

Dr. Justin Arner :

Welcome everyone. I'm Dr. Justin Arner from The University of Pittsburgh Medical Center in Pittsburgh, Pennsylvania. Today, I have the pleasure of speaking with Dr. Darren de Sa, assistant professor in the Department of Orthopedics at McMaster University. Dr. de SA was the senior author of the paper title "Tranexamic Acid Administration in Arthroscopic Surgery Is a Safe Adjunct to Decrease Postoperative Pain and Swelling: A Systematic Review and Meta-Analysis," which is impressed in the arthroscopy journal. Welcome Dr. de Sa thanks for joining us.

Dr. Darren de SA :

Thank you, Dr. Arner for the invitation as well as to the Arthroscopy journal. Happy to be here.

Dr. Justin Arner :

Yeah, this is great. First of all, congratulations on a great study and you've really got know how to do these systematic reviews in a very professional way and meta analysis. So, it's always great to read them from your group. So, tell us a little bit about how you got interested in this topic.

Dr. Darren de SA :

Thank you for that. As you know over at McMaster, with our max sports group, we do systematic reviews and meta analysis the idea being to convert these or to at least generate ideas that would lead to large scale multicenter, randomized control trials. So, constantly in the back burner, there's pan of what could be our next idea and what do we do to better what we are doing now and the care we offer our patients. And so, it happened to be serendipitous in the faculty that with this constant background machine for disease and research that we have, we were looking specifically and about to start a trial looking at reducing opioid consumption after our thoracoscopic surgery. And with that a few other adjuncts to overall improve the patient experience into particularly improve pain in the postoperative period.

So, there was that, and we were about to launch that study. And at the same time, I had reconnected with orthopedic surgeon and fellow Canadian, Jason Shin, who actually also completed his Pitt Sports Medicine fellowship the year before me. And so we had connected and were catching up on both personal and professional updates and in our discussions. And we had talked about research and the next thing. And came up as looking at TXA specifically. And then we had discussed a little bit in depth for the different ways to better understand this. And at the end of the day, we settled on at least starting as a first line with a systematic review. And so from there we discussed that further, discuss the methodology and the rest is history.

Dr. Justin Arner :

Yeah, that's great. It's always fun to be able to catch up with colleagues and do projects like this together. So, can you tell us a little bit about some of the basics of the mechanism of action or how we think TXA works and a little bit about history and it seems like it's a fairly safe drug.

Dr. Darren de SA :

TXA, it is not new. And for myself particularly I was familiar with it in the trauma setting. So, whether I currently also do emergency work and serve on the trauma service as well as trauma team. So, I'm certainly familiar with using in that context and had learned about it at different stages throughout my training. Briefly the mechanism of action is that it's a synthetic molecule it's supposed to replicate or

mimic Lysine. And so the way it's supposed to work is to directly or competitively bind Lysine binding sites on plasminogen which prevents plasminogen from becoming plasmin, which is important in breaking down the clot. So, if you're competitively binding this, the idea being that it's not able to plasma, you're not able to break down the clot and as such, you have less bleeding. That's basically in a nutshell it's mechanism action, but the history, I thought it was quite interesting, especially as we started to do a little bit more research and for this project was looking at... It's not new.

Again, it was developed usually in the early 1960s, but didn't start making it appearance in medicine until the early 1990s. And it first started initially to treat heavy menstrual bleeding females, other patients with hereditary bleeding disorders, things along that nature. But since then it had quite a broad scope. It's applied cardiac surgery, many other surgical fields with orthopedics, and it's extended to arthroplasty particularly hip and knee, fun ankle surgery as well, and is slowly starting to enter now sports medicine. So, the applications are quite wide, particularly in the context of trauma and postpartum hemorrhage. There's actually been shown to be mortality benefit in some studies as well. So, it's proposed by the synthetic mechanism to do that. And it's applications really seem quite wide.

To address your question about safety, the interesting thing is it's not for everyone, not right now. The literature at least does not have a lot of information on its application in the pediatric population.

For example, there's certainly contraindications so that the lists, we can discuss if it's of interest, but there're both contraindications, but also to be made given that the fact that it is a synthetic drug and that it is treated primarily to the kidney. So, in patients mainly with renal insufficiency, for example, dosing and other adjustments, if considering using it are important. That being said, there is no real across the literature documented adverse effect or significant complication that has been reported with its use in the current populations that it has been used in. And so I would just say, thinking about using it, although it appears to be safe now, particularly in the short term use, that that is available in the literature. Still think about this and approach it's used on an individual basis, you after discussing with the patient and also your anesthesiologist and internal medicine doctors as needed.

Dr. Justin Arner :

Yeah. That's an excellent summery and really a great plethora of information there. Can you tell us a little bit about the studies you encountered and basically the quality of some of the studies and the bias and just give us a brief summary of what you found in your systematic review and that analysis?

Dr. Darren de SA :

Yeah. So, by design again, which is usually finalized before we even undertake the study, we aim to include only randomized control trials. So, we wanted, although we broad understanding of where TXA is used in orthopedics, as it pertains to arthroscopic surgery, we did still want the highest level of evidence available. What we found in general is that, first of all, there's not a lot out there. So, 71 unique studies addressing TXA in the arthroscopic or sports medicine population at the time that we searched the databases. So, that was back in April 2020. Of that in applying our criteria for our specific purpose, we ended up with seven unique randomized control trials, but of that the majority four of those seven were specifically focused on ACL reconstruction and then one each in arthroscopic knee, surgery for meniscectomy, FAI, and rotator cuff repair.

And so overall not a lot out there are starting to touch on the different elements of arthroscopic surgery and sports medicine, but still not a lot within each individual realm. But that being said, and in particular, in this study, the study tended to be of high quality level one, or level two randomized control trials. As part of our methodology, we do always a quality assessment. And as it pertains to randomized

control trials, we apply the Cochrane risk-of-bias tool, version two for it. And so this goes after particular tenants of what's otherwise considered a high quality RCT, not all RCTs are good. And so there are different elements that you look at in terms of allocation concealment, attention to treatment analysis, the randomization procedure, how much is lost to follow up, things like this, and based on all these criteria and the bias tool, we found that by and large, the majority of our studies, essentially all of them were a minimal bias as it pertains to this assessment.

The one study did flag as moderate to high degree of bias, but that was mainly because that it was not clear in terms of how surgeons were blinded. And so based on the objective application of these metrics, that's why it rated that way. However, as we discuss in the paper, how much blinding of surgeons in this context and its effect on outcomes is debatable. And so that's the, if I can say a brief view of the quality and, and what's out there. What our particular paper found is across these seven studies comparing, and we were able to do a meta-analysis on this, but comparing patients that received TXA from those that didn't, we found were statistically significant decreases in the visual analog pain score, particularly in the short term.

So, at the two week mark, which appeared to confirm a benefit up to about six weeks post-surgery, there were decreases in the number of people that required aspiration of joints for swelling or post traumatic hemarthrosis in certain studies and applications. There were decreases in the reduction of opioid medication across the board, which in those studies were measured as morphine milligram equivalents. When you're looking at outcomes and post surgical outcomes, especially again, in the early period within those first six weeks, patients on TXA appear to have better knee range of motion and quadriceps strength in that early period. And interestingly, we found that across a host of patient reported outcomes, whether or not someone had TXA didn't appear to affect those in particular.

And those are positive findings. What's important to note also from a technical standpoint, is that it didn't appear to make any difference with regards to operative time or in an arthroscopic context, what we consider better visibility or ease of performing the procedure. And most importantly, there were no reported rates of venous embolism, whether by DVT or pulmonary embolism infection or fibrosis, or any adverse reaction or allergic reaction to the medication.

Dr. Justin Arner :

Yeah, that's awesome. I appreciate all that complete review. I think that's really interest regarding the visualization. It would be nice if we could see better arthroscopy especially if you're doing a cuff or whatever in the beach here, position to be able to keep people's blood pressure a little higher, especially in the older folks. So, that's great to know. Can you tell us a little bit about your knowledge and what you've read about and used clinically regards to IV versus in inject TXA and different joints and toxicity in that type of safety profile?

Dr. Darren de SA :

Yeah. So for those listing, we do talk a little bit about the chondro toxicity profile from limited in vitro studies that exist as opposed to, as it pertains to topical application of TXA sites. And there has been some suggestion that direct exposure can be harmful in that context. Prior to this study and even undertaking, it did not use TXA topically by practice and at this point still do not routinely use it.

What I found and what we found in the paper was that the administration or the route administration of this drug is variable. It can be administered early topical injection. And particularly in this paper, in the sports' medicine context about 40% of the patients that received TXA received it by way of a topical or intraarticular bolus immediately post up, 30% or so received it as an IV bolus, given one to throughout the procedure.

And that time period varied whether it was prior to tourniquet inflation, or just prior to tourniquet deflation, for example, about 20% or so received a combination of an IV infusion, as well as a bolus again, at different time points whether pre-op or post. And then the remainder or 10% or so, just under 10 received, it only is an IV infusion. So, where I use it in my practice, when I do use it is as a IV bolus, just prior to the conclusion of the procedure. And that's given its other elements in terms of half life and what I'm using it for, the purpose I'm using it for, but there's still much that needs to be determined in terms optimal way to administer this and even the dosing.

Dr. Justin Arner :

Yeah, that was one question I was going to ask you about the tourniquet. It doesn't seem from reading your study and others, that there's real consensus about timing. If you're going to do it, say it before and after, if you should do it in a certain time in with tourniquet use, is that what you found as well? We're really not sure the best timing with tourniquet use.

Dr. Darren de SA :

Yeah. I would agree with that. I think it's a fair statement to say that right now it's the application of it. And that perioperative period is quite variable. Where I'm using it now is a procedure for an ACL time, I let down the tourniquet. Once tourniquet is down, then the anesthesiologist administers an IV bolus, typically one gram, although it is weight based after, based on our discussion and that's time point usually where it shows up in my practice, but again, it's quite variable across different indications and different surgeries in patient population.

Dr. Justin Arner :

Yeah. That's great. Great to know that was one question I was going to ask you. For ACL, is that your main indication now, or can you tell us a little bit about some of your partners and colleagues or in your experience when people have anecdotally found it to be helpful beyond ACLs, or do you think most people are at your stage because the literature seems to... Will be a little bit all over the place regarding it's a role.

Dr. Darren de SA :

Yeah, it's interesting. I would say until... I guess the impress notice of this paper went out there, at least in my circle, I did not keep or much about people using TXA at all, or even thinking about using it. It's probably the same relative experience I had prior to undertaking the study. Once that paper surfaced that you started to hear one offs, at least in my experience of surgeons in different academic centers, as well as community centers using it. From my discussions with these people seemed to be mainly used in, was in lower extremity surgery, and in particularly in the knee. Oftentimes where there was some open component associated with it, whether it was for example multi ligament reconstruction, and also in the ACL population. I didn't see it too much used in hips, for example, or upper extremity. There were some people that we're using it again in the foot and ankle context, but again, that is to pertain to whether or not there was an open element to the surgery, as opposed to purely Arthroscopic. That's what I would say in that regard.

Dr. Justin Arner :

Yeah. That's awesome. So, can you tell us, since you're in Canada, obviously cost effectiveness, we can learn a lot from your system. Can you tell us regionally or, or North America and different countries,

does it seem like certain people have adopted TXA more and, and you did mention some cost effectiveness in your study. Can you tell us a little bit about those two topics?

Dr. Darren de SA :

Yeah, so what's interesting is, as I talked about here, I started to hear more and more about one off or more anecdotal experience of surgeons use with TXA. Once know this information started to become more public knowledge post-study. But what I found that was interesting is in our actual study, there was no North American representation. So, it appears that across the indications whether it's the ACL meniscus, FAI, rotator cuff repair that was looked at in our particular study. Surgeons were using this around the world essentially, there were studies that came from Taiwan, Italy, Turkey, India, New Zealand, Spain. So, everywhere except a real North American presence. And so what I've found is that people are starting to use it more in that regard and things before it makes it mainstream here, we still need a higher level trial looking at our patient population and unique aspects to that piece.

But that being said, it is pretty widely applicable. Regards to the cost effectiveness piece, which is very important. And this is part of the reason that I've started using it again on case by case basis at this point, and more just for anecdotal experience is that the cost actually pretty low. So, at least in Canada, based on our metrics and information, it comes out to \$40 Canadian or so per gram by our estimates. And that's the number we quote in our paper using convergence, the US that's even less.

That's 30 bucks or so a gram and so very, very minimal cost to the overall care. And then you have to frame that within the context of the potential benefit that it's aiming to address. So, in our case, particularly in orthoscopic surgery, he and postoperative pain and swelling are the big drivers that we are hoping to attack because... Especially in our current healthcare environments, we have limited access to net patients.

These are typically all done as outpatient surgery. And so inadequate pain control can be a reason for people to re-present to the emergency department, increase resources associated with those visits and potential hospital stays.

So if this is able to make a significant reduction in that you could potentially impact the number of pain medication and the types of pain medication that is used. You need for aspirations and the complications that can happen with prolonged chemosis like pooling of blood as a driver for say, septic arthritis, for example, or a fibrosis and things along those nature. So, very minimal incurred. Again, thinking that most doses, at least in the IV setting are roughly around one grand from the literature and also what I've experienced in my practice and those around us for potential huge cost savings should there be any complications as a result of bleeding pain and or swelling.

Dr. Justin Arner :

Yeah, that's a big driver, I think of its use so that's great to know. One question I had, you mentioned some of the risks and benefits and everything. Do you come across any data or any knowledge that you have regarding someone that has a history of A-fib or his history of DVT, I guess it'd be older patients with rotator cuffs, or maybe some people are doing total joints. Is there any conjure indication that you found for that population?

Dr. Darren de SA :

Yeah. So, in general, the contraindications... Again, it's not an exhaustive list by any means, but typically those that have a history of a thromboembolic event in the past, certainly I would not, at this point, recommend you an initial TXA in any setting. We quote other potential contraindications that we're aware of being, including abnormalities in patients with regards to renal failure. We talk about, for

example having to adjust the dose, if we're going to consider using it in patients with renal insufficiency. But what I'm aware of outside of sports medicine, arthroscopic surgery is the literature that it looks at the population particularly. And these are generally older patients with more comorbidities.

And generally speaking, there are a few trials and studies of different levels of evidence out there that have suggested that even in this population or what you'd say a high risk baseline population from a comorbidity standpoint, TXA even in this population, seems to be beneficial and does not seem to be exacerbate or cause things such as venous embolism or ischemic events, whether it's stroke or MIs or translating ischemic attacks, it doesn't seem to be associated with any of that.

The big warning or caution that does come out in the different fields outside of sports medicine is that one, because of the fact that most of it, over 95%, of this drug being synthetic is excreted essentially unchanged by the body and it's done so by the kidney. So, we particularly attended to patients with renal conditions would be the number one thing. And then what I would say just in general is for us, even though it's outpatient elective surgery in the sports' medicine context and to it's increasing now in spine surgery, as well as an art class for moving towards an outpatient setting. Still, it's important that patients are assessed and undergo preoperative consults, whether by anesthesia or internal medicine or both, and that you approach this and it's used on a case like case basis.

Dr. Justin Arner :

Great summary as always appreciate that. As we start wrapping up here, can you tell us... There's a lot of missing pieces to this puzzle. Tell us what you think in arthroscopic surgery, you alluded to it. What we're lacking, what trials, what do we really need to know before people are going to adopt it? Do you think this will be as say in 10 years standard of care, what do you think we need to do? And what do you think you see future with TXA and specifically our sports surgery?

Dr. Darren de SA :

It's hard obviously to predict the future based on what one of the good things about a systematic view. And I know there's people that can criticize them at many different levels, is that consider the quality of the studies that went into it. And so this particular one, although there were seven studies, these are all level one, two randomized control trials.

So, at least as it pertains to this topic and the literature that's currently available, it is what I would say the most thorough and high level evidence that we have at least to guide this. What you often have to remember is that with evidence based medicine, there's the research piece, there is the surgeon piece or clinical experience piece, as well as what the patient wants.

And so all of these have to meld together. What we saw here, like I talked about was that across all fields of orthoscopic surgeon, sports medicine, there were only 71 unique studies. Although the seven trials that we included were relatively high quality and minimal risk of bias, they were still small sample size individual studies altogether, anywhere from 45 to 70 or so patients.

And so I think first of all it's important that we continue to work towards doing larger studies, multi-centered studies that are large numbers of patients that are powered to go after the results that we want. You mentioned earlier that we weren't able to see a difference between TXA and say various patient report outcome measures. That could be true in that TXA and the dosing and the administration itself isn't enough to actually cause a meaningful difference in that regard.

But it could also be the fact that the studies visually we're under power to detect differences in those tests, for example. So, what we need is I think a call for greater collaboration and to work in that way. What we do see is that there're some fields of surgery that are being used, ACL, meniscus work, FAI

and rotator cuff repair. For example, we should look to expand that within our full gamut of surgery and offerings that we do in arthroscopic surgery, as well as increase the total numbers in those realms as well.

And I think we need to work towards getting the other elements of evidence-based medicine. We continue to build a research portfolio, time will tell in our discussions with patients in terms of how they prefer to go with this, whether or not they do or not.

And then we need that surgeon experience, particularly with those from our a more clinically experienced ones. So, right now there is no consensus out there at least that we could find on whether or not TXA should be even used in the Arthroscopic population. Most people are using it off label and in one off cases in particular surgical procedures. And so I think we need as an orthopedic source medicine community need to come together and get an idea of where everyone opinion stands on this topic and try to arrive at some consensus on preferred roots of administration, dosing, indicated procedures and other things along that nature.

Dr. Justin Arner :

Yeah. That's excellent. Darren, thanks for your information and exhaustive discussion about this literature is so helpful. So, appreciate your time and thanks for joining us. I really appreciate it.

Dr. Darren de SA :

And not problem. And please give my regards to everyone at The Arthroscopy Journal as well as back home at Pittsburgh. Take care.

Dr. Justin Arner:

Thanks a lot Dr. de SA. His article titled "Tranexamic Acid Administration in Arthroscopic Surgery Is a Safe Adjunct to Decrease Postoperative Pain and Swelling: A Systematic Review and Meta-Analysis," is in press in the Arthroscopy Journal and is available online at www.arthroscopyjournal.org. Thanks for joining us.

Dr. Justin Arner:

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