set. So very grateful to have such very inspiring folks around to just follow, pick up the phone, ask them questions, just send an email, and how absolutely available they are for with their interest to teach. Yeah, this is a perfect segue.

Joe: It was.

Ruchika: It's I think a great chance to express my thanks to some of the stalwarts.

Joe: Sure, well Steve Frank is also a "friend of the podcast." He was on episode 48 talking about bloodless medicine. I'm basically trying to get all of your mentors on the podcast at one point, Ruchika. Is that okay? Can I do that?

Ruchika: Oh yes, that's great! You know, Joe, like I mentioned before. To me, it's truly such an honor to me to have a chance to work with some of the stalwarts in the field of Transfusion Medicine. Mentors that I can just pick up the phone, call, bounce ideas off, and they're so willing to help and teach. So, certainly Aaron's like my mentor and our dear friend. I really a lot of regards and thank you for him for everything so far. Really hoping to do some great work together. Big shout out to Eshan [Patel], who is a less known, so far, but I would say like a "space to watch out for." Eshan just graduated from Master's in Public Health from Johns Hopkins, and applying to medical school. But immense fount of knowledge, just a fantastic colleague to work with, and thanks for all his help with the analysis and as we went through repeated steps, and really with every step.

My thanks again to Melissa [George], Steve [Frank], Dr. [Paul] Ness, Cliff [Takemoto], Ljiljana [Vasovic], for all her support. Sujit [Sheth], and Marianne [Nellis], my dear colleagues from Cornell, and Yvette, certainly, who's been at every step and helped me throughout with her guidance. Big shout out to the team and heartfelt thanks from myself and Aaron.

Our next step, I would take just a second to mention here, that the pediatric session, looking at the similar results in pediatric and neonatal population which is work that I have had a fortune of doing with Aaron and Cassandra [Josephson]. That's going to be presented as one of the plenary talks at AABB in October. So, we are still very actively working on the analysis and looking forward to sharing some interesting findings with everyone. I have a lot to be grateful for, and yeah, looking forward.

Joe: Well I know with your background in pediatrics that's going to be very near and dear to your heart, and I'm eagerly awaiting to hear those findings.

Ruchika: Sounds great. And yes, like you mentioned, Cassandra's on board, so it's just phenomenal to have her support and input.

Joe: Well Ruchika, I have no doubt that just based on, in the relatively short time that you've been in Transfusion Medicine, the impact that you've made already with the studies that you've been involved in, the things that you've written and participated in ... It's truly impressive and there is absolutely no doubt in my mind that as we go forward, you are going to be someone that we're going to be hearing from. You're going to help set the pace for the next generation of Transfusion Medicine physicians. So, I'm very excited to hear everything that you do going forward. I thank you for this paper, for everything that you've done with this, and for your willingness to share this with me and my audience today. Thank you so much, Ruchika.

Ruchika: Thank you, Joe. It's an honor. Thanks for the opportunity.

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Joe: Well, my thanks once again to Ruchika for joining us for that really, really interesting session. I hope that that was of value to you. I think that paper really has the potential to be revolutionary in terms of what we do in patient blood management, and moving forward in terms of describing risk for venous thromboemboli in postoperative patients.

So remember, you can go to www.wileyhealthlearning.com/transfusionnews and get an hour of totally free continuing education credit. Now that's both for doctors and laboratorians. You can also find references and other good stuff on the show page for this episode. You can find that at BBGuy.org/058. You'll also find the link to the actual paper there.

Also on the Blood Bank Guy site, you can find other episodes, including the most recent episode which was an interview with Dr. Brenda Grossman about "antibodies of undetermined significance." If you haven't checked that out, it's been been really popular, and I hope it's of great interest to you.

Speaking of that, you can also find this podcast really pretty much everywhere you find your podcasts which includes Apple Podcasts, Spotify, Google Play, Stitcher Radio, a whole bunch of different places. If you get the chance, if you can go to Apple Podcasts and give this podcast a rating and review, I would really, really appreciate it.

So the next episode is coming soon. It will be an interview with Dr. Megan Delaney on basically how we match blood and how we can match blood for the prevention of hemolytic disease of the fetus and newborn. It's really an interesting interview, and it will be coming out very, very soon. But until that time comes, my friends, as always, I hope that you smile, and have fun, and above all, never, EVER stop learning. Thank you so much for being here. I'll catch you next time on the Blood Bank Guy Essentials Podcast.