

Dr. Chris Tucke...: Welcome to the Arthroscopy Journal Podcast. I'm Dr. Chris Tucker from the Walter Reed National Military Medical Center and founding editor of the podcast. Today, we are discussing biologics and in particular platelet rich plasma. I'm excited to welcome back to the podcast of familiar voice to many listener, one of our prior hosts and a good friend and colleague of mine, Dr. Andrew Sheean, an active duty air force sports medicine specialist from the San Antonio Military Medical Center. Dr. Sheean is an avid researcher, resident educator, associate editor for the Arthroscopy Journal and an active member in AANA.

Dr. Sheean was the lead author on the recent infographic titled Platelet Rich Plasma: Fundamentals and Clinical Applications which was published in the September, 2021 issue of the Arthroscopy Journal. His co-authors include Adam Anz and James Bradley. Andy, congratulations on your work and welcome back to the podcast.

Dr. Andrew Shee...: Chris, thanks for having me. It's fun to be back here in the hot seat and I'd be remiss if I didn't acknowledge the hard work and mentorship of my other two, co-authors Dr. Anz and Dr. Bradley. It's been really great getting to know the both of these two gentlemen over the last handful of years and both of them have had a substantial impact and influence in the way that I think about orthobiologics and the way that I've been able to implement them in my practice thus far. These infographics are always fun to do. We've done a handful of them, but this one was particularly fun and I hope illuminating for the Arthroscopy Journal readers.

Dr. Chris Tucke...: Well, I have to say, I'm excited to have you back. It was a privilege to have you as a host for so long when we started this project and we're on to have you back as a guest again. So I'm excited to discuss this in particular with you because I think as with almost all practicing sports medicine surgeons there isn't a clinic now where I don't discuss biologics of some form or another with my patients. On that note, I want to dive right in. I think biologic can be a little bit intimidating or confusing for some because speaking the language is very important and it's sort of got a vocabulary, all of its own. I'm hoping you can demystify that for all of us today. Can you just start by covering the basics for us from a 30,000 foot view discussing biologics in general, what we even mean when we say the term biologics and then what PRP is and where it falls into that field?

Dr. Andrew Shee...: Yeah. I think that's a great way to get started and I think it's really important at the outset here for us to emphasize the importance of the language and the vocabulary that we're using. Regrettably, there's so much bad information out there and in many respects the way in which that orthobiologics have been discussed in the late press within the peer reviewed literature by orthopedic surgeons and non orthopedic surgeons has created a suboptimal situation. I think it's diminished the credibility of the innovation and the promise of orthobiologics and also regrettably it's hampered research progress. And I'll talk a little bit about that particular aspect as we get into our conversation here.

The way that I think about orthobiologics is a concept that Dr. Bradley had introduced and I've heard him lecture on many times. It's a cellular treatment hierarchy. And so if you think about, if you close your eyes and you're thinking about a diagram. You have your cellular treatment hierarchies kind of the top and then it splits off and then on the left you have platelet rich plasma. There's two main types of platelet rich plasma. There's the leukocyte enriched platelet rich plasma and there's leukocyte poor platelet rich plasma.

And then the other branch point is the stem cells are the medicinal signaling cells. I've heard Dr. Arnie Kaplan talk about whether or not it's appropriate to be calling them mesenchymal stem cells or medicinal signaling cells. So we'll just for the rest of this conversation just say MSCs. There's autogenic and allogenic MSCs. I think that most of what it is that orthopedic surgeons are talking about, reading about and implementing or trying to implement in their process are the autologous point of care, you are expanded MSCs and those have a couple different sources.

They can come from either marrow commonly harvested from the iliac crest, but also [Gus Mazak] and his group have recently published a lot of compelling literature to suggest that it can be harvested from the proximal humerus, which is obviously advantageous and particularly convenient considering that a very commonly used application of MSCs would be to augmented rotator cuff repairs and then adipose tissue being the other main source of autologous MSCs either abdominal adipose tissue that's been described similar to what's used in a lipo suction harvest or harvesting MSCs from the infrapatellar fat pad.

Dr. Jason Drago has published quite a bit and has demonstrated that the infrapatellar fat pad can be a viable source of these adipose derived MSCs. And so that's the overview. That's the way that I think about it and I think that, that's a 30,000 foot perspective that hopefully is easy for most of the listeners to get their minds around.

Dr. Chris Tucke...: I think it's a fantastic summary. You're obviously quite well versed in the language and I think you demystified it a fair amount out for us and clarified it, which I appreciate. So focusing on this specific infographic, we talk about PRP and its biologic activity with respect to two main areas of interest. It's anti-inflammatory effects for conditions such as osteoarthritis and its healing potential with respect to tendinopathies or tendon injuries or even repairs. Can you review for us the basics of how both of those actually work?

Dr. Andrew Shee...: Sure. You did a lot of the work for me with the way that you put the question together, but I think you're framing it nicely and there's really a dual mechanism of action here when we're talking about platelet rich plasma, and it pertains again to accelerating or augmenting the capacity of the target tissues to heal and then it's also diminishing inflammation or diminishing or ameliorating a deleterious immune response.

This is done in a couple different ways, but from a big picture perspective, PRP, we're pretty confident promotes collagen matrix generation while decreasing proinflammatory cytokines, IL receptor agonists, IL six, eight MMPs, all of these molecules that are in the milieu that we know are responsible for inflammation and matrix degeneration. And then another component of the PRP that we talk about in the infographic itself is the release of the alpha granules, which we know are these quanta of biologically active molecules.

I like to think of the alpha granules as the engines that drive the secretion of growth factors, VEGF, TGF beta are all things that we think are promoted by the presence of these alpha granules at the point of the point of entry or the point at which we're trying to affect a biologic process.

Dr. Chris Tucke...: So specifically talking about PRP, I was hoping you could dial in on the specifics of the classification, the PAW or P-A-W classification as you refer to in your infographic just so we can all speak the language and understand what those three variables are and why they're important.

Dr. Andrew Shee...: Yeah. So this was something that was published I think in 2012. Jeff Dulong along with the lead author on this. And Dr. Bradley's got a great slide in one of his talks where this PAW classification was actually dreamt up on the back of a styrofoam cup. He had a cookout or something like that. It was serendipitous but it's helpful really helpful. There's a number of different ways to talk about PRP. And so we'll go through the PAW. The P stands for the number of platelets, the platelet concentration. The A is the activation method and the W is the presence or absence of the white blood cells.

Now, the PAW has been implemented, embraced and I'd say if I had to characterize it, probably a limited fashion over the last decade or so. But I think what's, what's more important here and getting back to what I said earlier about language and the importance of the vocabulary that we're using is that however you're thinking about biologics, and in this case, PRP, and when you're reading it, you're reading it with a particular attention to the different factors that we know are so important. The leukocyte concentration, the platelet concentration and understanding that it's very easy to find yourself as in a circumstance in which regrettably authors or investigators are comparing apples to oranges and then concluding that there's no difference.

And we've talked about the problems and the pitfalls of type two error in general. But it's really, really important that in 2022 now that we're reading the literature with a very close, very exacting and very specific eye in understanding that all of these different things matter. And if we're really interested in arriving at the truth so that we can advance the state of the art and ultimately take the best care of our patients that we can is that we're acknowledging that each and then every one of these variables is important. And again, we're doing everything we can to put ourselves in a position in which we're comparing apples to apples in a clinical setting and a research setting in those respects.

Dr. Chris Tucke...: Yeah. I appreciate your perspective. I think being an associate editor for the journal, you get to see so much literature and review it with such a skilled eye that I think your perspective on this topic is valid and very timely. I think that's a great segue into my next question, which I think maybe we can help kind of discuss that bench to clinic transition of research to application. And if you could review for us the current clinical applications for PRP and what evidence there is to support those uses.

Dr. Andrew Shee...: Sure. So I think that certainly there is a preponderance of clinical evidence that would suggest that both the non-operative and operative treatment of rotator cuff tendonitis, tendinosis and tear either partial or complete tear can be affected, can be improved as far as the clinical trajectory of the patients go if PRP is added to a treatment regimen.

It was funny. I was just talking to a couple colleagues of mine and we were discussing the AOS, CPGs on PRP, which are not particularly hospitable, but when you go back you gig and say the world's published, I think in about 2019 And think about the research that goes into it. So much has been published since then. We've written a couple editorial commentaries on this issue or this application of PRP.

And so I think that there continues to be a growing body of evidence that would suggest that PRP particularly in the setting of augmenting rotator cuff repairs is particularly efficacious in enhancing healing rates, which as we know, particularly in the situations, circumstances involving younger patients that have a very strong preference for strength restoration that a healed repair is a stronger repair.

And so I'm a very big believer in the efficacy of platelet rich plasma in the operative and non-operative treatment of rotator cuff pathology. The other issue that I think is worth thinking about is everything that's come out and has been published within the last two to three years or so about the deleterious effects of a corticosteroid within a temporal proximity to a surgical intervention. And so if we have a preponderance of clinical data that is suggesting that PRP is as good or better or as good as a corticosteroid injection but obviously does not have the deleterious effects.

And we can talk about some of the downsides of PRP used in the clinic are. Then I think it becomes more and more of a no brainer, so to speak, as more and more of those types of studies are published.

I hinted at it, but knee osteoarthritis is also a very promising application for PRP and has been shown to be as efficacious as corticosteroids and hyaluronic acid or visco supplementation. And then Dr. Bradley has shown that PRP the setting of hamstring injuries and the non-operative management of hamstring injuries, partial hamstring tears have shown a lot of promise and returning high level elite athletes to return to sport quicker and accelerating their recovery, which

when you're talking about elite athletes, if you can accelerate return to sport by a matter of six days, that's a big deal.

And then the other historical issues or the historical applications of PRP that I think there's compelling data for lateral tendonitis that's been shown to be particularly efficacious. And the infographic gets it that I think it provides a nice overview of schematically of the areas that I think that the biologics and the PRP are, are worth people paying attention to.

Dr. Chris Tucke...: Yeah, I agree. I think the infographic has a very nice visual layout of those things, which obviously as we know is the point of the infographic. Now, for those who may not have biologics as a part of their practice currently but are looking to incorporate them, could you review some of the practical aspects of what's needed and how one might go about starting to use PRP either in the clinic or the operating room setting?

Dr. Andrew Shee...: Sure. And I'll speak to my practice specifically. I'm clinically active in a military treatment facility. So I acknowledge that a lot of the payer related issues that my civilian counterparts have to deal with and circumnavigate are not exactly applicable. And so it's been to the credit of our leadership here at the San Antonio Military Medical Center has been very hospitable to procuring PRP machines that are housed in both our clinic and our operating rooms. And so from a logistical standpoint, I've certainly been a part of clinical models in which PRP injection can be integrated into a otherwise normal clinical routine.

We've found here locally, that it makes sense to set aside some time. Usually we have a PRP clinic that will do my half day every other week. And so we'll have providers that are adept with ultrasound doing ultrasound. Got humeral joint injections with platelet rich plasma. The high level evidence I acknowledge is lacking in that respect but we are extrapolating what we've seen in the knee. We're actually getting ready to study that.

But then we've also got providers doing subacromial PRP injections for rotator cuff tendinopathy, partial thickness rotator cuff tears that are being treated non-operatively. And then interarticular knee injections which we're doing without ultrasound. You can certainly be using ultrasound. We generally aren't using ultrasound as an adjunct in that respect. And then in the operating, I use PRP regularly at the end of every rotator cuff repair. So we've got a machine in the room. We'll draw the requisite amount of blood before the case gets started, spin it while we're fixing our rotator cuff and then have it ready to go. At the end of the case, I will put the spinal lead on percutaneously to the repair site.

I will close my arthroscopy portals after I've evacuated the arthroscopic fluid from the subacromial space and then I'll inject the PRP at the end, which then I guess is really important. And it goes to not just what the formulation of the PRP is but specifically with respect to rotator cuff tears. It's how you do it. You put it at the repair site. You put it under direct visualization. You're not just shooting

in the subacromial space when you got a whole bunch of arthroscopic fluid in there.

And so that's how we've been approaching here and I think we've had really good success both in terms of the implementation and I think that the patients very much enjoy and appreciate the access to a really, really exciting innovation within our subspecialty focus area.

Dr. Chris Tucke...: Yeah, I appreciate those thoughts and tips from your own practice. This might be a slightly redundant question but I was wondering if you could just share with us your experience with the use of it clinically at least in terms of patient response and any clinical pearls or tips or lesson learned along the way with respect to how patients respond to it and how you've adjusted either your kind of timing of using it algorithms on when to do it, or any adjustments to your rehab protocols or anything like that.

Dr. Andrew Shee...: Yeah. So with respect to rotator cuff repair, I'm a big believer in like I mentioned the mechanism of action with respect to what it's doing at the repair site and what it does to help reconstitute the analgesic effect and that's anecdotally what I've appreciated here is I think that there is a substantial analgesic benefit that comes along with that in addition to everything else that we're doing from a multimodal standpoint and limiting the amount of narcotics our patients are dosing perioperatively.

And then from a non-operative standpoint, I think that there's several good clinical studies that would suggest that if you're treating rotator cuff tendon pathology, non-operatively patients can oftentimes benefit from a series of several PRP injections either two or three spaced between I'd say between 10 and 14 days apart. There's a logistical issue there but at the same time and it's not an exact comparison but patients are accustomed to coming back in for their series of hyaluronic acid injections and things like that and the other fiscal supplementation that require a series of injections.

I found that, that hasn't been a very tall order or tough sell and I think that we've seen good results here. And so we're excited about what we've been doing and what we're going to continue to do.

Dr. Chris Tucke...: So taking a step back from some of the more kind of tactical or logistical aspects of PRP and may just touching on some philosophical question, what do you think are some of the most important unanswered questions with respect to biologics or PRP and specifically, or what do you see as the most important next step for advancing this field?

Dr. Andrew Shee...: So I think it's an excellent question and I think there's two main areas that at least I'm interested in and what our research group has, has been looking into. And the first one is the way in which that bio inductive scaffolds can act as reservoirs for orthobiologics. And so we've talked about and we've learned a lot

within the last several years about... and I mentioned this earlier, about how important it is as far as how you go about delivering the biologic therapy in question.

And so as more and more energy and enthusiasm builds centered around bioinductive scaffolds, rotator cuff repair. The treatment of tendinopathies. Can we be creating or realizing a synergy between these scaffolds and the biologic that we're talking about? Can we be engineering these scaffolds in a way to provide a robust augmentation to the tissue that we are repairing or looking to heal. But then also having these scaffolds be constituted and or manufactured in a way in which they can hold on and potentially be alluding these biologic molecules in a way that makes sense kinetically.

The second main area of interest for me personally was actually something that was catalyzed by Adam Anz's work. Instantly in a paper that was published Arthroscopy Journal 2019. I did a podcast on it, but is the variability that individuals will demonstrate in the composition of their point of care blood products and more specifically what does an acute episode of exercise do 30 minutes prior to or an hour or two hours prior to a harvest.

And so we've just in my mind scratched the surface in terms of person to person variability, but also to variability amongst her specific two individuals. And so at this point some of the listeners are probably rolling their eyes saying there's too much variability. In certain respects, that's the case, but I think that we owe it to ourselves as clinicians and clinician scientists to be trying to attack these avenues or these areas of variability because I think what's going to lead us to finding the correct formulation, the correct delivery method, the correct preparation, all of these things that go into this.

I look at all of this variability as something that's exciting and it's going to be an area for so much investigation and innovation for years to come.

Dr. Chris Tucke...: Yeah, I share your enthusiasm. I think it's exciting too. I remember reviewing that podcast about two ago and I thought it was a fascinating concept of that point of care harvest and what variables can be affected. And I agree, there's a ton of variables and as you said, you can either look at that as a challenge and a barrier or you can look at as an opportunity. I applaud folks like yourself who continue to push the envelope and investigate this sort of stuff. Fantastic discussion. Do you have any other closing thoughts or comments before we conclude?

Dr. Andrew Shee...: No, I'm so appreciative of the opportunity to get back on the podcast and this has been a great conversation. It's really important. I opened up lamenting the fact that there's been so much bad information out there and regrettably some of it has come from individuals in our circles. And so I would encourage our listeners and all the investigators out there we're thinking about biologics and we were talking about biologics is that we're precise with the language that we're using. We're honest with respect to our outcomes and our findings and

we're measured in our adoption. And I think that if all of us are approaching biologics using that framework I think then that's going to maximize the likelihood of again of us proceeding towards innovating in a responsible way, in a way that doesn't leave the science vulnerable to the biases and to all the pitfalls that we've discussed and then ultimately really solidifies our position as orthopedic surgeons as the experts in this particular multi-skills space. I think we owe that to ourselves and we owe that to our patients.

Dr. Chris Tucke...: Absolutely. Andy, I want to congratulate you and your co-authors again on this important work and thank you for sharing your time and your thoughts with all of us today.

Dr. Andrew Shee...: Thanks so much, Chris.

Dr. Chris Tucke...: Dr. Sheean's infographic titled Platelet Rich Plasma: Fundamentals and Clinical Applications can be found in the September, 2021 issue of the Arthroscopy Journal which is available online at www.arthroscopyjournal.org. This concludes this edition of the Arthroscopy Journal Podcast. The views expressed in the podcast do not necessarily represent the views of the arthroscopy association or the arthroscopy journal. Thank you for listening. Please join us again next time.