Intradiskal Steroids: A Viable Treatment for Low Back Pain?

CASE SCENARIO

E. J. is an otherwise healthy 34-year-old graphic designer at a technology company. He first developed low back pain approximately 1 year ago while helping a friend move a couch. At that time, he had an abrupt onset of severe and debilitating low back pain without any radiation into the lower limbs. This severe pain spontaneously resolved within 2 weeks, but he has continued to experience a dull aching low back pain that he rates a 4-6/10. His pain is worse with sitting and better with standing. He notes that the pain interferes with his ability to sit at a computer and work.

Results of his physical examination demonstrate no neurologic deficits in the lower limbs, with intact and symmetric reflexes and strength throughout. He has no focal tenderness to palpation. He has a negative seated slump and straight leg raise bilaterally. He has no pain with flexion abduction and external rotation (FABER) or any movement of the hips bilaterally. The only maneuver that aggravates his pain is forward flexion of the lumbar spine, but he still has full range of motion. Recent magnetic resonance imaging was grossly normal except for the L5/S1 disk, which has a broad-based posterior protrusion and a high-intensity zone, without any neuroforaminal narrowing. There were no Modic end plate changes demonstrated at any level. The patient does not have any depression but does note that the pain is substantial and interferes with his job and recreational activities. Bradly S. Goodman, MD, Matthew R. Willey, MD, Matthew T. Smith, MD, and Srinivas Mallempati, MD, will argue that intradiskal steroids are a viable option for this patient, and Gwendolyn A. Sowa, MD, PhD, and Marzena Buzanowska, MD, will argue that intradiskal steroids are not an ideal treatment for this patient.

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The case of E. J. is one that is very common among many physiatrists and other spine specialists, that is, an otherwise healthy young individual with intact neurologic status but function-limiting, chronic low back pain. Statistically, the most common cause of chronic low back pain is from lumbar disk pathology, with the prevalence estimated to be up to 4% [1,2]. This case certainly fits that profile. E. J.'s pain is reproduced with bending, and his magnetic resonance imaging (MRI) demonstrates disk desiccation with a posterior annular fissure. Although more diagnostic procedures may be performed to further elucidate the source of his pain, for arguments sake, we will assume that the lumbar disk is the culprit [3].

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Our typical approach to this scenario would focus on conservative measures, for example, dynamic stabilization exercise, and other ancillary treatments, for example, modalities and traction. Other treatment options include a variety of oral medications [4]. Although the latter may benefit some individuals, there are unwanted adverse effects to consider. Opioids, for example, can create an entirely new and potentially worse problem of addiction, hypogonadism, and opioid-induced hyperalgesia [5]. Chronic nonsteroidal anti-inflammatory drugs use may upregulate matrix metalloproteinase activity, delay healing, and blunt many of the benefits of therapeutic exercise by impairing satellite cells [6,7]. Finally, a series of interventional treatments may be used. One study shows that epidural injections with anesthetic and with or without corticosteroid may be effective in certain individuals with axial low back pain, but this has not been reproduced in the literature [8]. Proceeding with facet and/or sacroiliac (SI) joint injections also may be helpful for diagnostic and therapeutic purposes [9].

However, if these treatments have not helped and E. J. continues to have function-limiting low back pain, we may need to consider other options that address the disk more directly. Before doing so, it is useful to first consider the underlying pathology of diskogenic pain so that the practitioner may be able to best choose an intervention that will address it. Diskogenic pain usually is associated with a variety of changes that may be seen on MRI. Findings may include a high-intensity zone in the annulus that is brighter on T2 than the cerebrospinal fluid, hypointense nuclear signal, and Modic signal changes in the adjacent vertebral bodies [10]. These radiographic findings have been correlated histologically in the literature and represent desiccation and reduced proteoglycan content in the nucleus, annular fissures, and a progression from edema to fibrosis in the end plates, respectively [11]. This degeneration leads to an uneven distribution of forces across the end plates. Possibly as a compensatory mechanism, the body attempts to repair these lesions with the ingrowth of vessels and nerves, which results in a highly innervated annulus adjacent to a deteriorated nucleus [12]. Thus, diskogenic pain seems to arise from the combination of disk and peridisk pathology with aberrant nerve growth, which results in the disk becoming a pain generator.

Given an adequate understanding of the unique etiology of diskogenic pain, it may be possible to make more sense of proposed and practiced interventions. In general, there are 3 criteria that must be met for any intervention to be effective and worthwhile. The first is that the correct diagnosis must be made. The second is that the intervention must have a sufficient likelihood of successfully treating the diagnosed pathology. The third is that the chosen intervention has an acceptable risk-to-benefit ratio. In the future, we might have available regenerative therapies introduced by minimally invasive means to maximize these 3 criteria. Currently, however, our available interventions do not include therapies to reverse degeneration; the closest we may come is to alleviate pain and reduce inflammation.

Among these interventions are intradiskal steroid injections (IDSI). There are those who argue that IDSIs are not effective and are too risky, and predispose patients to increased disk degeneration, thus potentially worsening the original pathology and, therefore, should not be considered for chronic back pain. However, we propose that the propositions used to support this conclusion are not represented by the totality of the evidence. Further, we argue that this conclusion is discordant with our aggregated clinical experience, which has included many IDSIs over the past 20 years. Thus, although the ideal treatment of diskogenic low back pain would be a minimally invasive procedure that causes permanent resolution of pain by complete regeneration of the disk, the totality of our current treatment options, including IDSIs, falls short. Yet, when compared with other current options, intradiskal steroid injections may be reasonable for some patients. We have found that this procedure can be a valuable, safe, and inexpensive tool for the management of acute and chronic low back and radicular pain when coupled with adequate diagnostic rigor.

To understand some of the dissenting opinions regarding IDSIs, it is instructive to examine the varied and sometimes contradictory conclusions made by some researchers over the past 60 years. The use of intradiskal steroids was first described in the 1950s by Feffer [13] for treatment of herniated disks and radiculopathy. IDSIs gained a modest increase in popularity over the next 30 years for the treatment of low back pain because chymopapain had come and gone as a similar procedure for diskogenic pain. Since the mid 1990s, however, the popularity of IDSIs has diminished in conjunction with the publication of studies that have been largely interpreted as showing that IDSIs are not effective. For example, Khot et al [14] examined IDSIs on diskogenic pain "confirmed" with diskography and noted no improvement at 1 year. Yet, typical of many studies quoted as proving the ineffectiveness of IDSIs, the usable information from this study is limited. One of the most obvious shortcomings of this study is that outcomes are measured at only 1 point in time. Khot et al [14] criticized IDSIs for not providing pain relief of 1 year's duration. However, they do not comment on the fact that there is no criterion standard intervention for diskogenic axial low back pain that provides statistically significant pain relief for that long of a period. Thus, although IDSIs in this study do not provide pain relief at the study's temporal end point, they do not fall short of any other current treatment or standard of care for diskogenic pain. Statistical insignificance at an arbitrary point in time does not necessarily denote clinical insignificance. If an IDSI were performed on E. J. and it gave him 11 months of near total relief of pain, he would have been considered a "failure" in this study.

Although the singular temporal end point of Khot et al [14] creates difficulty in clinical implementation of its findings, it is not the study's only liability. The diagnostic specificity of this study also may be called into question. Although Khot et al [14] correlated diskogenic pain with positive single-level diskography, they did not correlate this with MRI or other imaging findings. This is important because there are subtypes

of degenerative disk disease that may be more likely to respond to intradiskal steroids. Relatively recent studies of patients with type 1 and 2 Modic end plate changes adjacent to the degenerative disks demonstrated statistically significant pain relief with IDSIs [15-17]. With regard to E. J., a more compelling argument for therapeutic IDSI may be made if his MRI showed type 1 or 2 Modic changes.

Another common perception is that the literature "shows" that IDSIs may accelerate disk degeneration. Kato et al [18] in 1993 stated that IDSIs appear to be effective by accelerating the Kirkaldy-Willis degenerative cascade toward stabilization. In that study, methylprednisolone was injected into the herniated disks of 79 individuals. At least half of these individuals had appreciable relief and needed no further intervention. A year later, repeated MRIs on these subjects demonstrated that the disks had further degenerated. Although this study was done without a control group, Kato et al [18] concluded that the steroid accelerated disk degeneration, which causes the disk to shrink and induce analgesia by cicatrix. However, because of the lack of a control arm, it is impossible to determine whether the procedure caused the increased degenerative findings.

A similar study was performed by Aoki et al [19] in a rabbit model. Although the findings of Aoki et al [19] are frequently quoted by those critical of IDSIs as causing accelerated disk degeneration, there may be a more narrowed conclusion. Similar to Kato et al [18], Aoki et al [19] injected methylprednisolone into the lumbar intervertebral disks (IVD) of rabbits. Aoki et al [19] hypothesized that they may have inadvertently introduced a confounder, however, because methylprednisolone acetate is formulated with polyethylene glycol as its solvent. Polyethylene glycol is known to be particularly toxic to chondrocytes. Aoki et al [19] hypothesized that polyethylene glycol may have caused the increased disk degeneration. To test this hypothesis, they compared disks injected with just polyethylene glycol with disks injected with methylprednisolone sodium succinate, which is not suspended in a polyethylene glycol solvent. As hypothesized, the disks injected with polyethylene glycol showed degeneration, whereas the latter disks did not. The appropriate conclusion from this study is not that IDSI causes degeneration but rather that polyethylene glycol causes disk degeneration in rabbits. The idea that the solvent may be the cause of accelerated disk degeneration also was explored by Ito et al [20]. His group noted little to no statistical increase in calcification in disks injected with betamethasone (solvents polysorbate 80 and benzalkonium chloride) compared with previous studies that show a much higher increase in calcification with the injectate, including methylprednisolone (solvents polyethylene glycol and myristyl-r-picolinium) and triamcinolone (solvents benzyl alcohol, polysorbate 80, and sodium carboxymethylcellulose), which did show calcifications. However, this phenomenon is not limited to the disk space. Jin et al [21] describe similar findings of epidural calcification after serial injections of triamcinolone acetonide via the transforaminal approach. Thus, it is likely that it is not the intradiskal procedure that is harmful per se but the type of corticosteroid, and its associated solvent, used that is most important.

The studies of Khot et al [14], Kato et al [18], Aoki et al [19], Ito et al [20], and others are important because they show that the confusion over the effectiveness of IDSIs arises not only from different methods of diagnosing diskogenic pain but also from different methods of performing the procedure. Regarding the diagnosis, some studies use only diskography, whereas others use only MRI with or without high-intensity zones, or MRI with or without Modic changes, or a combination of these findings. Regarding the procedures, some studies use different corticosteroids with different solvents and others add injectates, such as intradiskal antibiotics, that may have unforeseen effects [22]. There are outspoken critics of IDSIs, for example, Carragee [23], but they tend not to take into account the wide disparity in these diagnostic and technical issues that lead to broad accusations about the use of this procedure. In addition, the confounders of studies such as Aoki et al [19] are not always recognized, which leads to an erroneous negative conclusion. It is our belief that the generalized conclusion that IDSIs are ineffective for presumed diskogenic low back pain is not supported by the literature.

Of at least equal importance as to whether IDSIs provide adequate therapeutic value is whether they may cause iatrogenic damage, which implies that those who perform IDSIs are not abiding by the dictum of primum non nocere, first do no harm. The two most common concerns in this regard include the potential mechanical damage from intradiskal needle placement as well as the risk of infectious diskitis. Carragee et al [24] demonstrated accelerated disk degeneration in control disks after lumbar diskography. Moreover, other investigators have demonstrated that contrast and anesthetics are harmful to chondrocytes in vitro [25,26]. We agree that, all things being equal, a normal IVD is better left with its annulus fibrosis unpunctured and its nucleus pulposus free of any foreign injectate. It is unlikely that many reasonable physicians would argue otherwise. IDSIs, however, are not performed on healthy disks. They should only be performed on disks in which the degenerative cascade has already started. A more ideal diagnostic tool for diskogenic pain would be one in which an injection is only performed on the degenerated IVD. IDSI fulfills this criterion and may thus be used to aid in diagnosis as well as simultaneously providing pain relief [27,28].

Regarding diskitis, although an incidence has been reported to be as high as 2.7% with diskography, Guyer and Ohmeiss [29] found, in a review of the literature, an incidence closer to 0.1%-0.2%, with many of the included studies having not used antibiotics. Cohen et al [30] reported an incidence of 0% with the use of intradiskal antibiotics. Furthermore, it is necessary to factor in that these studies include the injection of relatively healthy control disks. This is important because normal disks are likely more

prone to diskitis when punctured because they have little vascularity in comparison with degenerated disks [31]. In our 20 years of injecting degenerative disks, and with regular use of both intravenous and intradiskal antibiotics, we are unaware of a case of diskitis caused by this procedure. If the incidence is truly 1%-3% as reported by some investigators, we should have at least had 5 cases of diskitis over the past year and 100 over the past 20 years (based on an estimate of 500 IDSIs yearly performed by our group). Because we have ample evidence that IDSIs can be performed without the adverse event of intradiskal infection, if a practitioner's incidence of diskitis is truly 1%-3%, then he or she should probably not be performing them. We argue that, with a proper sterile technique and the use of antibiotics, this procedure carries much less risk than the alternatives, notably long-term opioids, surgical intervention, or the other aforementioned minimally invasive techniques.

Although there is a small risk of infection with annular puncture, as seen with diskography, that may or may not be comparable with IDSI, the latter procedure, nonetheless, is less invasive and less risky than alternative procedures. Intradiskal electrothermy (IDET) includes annular puncture, manipulation of the electrode through a large portion of the annulus or nucleus pulposus, and electrocautery of these tissues. Surely this involves vastly more risk than a simple IDSI. Similarly, a partial diskectomy or nucleoplasty completely obliterates portions of the disk, which risks nerve root or cord injury if performed above L1. In a patient with unremitting axial pain and loss of function secondary to an established disk pathology, annular puncture and the injection of corticosteroids are relatively low risk when compared with possible benefit.

Although IDSIs have failed to gain universal traction, the goal of developing an antidote to diskogenic pain remains. Every few years a new technique arises that promises to be the definitive treatment of diskogenic pain. The advent of radiofrequency ablation spawned IDET. Oratec Interventions (Menlo Park, CA), a company previously dedicated to the development and marketing of radiofrequency devices, introduced the SpineCATH, a navigable IDET catheter. This procedure generated sales of 21 million in 2001 according to a report by Smith and Nephew, the company that later purchased Oratec [32]. A case series of 36 patients by Karasek and Bogduk [33] reported an average of 67% improvement in visual analog scale (VAS) and 41% improvement in Oswestry disability index (ODI) with IDET. This procedure was touted as "unparalleled" in the treatment of diskogenic pain and garnered notable popularity until further research demonstrated possibly less benefit than previously thought [23,34,35]. We believe that marketing pushes some procedures to the forefront. Yet, there is no company that stands to benefit from sponsoring IDSIs and thus no marketing is done. However, it is important not to conflate lack of marketing for lack of usefulness.

In conclusion, our purpose is not to convince the spine community to embrace intradiskal steroids unequivocally, instead, our aim is to discuss our own experience and some of the subtleties of the available literature. Our goal also is to contrast our experience with what we believe are misunderstandings regarding the safety and effectiveness of this procedure. Yet, although we believe that IDSIs have a place among other well-established percutaneous spine interventions, a definitive and universal treatment for chronic axial back pain has proven to be elusive. Nonetheless, for patients such as E. J., we believe that the potential benefits of an IDSI are vastly greater than the risks and that this is a reasonable intervention at this point in his care.

REFERENCES

1. Schwarzer AC, Aprill CN, Derby R, Fortin J, Kine G, Bogduk N. The prevalence and clinical features of internal disc disruption in patients with chronic low back pain. Spine (Phila Pa 1976) 1995;20:1878-1883.
2. DePalma MJ, Ketchum JM, Saullo T. What is the source of chronic low back pain and does age play a role? Pain Med 2011;12:224-233.
3. Zhou Y, Abdi S. Diagnosis and minimally invasive treatment of lumbar discogenic pain: A review of the literature. Clin J Pain 2006;22:468-481.
4. Saal JS, Saal JA. Lumbar stabilizing exercises for the nonoperative treatment of disc lesions. West J Med 1990;153:432.
5. Reddy RG, Aung T, Karavitaki N, Wass JAH. Opioid induced hypogonadism. BMJ 2010;341:606-607.
6. Wilson PR, Watson PJ, Haythornthwaite JA, Jensen TS, eds. Chronic Pain. 2nd ed. London: Hodder Arnold; 2008, 193-230.
7. Mackey AL, Kjaer M, Dandanell Jorgensen S, et al. The influence of anti-inflammatory medication on exercise-induced myogenic precursor cell responses in humans. J Appl Physiol 2007;103:425-431.
8. Manchikanti L, Cash KA. A randomized, double-blind, active-controlled trial of fluoroscopic lumbar interlaminar epidural injections in chronic axial or discogenic low back pain: Results of 2-year follow-up. Pain Physician 2013;16:E491-E504.
9. Chou R, Loeser JD, Owens DK, et al. Interventional therapies, surgery, and interdisciplinary rehabilitation for low back pain: An evidence-based clinical practice guideline from the American Pain Society. Spine (Phila Pa 1976) 2009;34:1066-1077.
10. Schellhas KP, Pollei SR, Gundry CR, Heithoff KB. Lumbar disc high-intensity zone: Correlation of magnetic resonance imaging and discography. Spine (Phila Pa 1976) 1996;21:79-86.
11. Hutton MJ, Bayer JH, Powell JM, Sharp DJ. Modic vertebral body changes. Spine (Phila Pa 1976) 2011;36:2304-2307.
12. Peng B. Pathophysiology, diagnosis, and treatment of discogenic low back pain. World J Orthop 2013;4:42-52.
13. Feffer HL. Therapeutic intradiscal hydrocortisone: A long-term study. Clin Orthop Relat Res 1969;67:100-104.
14. Khot A, Bowditch M, Powell J, Sharp D. The use of intradiscal steroid therapy for lumbar spinal discogenic pain: A randomized controlled trial. Spine (Phila Pa 1976) 2004;29:833-836; discussion 837.
15. Mefford J, Sairyo K, Sakai T, et al. Modic type I changes of the lumbar spine in golfers. Skeletal Radiol 2011;40:467-473.
16. Buttermann GR. The effect of spinal steroid injections for degenerative disc disease. Spine J 2004;4:495-505.
17. Cao P, Jiang L, Zhuang C, et al. Intradiscal injection therapy for degenerative chronic discogenic low back pain with end plate Modic changes. Spine J 2011;11:100-106.
18. Kato F, Mimatsu K, Kawakami N, et al. Changes in intervertebral disc after discography with intradiscal injection of corticosteroids observed with MRI. J Neurol Orthop Med Surg 1993;14:210-216.
19. Aoki M, Kato F, Mimatsu K, Iwata H. Histologic changes in the intervertebral disc after intradiscal injections of methylprednisolone acetate in rabbits. Spine (Phila Pa 1976) 1997;22:127-132.

20. Ito S, Usui H, Maruyama K, Muro T. Roentgenographic evaluation of ossification and calcification of the lumbar spinal canal after intradiscal betamethasone injection. J Spine Disord 2001;14:434-438.
21. Jin YJ, Chung SB, Kim KJ, Kim HJ. Dystrophic calcification in the epidural and extraforaminal space caused by repetitive triamcinolone acetonide injections. J Korean Neurosurg Soc 2011;50:134-138.
22. Albert HB, Sorensen JS, Christensen BS, Manniche C. Antibiotic treatment in patients with chronic low back pain and vertebral bone edema (Modic type 1 changes): A double-blind randomized clinical controlled trial of efficacy. Eur Spine J 2013;22:697-707.
23. Carragee EJ. Intradiscal treatment of back pain. Spine J 2011;11:97-99.
24. Carragee EJ, Don AS, Hurwitz EL, Cuellar JM, Carrino JA, Herzog R. 2009 ISSLS Prize Winner: Does discography cause accelerated progression of degeneration changes in the lumbar disc: A ten-year matched cohort study. Spine (Phila Pa 1976) 2009;34:2338-2345.
25. Eder C, Pinsger A, Schildboeck S, Falkner E, Becker P, Ogon M. Influence of intradiscal medication on nucleus pulposus cells. Spine J 2013;13:1556-1562.
26. Gruber HE, Rhyne AL III, Hansen KJ, et al. Deleterious effects of discography radiocontrast solution on human annulus cell in vitro: Changes in cell viability, proliferation, and apoptosis in exposed cells. Spine J 2012;12:329-335.
27. Yu Y, Liu W, Song D. Diagnosis of discogenic low back pain in patients with probable symptoms but negative discography. Arch Orthop Trauma Surg 2012;132:627-632.
28. Ohtori S, Kinoshita T, Yamashita M, et al. Results of surgery for discogenic low back pain: A randomized study using discography versus discoblock for diagnosis. Spine (Phila Pa 1976) 2009;34:1345-1348.
29. Guyer RD, Ohmeiss DD. Lumbar discography: position statement from the North American Spine Society Diagnostic and Therapeutic Committee. Spine (Phila Pa 1976) 1995;20:2048-2059.
30. Cohen SP, Larkin TM, Barna SA, Palmer WE, Hecht AC, Stojanovic MP, et al. Lumbar discography: A comprehensive review of outcome studies, diagnostic accuracy, and principles. Reg Anesth Pain Med 2005;30:163-183.
31. Goodman BS, Lincoln CE, Deshpande KK, Poczatek RB, Lander PH, Devivo MJ. Incidence of intravascular uptake during fluoroscopically guided lumbar disc injections: A prospective observational study. Pain Physician 2005;8:263-366.
32. Smith and Nephew Corporate. News and Media. Smith and Nephew reaches agreement to acquire Oratec. Available at http://www.smith-nephew.com/news-and-media/news/smith-and-nephew-reaches-agreement-to-acquire-ora/. Accessed May 17, 2014.
33. Karasek M, Bogduk N. Twelve-month follow-up of a controlled trial of intradiscal thermal annuloplasty for back pain due to internal disc disruption. Spine (Phila Pa 1976) 2000;25:2601-2607.
34. Pauza KJ, Howell S, Dreyfuss P, et al. A randomized, placebo-controlled trial of intradiscal electrothermal therapy for the treatment of discogenic low back pain. Spine J 2004;4:27-35.
35. Freeman BJC, Fraser RD, Cain CMJ, Hall DJ, Chapple DC. A randomized, double-blind controlled trial: Intradiscal electrothermal therapy versus placebo for the treatment of chronic discogenic low back pain. Spine (Phila Pa 1976) 2005;30:2369-2377; discussion 2378.

Gwendolyn A. Sowa, MD, PhD, and Marzena Buzanowska, MD, Respond

Interventional spine procedures have seen enormous growth over the past decade. However, outcomes for patients with axial low back pain remain poor. IDSI represents an intuitively attractive potential therapy for individuals with disk pain, given the anti-inflammatory effect of steroids and the association of inflammation with pain. However, the risks associated with any interventional procedure must be considered given the unclear mechanism of action of intradiskal steroids. The concerns over proceeding with an IDSI in this patient include (1) obtaining an accurate diagnosis; (2) complications with additional diagnostic tests; (3) complications of the procedure itself; (4) toxicity of the injectates; and (5) questionable efficacy of the treatment, which results in a poor risk-benefit ratio for the patient.

The first and perhaps most important aspect of the presented case lies in making an appropriate diagnosis on which to base the treatment plan. Although it is clear that the patient has typical features associated with disk-related pain, the identity of the pain generator is not certain. The changes demonstrated on MRI represent a history of what has happened to the patient's spine, not a representation of current pain generators. Although the current patient only has 1 abnormal disk on MRI, these changes may be representative of his acute pain 1 year before presentation and may not be the current pain generator. The incidence of asymptomatic disk changes is high [1], and disk protrusions in particular are found at high rates in subjects who are asymptomatic, which increases the risk that their identification on MRI is not a causal explanation of pain [2]. The clinical importance of the observed high-intensity zone is even less clear. The need for specific identification of pain generator becomes more important when considering an interventional procedure directed at a specific pathology, such as an IDSI compared with using a less-specific, but commonly efficacious, treatment such as oral medications or physical therapy.

If one considers performing a diskogram before intradiskal steroids in an effort to increase the certainty of the diagnosis, the patient is subjected to an additional interventional procedure with associated morbidity and questionable utility. Diskograms are fraught with a poor positive predictive value [3] and have been suggested to accelerate degeneration [4]. In fact, the most common mechanism by which degeneration is induced in animal models is by annular puncture with a needle. Importantly, size does matter, with increasing rates of alteration of mechanical properties observed with increasing needle sizes [5]. In addition, high levels of pressure have a negative impact on disk cell metabolism, literally adding insult to injury by creating pressure-induced apoptosis and anti-anabolic signals in addition to the annular defect, all of which contribute to the degenerative cascade. Regardless of your position on the controversial issue of diskography, even in the absence of performing a diskogram on this patient before proceeding with an IDSI, an annular defect will be created by the procedure itself, with the potential to hasten the degenerative cascade.

When considering the proposed interventional procedure itself, the risk-benefit ratio must be clearly outlined for the patient. The patient must be counseled regarding the risk associated with any interventional procedure. The clinical studies that have been performed have lacked adequate controls, which prevents assessment of differing effects from natural history in these cohorts of patients. Clinical results are mixed and, at best, demonstrate a small, temporary benefit. The clearest benefits have been shown for subjects with Modic changes (which are not present in our current patient) [6]. However, even findings among patients with Modic changes are inconsistent in the literature. This uncertain benefit must be weighed against the potential for detrimental long-term effects. Importantly, long-term outcome studies with sufficient follow-up to identify detrimental effects, if they exist, have not been performed. A 6-month to 2-year follow-up is unlikely to be sufficient to assess the long-term effects on chronic degeneration.

Because clinical results are inconclusive and long-term outcome studies are not available, we must turn to the basic science literature in an effort to glean insight into the intradiskal effects of corticosteroid. In fact, the basic science literature is filled with evidence of adverse effects of corticosteroid on chondrocyte viability and metabolism. Administration of glucocorticoids has been shown to increase cell apoptosis [7]. Although these data are from articular cartilage, the nucleus pulposus cells have a chondrocytic phenotype as well. In fact, direct evidence for a toxic effect on disk cells exists. Nucleus pulposus cells exposed to triamcinolone acetonide demonstrated decreased cell count and cell proliferation [8]. In addition, loss of notochordal cells, associated with accelerated disk aging, has been demonstrated in response to intramuscular hydrocortisone in an animal model [9]. Although the administration was systemic, the greater effects observed in the disk periphery and the dose response suggest a local effect as well. Because one of the key events in disk degeneration is decreased cellularity and metabolic activity of resident cells, loss of disk cells will have a negative effect on matrix homeostasis. Consistent with this effect, rabbits that undergo intradiskal methylprednisolone acetate injection demonstrated accelerated degeneration [10], and, of note, this may be affected by the preparation used and the vehicle. Other agents that may be used during the procedure or in preparation for the procedure, including local anesthetic and diskography contrast [11,12], also demonstrate cellular toxicity. Importantly, lidocaine has been shown to potentiate the cytotoxic effect of corticosteroids on chondrocytes [7,13].

Because of the modest, at best, potential treatment effect shown in clinical studies and the clear evidence for negative effects on the disk health in preclinical studies, it is recommended that long-term studies be performed to establish the safety of this minimally efficacious procedure before advocating for widespread use of intradiskal injections. In particular, our current case describes a young, otherwise healthy individual for whom accelerating the degenerative cascade will likely have more negative long-term effects than pursuing another noninterventional management. Interventional procedures with the potential for harm should be reserved for patients who do not respond to other treatments. The current patient has few risk factors, other than the chronicity of his pain, for a poor outcome, and noninterventional treatments should be considered, with less chance of long-term harm. Therefore, for this young patient, the short-term gain associated with temporary pain relief must be weighed against the risk of accelerating degeneration by violating the IVD with a needle and bathing the disk cells in compounds with cellular toxicity.

REFERENCES

1. Weishaupt D, Zanetti M, Hodler J, Boos N. MR imaging of the lumbar spine: Prevalence of intervertebral disk extrusion and sequestration, nerve root compression, end plate abnormalities, and osteoarthritis of the facet joints in asymptomatic volunteers. Radiology 1998;209:661-666.
2. Boos N, Rieder R, Schade V, Spratt K, Semmer N, Aebi M. 1995 Volvo Award in clinical sciences. The diagnostic accuracy of magnetic resonance imaging, work perception, and psychosocial factors in identifying asymptomatic disc herniations. Spine (Phila Pa 1976) 1995;20:2613-2625.
3. Carragee E, Lincoln T, Parmar V, Alamin T. A gold standard evaluation of the "discogenic pain" diagnosis as determined by provocative discography. Spine (Phila Pa 1976) 2006;31:2115-2123.
4. Carragee E, Don A, Hurwitz E, Cuellar J, Carrino J, Herzog R. 2009 ISSLS Prize Winner: Does discography cause accelerated progression of degeneration changes in the lumbar disc: A ten-year matched cohort study. Spine (Phila Pa) 2009;34:2338-2345.
5. Elliott D, Yerramalli C, Beckstein J, Boxberger J, Johannessen W, Vresilovic E. The effect of relative needle diameter in puncture and sham injection animal models of degeneration. Spine (Phila Pa 1976) 2008;33:588-596.
6. Cao P, Jiang L, Zhuang C, et al. Intradiscal injection therapy for degenerative chronic discogenic low back pain with end plate Modic changes. Spine J 2011;11:100-106.
7. Farkas B, Kvell K, Czompoly T, Illes T, Bardos T. Increased chondrocyte death after steroid and local anesthetic combination. Clin Orthop Relat Res 2010;468:3112-3120.
8. Eder C, Pinsger A, Schildboeck S, Falkner E, Becher P, Ogon M. Influence of intradiscal medication on nucleus pulposus cells. Spine J 2013;13:1556-1562.
9. Higuchi M, Abe K. Ultrastructure of the nucleus pulposus in the intervertebral disc after systemic administration of hydrocortisone in mice. Spine (Phila Pa 1976) 1985;10:638-643.
10. Aoki M, Kato F, Mimatsu K, Iwata H. Histologic changes in the intervertebral disc after intradiscal injections of methylprednisolone acetate in rabbits. Spine (Phila Pa 1976) 1997;22:127-131; discussion 132.
11. Chee A, Ren J, Lenart B, Chen E, Zhang Y, An H. Cytotoxicity of local anesthetics and nonionic contrast agents on bovine intervertebral disc cells cultured in a three-dimensional culture system. Spine J 2014;14:491-498.
12. Lee H, Sowa G, Vo N, et al. Effect of bupivacaine on intervertebral disc cell viability. Spine J 2010;10:159-166.
13. Seshadri V, Coyle C, Chu C. Lidocaine potentiates the chondrotoxicity of methylprednisolone. Arthroscopy 2009;25:337-347.

Bradly S. Goodman, MD, Matthew R. Willey, MD, Matthew T. Smith, MD, and Srinivas Mallempati, MD, Rebut

Drs Sowa and Buzanowska present 5 concerns regarding the use of IDSIs for axial low back pain. They then very clearly and systematically cite data from some of the same literature that we have reviewed to assess the relative risks and benefits of IDSIs. Although their methods and source material are similar to ours, they come to a different conclusion than the one that we derived. Their conclusion is that IDSIs are largely unwarranted. In the following rebuttal, we will address why Drs Sowa and Buzanowska's and our arguments differ. We will describe why we judge IDSIs to have a risk-benefit ratio that is favorable to a sizable portion of patients with diskogenic axial back pain. We then will conclude with the assertion that this procedure rightfully has a place within the procedural armamentarium of the interventionalist.

The first and second concerns described by Drs Sowa and Buzanowska are in regard to the difficulty of diagnosing diskogenic axial back pain and the relative risk of using percutaneous procedures to do so. It is well documented that there is not a one-to-one correlation with IVD abnormalities on MRI and symptoms experienced by the patient. For instance, radiographic changes frequently associated with diskogenic pain, such as T2 high-intensity zones in the annulus, disk bulges, end plate Modic changes, and disk desiccation, are seen with patients who are symptomatic and those who are asymptomatic alike. Because of this, Drs Sowa and Buzanowska criticize the use of diskograms and IDSIs because of the possible damage to the IVD caused by iatrogenic annular puncture and injection of contrast, anesthetic, and corticosteroid. They state that we may be doing more harm than good by performing these invasive procedures because these procedures have a nonzero risk and that diskography, in particular, may have poor prognostic value. Yet, although these arguments have merit, they must be taken in context. Regarding MRI findings and any individual's symptoms, just because there is not a one-to-one correlation does not mean that there is no correlation [1,2]. Diskogenic pain is a well-documented phenomenon, and, although it does not occur with every patient with a specific set of imaging abnormalities, it certainly occurs more frequently with those with abnormal-appearing disks than those whose disks are normal appearing. It does not follow that because diskogenic pain is difficult to assess that a clinician cannot, or should not, use other means to further elucidate a diagnosis.

Drs Sowa and Buzanowska elaborate on their argument by stating that a definitive diagnosis of diskogenic pain may be unnecessary because physical therapy and oral medications have the potential to relieve symptoms without a definitive diagnosis and without the perceived risks of an IDSI. We contend that, if physical therapy were universally effective as a stand-alone treatment or if the benefit-risk ratio of most oral medications prescribed for diskogenic pain were always favorable, then this argument would render our position moot. Yet the literature and our experience indicate that this is not the case [3]. With regard to physiotherapy, although its use is often helpful and certainly a part of a multidisciplinary approach to treating low back pain, it usually is insufficient if a patient cannot participate due to functionally limiting pain. Furthermore, even if he or she is able to fully participate, physiotherapy is not always adequately effective. The case for oral medications is even more suspect. Relatively "benign" medications such as nonsteroidal anti-inflammatory drugs negatively affect the gastrointestinal, cardiovascular, and renal systems, and even the musculoskeletal system [4]. Moreover, although the risks of nonsteroidal anti-inflammatory drugs are undesirable, they are dwarfed by the risks of opioids and systemic corticosteroids [5,6]. Thus, even if a physician prefers to avoid direct intervention at the IVD, he or she is not guaranteeing his or her patient full relief or complete safety.

The third and fourth concerns elucidated by Drs Sowa and Buzanowska are with regard to the risks of IDSIs because of damage to the annulus from needle puncture and the perceived toxicity of the frequently used injectates to the other components of the IVD. As stated in our original argument, the literature that addresses these risks contains critical subtleties that are frequently overlooked and that paint a more nuanced picture when properly considered. Foremost among these subtleties is the fact that the studies that analyze the damage to the IVD from annular puncture and various injectates do so on healthy disks. Although these studies may be germane to the use of diskography on "normal" control disks, they are less so to those disks in which degeneration has already occurred and in which the degeneration is an ongoing and presumed painful process. Furthermore, as noted in our primary response and, in particular, our analysis of corticosteroids and their respective solvents, not all injectates are created equal. Many may be less destructive to healthy disks (and some potentially more destructive) than previously believed.

The fifth and final concern presented by Drs Sowa and Buzanowska is regarding the effectiveness of IDSIs in treating axial pain. Drs Sowa and Buzanowska state that, because IDSIs have not yet been shown to provide pain relief beyond 2 years, IDSIs should not be performed until more "long-term" studies are conducted. Our response to this is 2-fold. First, as alluded to earlier, it is common for functionally limiting diskogenic pain to prevent patients from being sufficiently active, either in the context of physical therapy or a home exercise program. Yet, even very brief periods of physical inactivity are well-documented causes of degenerative cascades in nearly every organ system [7]. Furthermore, to literally add physical insult to injury, the catabolic and proinflammatory milieu

promoted by inactivity is known to negatively affect the IVD and surrounding spinal structures, precipitating continued degeneration and pain [8,9]. Although IDSIs have not yet been shown to provide statistically significant pain relief in perpetuity, they, nonetheless, have been shown to be very helpful with select patients for a sizable amount of time. We contend that, for many patients, the relief provided by an IDSI is sufficient to break this vicious cycle of inactivity and continued degeneration [10-12]. Second, it is our clinical experience that there are many individuals for whom an IDSI has been the only treatment that has provided adequate relief of diskogenic pain. This patient population extends beyond those typified by this case scenario and includes individuals with diskogenic pain adjacent to lumbar fusions as well as those who have exhausted all other pharmacologic, physiotherapeutic, interventional, and even surgical options. In our 20-plus years of performing this procedure, we have seen numerous examples in which a patient has tried all else except an IDSI, and it ends up being this procedure that allows him or her to return to a more active life.

We do not argue that IDSIs are a perfect procedure for all individuals with an abnormal disk on MRI and with axial low back pain. We do argue, however, that IDSIs have been shown to work for certain patients for a clinically significant amount of time, and this duration may be critically important in halting the degenerative process and resultant pain. We also argue that, although IDSIs have an associated risk, this risk is comparable and frequently less than other procedures and surgeries performed for this condition. From these arguments, we conclude that IDSIs are a valuable tool within the arsenal of comprehensive spine care.

REFERENCES

1. Hebelka H, Hansson T. HIZ's relation to axial load and low back pain: Investigated with axial loaded MRI and pressure controlled discography. Eur Spine J 2013;22:734-739.
2. O'Neill C, Kurgansky M, Kaiser J, Lau W. Accuracy of MRI for diagnosis of discogenic pain. Pain Physician 2008;11:311-326.
3. van Middelkoop M, Rubinstein SM, Kulipers T, et al. A systematic review on the effectiveness of physical and rehabilitation interventions for chronic non-specific low back pain. Eur Spine J 2011; 20:19-39.
4. Harirforoosh S, Asghar W, Jamali F. Adverse effects of nonsteroidal antiinflammatory drugs: An update of gastrointestinal, cardiovascular and renal complications. J Pharm Pharm Sci 2013;16: 821-847.
5. Benyamin R, Trescot AM, Datta S, et al. Opioid complications and side effects. Pain Physician 2008;11(Suppl):S105-S120.
6. Stanbury RM, Graham EM. Systemic corticosteroid therapy: Side effects and their management. Br J Ophthalmol 1998;82:704-708.
7. Brower RG. Consequences of bed rest. Crit Care Med 2009;37: S422-S428.
8. Belavy DL, Bansmann PM, Bohme G, et al. Changes in intervertebral disc morphology persist 5 mo after 21-day bed rest. J Appl Physiol (1985) 2011;111:1304-1314.
9. Goodson NJS, Smith BH, Hocking LJ, et al. Cardiovascular risk factors associated with the metabolic syndrome are more prevalent in people reporting chronic pain: Results from a cross-sectional general population study. Pain 2013;159:1595-1602.
10. Brisby H, Wei AQ, Molloy T, Chung SA, Murrell GA, Diwan AD. The effect of running exercise on intervertebral disc extracellular matrix production in a rat model. Spine (Phila Pa 1976) 2010;35: 1429-1436.
11. Chan SC, Ferguson SJ, Gantenbein-Ritter B. The effects of dynamic loading on the intervertebral disc. Eur Spine J 2011;20:1796-1812.
12. Paul CP, Zuderbaan HA, Zandieh Doulabi B, et al. Simulated-physiological loading conditions preserve biological and mechanical properties of caprine lumbar intervertebral discs in ex vivo culture. PLoS One 2012;7:e33147.

Gwendolyn A. Sowa, MD, PhD, and Marzena Buzanowska MD, Rebut

We are clearly in agreement with Drs Goodman, Willey, Smith, and Mallempati that a typical approach to this patient would include noninterventional measures before consideration of intradiskal procedures. In addition, we agree with the important limitations of current studies that were appropriately raised. However, flaws in the design of studies that demonstrate a lack of benefit or harm cannot be interpreted as evidence in favor of the intervention as suggested by Drs Goodman, Willey, Smith, and Mallempati, who criticize the study by Khot et al [1] as choosing an arbitrary time point and lack of diagnostic specificity, and conclude that the study does not necessarily denote clinical insignificance. Although valid criticisms are raised, Drs Goodman, Willey, Smith, and Mallempati fail to cite studies from other investigators that include earlier (10-14 days [2]) and later (more than 2 years [3]) time points that also demonstrated poor clinical outcomes. Although it is agreed that the current studies have significant limitations, it is difficult to advocate for a procedure that does not have strong studies that demonstrate benefit, particularly in the absence of Modic changes, which are not present in our current patient. Drs Goodman, Willey, Smith, and Mallempati refer to their clinical experience in support of IDSIs. In fact, if they have data that demonstrate this benefit, then it would be of benefit to the physiatric community if those data were disseminated through publication. They also state that they are unaware of any cases of diskitis within their practice, but this represents anecdotal evidence, which, in the absence of targeted patient follow up to ensure proper capture of complications, should be avoided.

Drs Goodman, Willey, Smith, and Mallempati claim that IDSIs should only be performed on disks in which the degenerative cascade has already started. However, the basis of this claim is unclear, and, more importantly, it is unclear how this would be definitively identified. On histologic examination, degeneration can be detected before the imaging findings on MRI. In addition, disks that appear degenerated on MRI may reflect only a history of what has occurred but

not reflect active disease and inflammation, which is what the IDSI is purported to address. They also make the statement that an IDSI would be less risky than other interventional procedures. To our knowledge, studies that directly compare the IDSI with other intradiskal procedures to assess relative risk have not been performed, and choosing the lesser of 2 evils does not constitute a valid clinical decision-making plan.

The literature is full of evidence of our overutilization of medical and surgical treatments for low back pain care without associated improvements in outcomes. As we strive to "do no harm," we as clinicians must resist the urge to do something, particularly when the efficacy of a potentially harmful intervention has not been demonstrated. Focusing on maximizing the patient's function despite his disk changes and low back pain should remain the primary goal of the physiatrist. In fact, Drs Goodman, Willey, Smith, and Mallempati point out that a typical approach would be to focus on conservative measures first, but they also conclude that intradiskal steroids would be a reasonable intervention at this point in his care. This contradictory statement is consistent with the wide variability in practice patterns for axial low back pain, which has contributed to the difficulty of physiatrists practicing evidence-based medicine to secure reimbursement for indicated procedures. Because the vast majority of the literature demonstrates insufficient benefit as well as evidence of harm, it is suggested that advocates of IDSIs consider publishing their findings to support this procedure if a benefit exists. Overall, I think that we are in agreement with Drs Goodman, Willey, Smith, and Mallempati in that additional research is much needed in this area, and we hope that the preceding discussion will stimulate interest in future studies that address this important topic.

REFERENCES

1. Khot A, Bowditch M, Powell J, Sharp D. The use of intradiscal steroid therapy for lumbar spinal discogenic pain: A randomized controlled trial. Spine (Phila Pa 1976) 2004;29:833-836; discussion 837.
2. Simmons JW, McMillin JN, Emery SF, Kimmich SJ. Intradiscal steroids: A prospective double-blind clinical trial. Spine (Phila Pa 1976) 1992; 17(Suppl):S172-S175.
3. Wilkinson HA, Schuman N. Intradiscal corticosteroids in the treatment of lumbar and cervical disc problems. Spine (Phila Pa 1976) 1980;5: 385-389.

Web Poll Question

For the case scenario presented herein, are intradiskal steroids a viable option for this patient with low back pain?

a. yes
b. no

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Results of April's Web Poll

For the case scenario presented in Medical Marijuana for Failed Back Surgical Syndrome: A Viable Option for Pain Control or an Uncontrolled Narcotic, is medical marijuana a viable option for pain control?

50% - viable option
50% - uncontrolled narcotic