

Review Article

Intraosseous Antibiotic Infusion- An old solution for an older problem

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Acute and chronic osteomyelitis are historical diseases that remain difficult to treat. Globally, Patients are impoverished and disabled due to our inability to treat this effectively. Particularly, patients with diabetes mellitus and multiple comorbidities suffer amputation and early death. Intraosseous antibiotic treatment at the infection site offers an opportunity to treat these patients efficaciously and economically.

A HISTORIC DISEASE WITH GLOBAL DIMENSIONS

Acute and chronic osteomyelitis have been major health issues with wide ranging social and economic impacts for thousands of years throughout all parts of the world. In the USA and Europe, a large number of diabetic patients and post-traumatic patients undergo amputation annually after failing lengthy, expensive and labor-intensive care that often leaves them destitute and invalid (Geraghty and La-porta 2019). In other locales, hematogenous osteomyelitis is also an important factor. Why do these patients fail current methods of care?

First, many of these patients are immunocompromised with systemic diseases or injuries, diseased vasculatures, marginal organs and weakened immune systems.

Second, because of the first, the infections have a susceptible host with the inability to deliver or tolerate therapeutic levels of medication without suffering further injury or comorbidities from the antibiotics. Taking the diabetic foot or the chronically infected tibial non-union as an example, the systemic blood supply is often diseased, but the local blood supply is always limited by the body's local response to the infection with vessel occlusion, fibrosis and thickened cortical bone attempting to wall off the intruder (Wilensky 1934). Very likely, even the otherwise perfectly

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c Selene Parekh, M.D. (also known as the "Fantasy Doctor") is an orthopaedic surgeon and foremost expert on sports injuries who's fast becoming the go-to expert for the multibillion dollar fantasy sports industry. His data-driven insights and medical expertise make for powerfully accurate predictions of how anything from common sprains to devastating season-ending injuries will affect players' careers and the success of millions of fantasy teams.

Fantasy sports for Parekh is far more than a hobby: He authored and published two foundational research papers using Fantasy football data to track the epidemiology and outcomes of tendon and ligament ruptures in the NFL.

Dr. Parekh joined the North Carolina Orthopaedic Clinic and Duke Orthopaedics in 2009, where he is a Professor of Orthopaedic Surgery. Prior to his tenure at Duke, Dr. Parekh was a Foot and Ankle Surgeon at the University of North Carolina (UNC). While there, he was integrally involved in the teaching of medical students and residents. Furthermore, he served as the foot and ankle consultant to the Athletic Department, treating many of the well-known UNC athletes. In his current practice, he continues to treat competitive athletes of all levels.

A graduate of the Boston University School of Medicine, Dr. Parekh completed his internship and residency at the Hospital of the University of Pennsylvania and his fellowship in foot and ankle surgery under the direction of some of the leading global authorities at the University of Pennsylvania.

The Fantasy Doctor is an avid runner and has completed the Boston Marathon, and in his former life as a high school athletic star, was offered football scholarships from several Ivy League schools and was the recipient of the Brian Piccolo Award. Dr. Parekh is married and he and his wife are the proud parents of three kids.

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Retrograde Flow-Screw Calcaneal Intraosseous Venogram in osteomyelitis patient with previous debridement.

healthy patient with chronic osteomyelitis is oftentimes unable to tolerate the systemic dosages of antibiotics needed to achieve the local concentrations required to treat a chronic infection without sustaining some organ damage.

Third, the infecting organisms adapt. Not only do they mutate into resistant forms and persist in biofilm slime, but recent work has demonstrated that *Staphylococcus Aureus*, at least, can hide and multiply in healthy appearing bone and intracellularly in osteocytes, osteoblasts and osteoclasts (Krauss et al. 2019). The demands that these factors place on antibiotics have rendered our historical reference, the Minimal Inhibitory Concentration (MIC), irrelevant in these patients and have led to new acronyms, the Minimal Biofilm Inhibitory Concentration (MBIC), and the Minimal Biofilm-Eradication Concentration (MBEC), that are attempting to give partial insight into local levels needed for successful treatment (Bayramov and Neff 2017).

So, we have marginal patients with damaged local blood supply trying to fight organisms that can mutate, lay dormant, and hide. If we increase systemic antibiotic levels or use them in combination, we may injure the patient's organs. If we debride until all of the infection is grossly gone, it is likely still present at the microscopic level.

Systemic antibiotics combined with local depot delivery has had some success after debridement but may also stimulate resistant mutation as local levels taper to sub-therapeutic levels (Bayramov and Neff 2017). Hyperbaric chambers and magnetic fields have shown success in some treaters' hands, while revascularization procedures have proved a very useful new weapon.

Regardless of the modalities at our disposal, the infection often wins, and many patients go on to amputation

and an early subsequent demise. Recent estimates are that up to 50% of diabetic amputation patients die within 2-3 years after amputation (Geraghty and Laporta 2019).

Progress in developing new antibiotics that will help us treat these patients in the future is fraught with frustration. This path of discovery is uncertain, expensive, fraught with delays and unlikely to reach developing countries.

POSSIBLE SOLUTION

What novel options can we implement now? It may be that a partial solution is easily available. For almost 100 years, physicians have used the intraosseous (IO) space to deliver systemic fluids and medication (Drinker, Drinker, and Lund 1922). Today, this method is used routinely on the battlefield and in acute civilian trauma resuscitation as well as pediatric emergencies where venous access is not readily available.

In recent decades, antibiotics have been delivered systemically by the same methods. The online literature provided by manufacturers of 510k cleared IO needles list many antibiotics and other drugs that are safely delivered through their devices such as the EZ-IO needle by Teleflex (Teleflex 2017). Despite current documentation of safety and long historical usage, no antibiotics are FDA cleared for intraosseous delivery. Efforts to have devices cleared for antibiotic intraosseous delivery result in the requirement that the antibiotic be cleared also. Additionally, there are no infusion pumps cleared for IO delivery of anything, so the challenge continues.

From an Intraosseous delivery perspective, antibiotics fall into multiple groupings. First, do they enter the systemic circulation directly or do they accumulate in the infused bone? Second, do they injure the local tissues with elevated concentrations or are they benign actors?

Serendipitously, a few of our most effective antibiotics collect in the bone and have low systemic levels when used via IO infusion. These same antibiotics need to be present in very high concentrations before local cells are damaged. Tobramycin and particularly vancomycin act in this way with IO infusion (Jaimovich 1991; Rathbone et al. 2011). These antibiotics may be able to achieve safe, hyper-therapeutic concentrations that could overwhelm active bacterial resistance mechanisms and penetrate biofilm to kill senescent bacteria.

FINDINGS IN CURRENT LITERATURE

Theoretically, IO infusion of antibiotics should increase local therapeutic levels while decreasing concern for systemic injury. A study from the Association of Bone and Joint Surgeons in 2017 conducted a randomized controlled trial investigating tissue concentration of vancomycin achieved with intraosseous regional prophylaxis in revision TKA. They ultimately discovered that higher tissue and bone concentrations were consistently achieved in patients treated with IO antibiotic administration (de Mattos et al. 2019). More importantly, the pharmacokinetic -pharmacodynamic parameter most predictive of efficacy of vancomycin is the area under the concentration time curve

divided by the MIC; therefore, higher vancomycin tissue concentrations are likely to enhance effectiveness (Craig 1998). Additionally, animal model experimentation supports the hypothesis that low dose intraosseous regional administration of vancomycin is more effective than standard-dose systemic vancomycin in preventing periprosthetic joint infections in total knee arthroplasty procedures.

The role of prophylactic IO vancomycin has proven to be a safe and effective alternative to using preoperative IV vancomycin in primary and revision TKA (Harper et al. 2020). Studies show that patients who receive IO vancomycin have equivalent 30- and 90-day complication rates in primary and revision TKA cases, even in patients with higher body mass indexes (Harper et al. 2020; Chin et al. 2018). Surgical complications such as AKI have been associated with patient comorbidities such as diabetes, with a large contributor to these incidences being patients who have high serum concentrations of vancomycin (Harper et al. 2020; Ma, Hoffman, and Mcneil 2019). IO administration of vancomycin after tourniquet inflation has been shown to keep serum concentrations undetectable during surgery (Young et al. 2018). This property of IO delivery is likely to contribute to a decreased incidence of AKI in total joint patients. To date, there are no clinical trials investigating the efficacy of IO antibiotic infusion in diabetic patients suffering from osteomyelitis, but similar indications of IO antibiotic infusion yield promising results that warrant more investigation. A study of such magnitude will likely yield heralding results that will directly benefit this particularly vulnerable patient population.

Talks with orthopaedic surgeons from developing countries in Africa, Asia and Central America yielded accounts of hospital wards in every country with chronic osteomyelitis patients receiving treatment to suppress their infections for a while rather than amputate. The most common story is the bicyclist with a chronically infected, open tibial non-union after a collision with a motor vehicle. Once productive contributors to their family and society, they are now disabled and dependent. Maybe these patients can be treated with tools already in our possession that just need to be used differently.

INDUSTRY INNOVATOR COMMENTS

THE FLOW-FX PROPOSAL

Flow-FX LLC is working with the FDA for approval of an IND for a pilot study of diabetic patients with chronic osteomyelitis who have failed all care and been recommended amputation. The protocol uses Flow-Screw™ with its IO Adapter as an infusion device for the treatment period.



Flow-Screw™ with IO ADAPTORS demonstrating proposed infusion and gravity drainage in calcaneal sawbones

Flow-Screw is a 510k cleared titanium alloy implant indicated for fracture fixation and bone void filler delivery.

At this point, our devices are grouped with vancomycin or tobramycin as a combination product that both CDER and CDRH have interest in. If proven to work, this treatment can change the lives of innumerable people and save the US Government billions of dollars annually.

During our ongoing journey developing this technology we've had the opportunity to learn quite a bit about local effects of antibiotics on bone, corrosion characteristics of titanium alloys, bacterial resistance mechanisms and of course, the pros and cons of our regulatory system.

As we're convinced that IO delivery of biologics, growth factors and other medications will be essential to successfully treat our most challenging patients, we will try to keep everyone informed as we progress. A recent white paper provided to FDA regarding the safety and local effects of antibiotics may be of some interest and I'm happy to share if emailed at P.sweeney@flow-fx.net.

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