Complications from Intradiscal Biologic Interventions

Mathew Saffarian, DO1; Ryan Mattie, MD2; Haewon Lee, MD3; Byron Schneider, MD4,5; Zachary L. McCormick, MD6; and Jaymin Patel, MD7

on behalf of the Spine Intervention Society’s Patient Safety Committee

1Michigan State University, Department of Physical Medicine and Rehabilitation, East Lansing, Michigan, USA;  
2Providence Cedars-Sinai Tarzana Medical Center, Department of Interventional Pain & Spine, Los Angeles, California, USA;  
3University of California, San Diego, Department of Orthopedic Surgery, San Diego, California, USA;  
4Vanderbilt University Medical Center, Dept of Physical Medicine & Rehabilitation, Nashville, Tennessee, USA;  
5Vanderbilt University Medical Center, Center for Musculoskeletal Research, Nashville, Tennessee, USA;  
6University of Utah School of Medicine, Department of Physical Medicine & Rehabilitation, Salt Lake City, Utah, USA;  
7Emory University, Department of Orthopaedics, Atlanta, Georgia, USA

The lumbosacral intervertebral discs (IVDs) are believed to be a common source of chronic low back pain (LBP). The IVD is the largest avascular structure in the body. Intradiscal biologic interventions are being increasingly used for patients suffering from chronic severe LBP [1]. There are various types of biologic injectates, including platelet rich plasma (PRP), bone marrow aspirate concentrate (BMAC), allogenic stromal cells, mesenchymal precursor cells, adipose-derived stem cells, as well as cultured and expanded stem cells. The risks of performing intradiscal biologic injections must be understood by any physician performing them, particularly since the efficacy of intradiscal biologic injections remains uncertain [1]. Accordingly, the risk-benefit ratio of potentially proceeding with such procedures must consider this uncertainty regarding potential benefit.

Fact: Although the available evidence on intradiscal biologic interventions is limited, it nonetheless shows a non-zero risk of complications. Until larger sample sizes are reported, the actual magnitude of the risk cannot be ascertained. In the meantime, physicians who perform intradiscal injections of biologics should conscientiously consider the risk-benefit of these procedures.

Published Case Reports of Adverse Events

The first published case of an infection following an IVD biologic injection was described in 2012 [2]. A 61-year-old male underwent “bone marrow aspirate, unseparated harvested adipose tissue autograft, and plasma from peripheral blood draw injection into his L3-L4 and L5-S1 IVDs.” Authors did not comment on the use of prophylactic antibiotics, either orally or injected within the disc, nor did they comment on the use of single- or double-needle technique. About one month later, the patient began experiencing fevers, increasing low back pain, and signs of acute cauda equina syndrome. A subsequent MRI revealed discitis, osteomyelitis, and an epidural abscess. The patient underwent emergency decompression, and cultures identified methicillin-resistant Staphylococcus epidermidis. Treatment consisted of IV and PO antibiotics and spinal fusion surgery. The patient eventually regained bladder function and motor control. The authors did not state whether there were any permanent partial neurological deficits.

A case of spondylodiscitis following a PRP injection into the L5-S1 IVD using a double-needle extrapedicular technique has also been reported [3]. No prophylactic antibiotics were administered. Symptoms began several weeks later with increased LBP, night sweats, and decreased mobility. The authors did not comment on specific neurological deficits. A biopsy showed Cutibacterium acnes. IV Ceftriaxone was given for 6 weeks, and at one-year post-injection, the patient had no signs of infection and required no surgical intervention. The authors did not state whether there were any permanent partial neurological deficits.

A 32-year-old male underwent a biologic treatment to the L4-L5 IVD [4]. The exact details of the procedure were not provided as the injection was not performed by the study authors; however, he was thought to have been injected with a combination of PRP and BMAC. The authors did not specify if prophylactic antibiotics were administered, nor did they comment on the use of single- or double-needle technique. Two weeks later, he presented to the emergency department (ED) with lower extremity radicular pain, weakness, saddle anesthesia, and progressive low back pain. Laboratory results were within normal limits. An MRI of the lumbar
spine did not demonstrate any signs of discitis or osteomyelitis. Two separate image-guided aspirations demonstrated no bacterial growth. A repeat biopsy was performed, and again, no signs of osteomyelitis or malignancy were noted. About one month later, the patient returned to the ED with worsening symptoms. The MRI showed evidence of discitis and osteomyelitis at L4-5 and L5-S1. A biopsy was performed, and *Cutibacterium acnes* was found. IV daptomycin was given for 12 weeks, and at one-year follow-up he had stable LBP without radiculopathy.

Another publication reported three additional cases of adverse events [5]. The first case included a 55-year-old male who underwent BMAC injections to the L4-L5 and L5-S1 IVDs along with the left L4-L5 and L5-S1 facet joints via double-needle technique. Prophylactic IV cefazolin and 500mcg of intradiscal gentamicin were administered. The patient experienced post-procedure pain that increased until day 19 post-injection, at which point, he sought treatment. He was found to have an elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) but a normal white blood cell (WBC) count. An MRI with and without contrast demonstrated L5-S1 spondylodiscitis and enhancement of the L4-5 facet joints with extension into the right L4-L5 paravertebral space and right psoas muscle. He was treated with IV cl vaccillin for six weeks followed by oral rifampicin and moxifloxacin for an additional six weeks. At three-month follow-up, no further signs of infection were observed, and a subsequent MRI showed resolution of the spondylodiscitis. The authors did not state whether there were any permanent neurological deficits.

An additional case involved a 35-year-old male who underwent BMAC injections to the L4-L5 and L5-S1 IVDs. Prior to the BMAC injection procedure, he had prophylactically received 1g of IV cefazolin. The authors did not comment on the use of single- or double-needle technique. Seven days after the injection, he was hospitalized for worsening, intractable pain along with fever and constipation. He was found to have an elevated CRP and ESR, but normal WBC. Blood cultures were negative. An MRI revealed L3-L4 discitis and an epidural abscess. He underwent a CT-guided aspiration of the cerebrospinal fluid, and culture results showed no bacterial growth. He was treated with IV cefepime and vancomycin for six weeks. Intractable pain persisted, and he subsequently was treated with high-dose dexamethasone. There was significant improvement within 24 hours; however, he continued to report pain for five months following the procedure. At the time of the publication, there was no confirmation of the infectious organism. The authors did not state whether there were any permanent neurological deficits.

A final case involved a 34-year-old male who underwent leukocyte-poor two level PRP injection to the L4-L5 and L5-S1 IVDs on two separate occasions. It is unknown whether he received prophylactic antibiotics prior to the PRP treatments. The authors did not comment on the use of single- or double-needle technique. Due to continued pain, he underwent BMAC injections at the same IVDs. Prior to the BMC injections, he was treated with prophylactic IV cefazolin. At two weeks, he had persistent, severe pain and underwent an MRI that showed mildly increased T2 signal in the L4-L5 high intensity zone and an increased disc protrusion at L5-S1. It is not clear from the articles whether these were new imaging findings compared to pre-injection lumbar MRI. He subsequently developed a fever, and a CT-guided biopsy was performed showing *Cutibacterium acnes* within the L5-S1 IVD. CRP and ESR were elevated, while his WBC count remained normal. A repeat MRI was performed at four weeks, which showed increased endplate changes and central vertebral body remodeling at L5 and the sacrum. He was treated with IV ceftriaxone for 42 days followed by oral amoxicillin for another 42 days. At three months, his blood work normalized, his pain improved to baseline, and he had no ongoing neurological or infectious symptoms.

*Published Research Studies Reporting Adverse Events*

A recently published study reported data on the efficacy and safety of allogenic stromal antigen-3 mesenchymal precursor cells combined with hyaluronic acid into a single lumbar IVD in 100 patients [6]. Each patient received both a diagnostic injection and either a therapeutic or a control injection. Prophylactic IV antibiotics were given, but specifics were not described. Single needle disc access technique was used. Adverse events were documented as treatment-emergent adverse events (TEAE). Worsening LBP was found to be the most common post-procedural complaint. Three subjects discontinued the study due to worsening LBP; the investigators did not believe this was related to the procedure. One patient experienced severe LBP thought to be related to the study agent and did not continue with the study. One patient experienced “implant site infection,” which was not further defined. The patient continued with the study. The adverse outcomes and their causes were not clearly reported. However, it appears that there were four cases of severe LBP leading to participant withdrawal from the study and another case of possible infection that did not lead to withdrawal from further participation.
Another recent study explored the effectiveness of intradiscal PRP for discogenic low back pain without Modic changes [7]. A single needle technique was used to access the disc in 49 patients who received intradiscal PRP without prophylactic antibiotics. One patient suffered from spondylodiscitis and recovered with antibiotic treatment and surgical debridement. It was not reported whether there were any residual neurologic deficits.

Published Research Studies Without Adverse Events
In all of the published cohort studies, a total of 378 patients underwent biologic lumbosacral IVD injections [5]. Injectates included bone marrow mesenchymal stem cells, adipose-derived stem cells, PRP, cultured and expanded stem cells, and activated platelet-derived growth factors. No infections or major complications were reported in any of the 378 participants. The majority of the studies reported follow-up of 6-12 months [8-20]. Several studies reported follow-up as far out as 4-9 years [21-25]. Five studies treated subjects (n= 69) with prophylactic IV antibiotics prior to injection [12,15,17,18,20]. One study (n= 22) utilized intradiscal injection of gentamicin along with PRP [13].

Discussion

Studies investigating biologic treatments for the lumbosacral IVDs have had small sample sizes, and in aggregate, total fewer than 500 patients. There are six case reports and one published research study documenting infectious adverse events. There are no large cohort studies that have documented safety or allow for a high degree of confidence in the precise incidence of complications. Further research including larger patient populations is needed in order to better define the scope of complications as well as to define more accurate incidence rates.

Two types of complications have been reported in case studies – increased pain and spinal infection. The etiology of the infections is unclear. The multi-step process of preparing biologic injectates – from tissue collection, processing, and transfer prior to the injection – provides a greater number of opportunities for an infection to occur when compared to other procedures that access the intervertebral disc. There is therefore likely an increase in the risk of infection inherent in biologic injections when compared to other intradiscal procedures based on this logic, but currently insufficient evidence to support this theory.

The role of prophylactic intradiscal antibiotics in intradiscal biologic injections has been debated given the possible deleterious effects of antibiotics on cell proliferation [26]. Infections have occurred in patients who received prophylactic antibiotics as well as those who did not. A previous FactFinder has been published outlining the use of antibiotics for non-biologic disc injections [27]. With regard to infectious complications, additional research is needed to better delineate the role of prophylactic antibiotics, both IV and intradiscal, single- versus double-needle disc access technique, as well as to identify both modifiable and non-modifiable risk factors for spinal infection. Such information will help inform the shared decision-making process between physicians and patients regarding the risk-benefit ratio unique to each individual who is considering an IVD biologic injection.

References


