Prospective, double-blind, randomized placebo-controlled trials in interventional spine: what the highest quality literature tells us

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Abstract

BACKGROUND CONTEXT: The prospective, double-blind, randomized, placebo-controlled study design is essential in the interventional spine literature to truly evaluate whether or not a procedure is effective.

PURPOSE: This article will critically evaluate the highest quality interventional spine literature with strict interpretation of the results of these trials.

STUDY DESIGN: Review article.

METHODS: Extensive Medline/Pubmed searches and searches of the large review articles on the major interventional spine topics were performed to find all prospective, double-blind, randomized placebo-controlled trials in the English language interventional spine literature.

RESULTS: The results from each topic are detailed in the text.

CONCLUSIONS: Statements about the efficacy of each procedure, including lumbosacral and cervical epidural corticosteroid injections, lumbosacral and cervical intra-articular zygapophyseal joint corticosteroid injections, lumbar and cervical medial branch corticosteroid injections, percutaneous radiofrequency neurotomy of the lumbar and cervical medial branches, intra-articular sacroiliac joint corticosteroid injections, IDET, percutaneous radiofrequency neurotomy of the ramus communicans, and intradiscal corticosteroid injections are detailed in the text.

Keywords: Interventional spine; Prospective double-blind randomized placebo-controlled trials

Introduction

Multiple observational and retrospective studies have been reported in the interventional spine literature. However, because of the subjective nature of pain, bias can never be eliminated from such studies. Therefore, to truly evaluate interventional spine procedures, prospective, double-blind, randomized, placebo-controlled trials (PDBRPCTs) are necessary. Unfortunately, the interventional spine literature is scarce when it comes to this type of study design. Equally as discouraging, these limited studies are often misinterpreted, both by proponents and by opponents of the procedures. The purpose of the current study was to find all PDBRPCTs in the interventional spine literature and summarize them in one article, so that physicians can easily review the best quality data that this field of medicine has to offer.

To find all PDBRPCTs in the English language interventional spine literature, extensive Medline/Pubmed searches were performed using the limits “humans” and “randomized controlled trial” without date limitations. All resulting articles were dated between 1973 and December 2007. Under these limits, each of the following terms were searched: spine injection, radiculopathy, sciatica, transforaminal, interlaminar (IL), epidural steroid injection, selective nerve root block, selective nerve root injection, facet, zygapophysial, sacroiliac, intradiscal, ramus communicans, intradiscal electrothermal therapy, intradiscal electrothermal annuloplasty, IDET, and intradiscal heating. This search resulted in 692 citations (some of which were repeats), which were reviewed. Additionally, searches of the large review articles on the major interventional spine topics were performed. One article that originally appeared to meet the criteria for inclusion was excluded at the discretion of this author because the investigators stated that several patients were excluded from the study because they had started the
process of litigation of insurance claims and their subjective analysis of pain relief might therefore be trustworthy.’’ Additionally, it was unclear whether or not this study was double-blinded [1]. See Table 1 for a list of the number of PDBRPCTs in the intervention spine literature.

The PDBRPCTs will be reviewed with strict interpretation of their results. For topics in which trials were available that used key components of a high-quality study (ie, fluoroscopic guidance for epidural injections), only these trials will be included in the current article (ie, the randomized controlled trial of intra-articular zygapophysial joint corticosteroid injections that did not use a diagnostic injection for patient selection was not included in this article). The rationale behind these exclusions is explained in the text.

**Review of the literature by topic**

**Epidural corticosteroid injections in the treatment of lumbosacral radiculopathy**

Multiple PDBRPCTs have been reported in the epidural steroid literature. However, not all epidural steroid injections are equal. Given the improved accuracy of fluoroscopically guided injections, and the improved results with the transforaminal approach to the epidural space, only fluoroscopically guided transforaminal epidural steroid injection (TFESI) studies will be reviewed in the current article.

Non–image-guided IL and caudal injections are not in the epidural space 8% to 53% of the time [2–12]. In the two studies that reported on medication delivery to the site of pathology, despite very high accuracy rates of needle placement in the epidural space in these studies (91–92%), only 26% to 43% obtained contrast flow to the pathologic site [4,6]. Furthermore, in the only prospective randomized controlled trial that compared image-guided to non–image-guided epidural injections, statistically significant benefit was demonstrated in the fluoroscopically guided TFESI group over the non–image-guided IL epidural steroid injection group [13].

In addition to the improved outcomes from the use of image guidance, better outcomes have been shown from the transforaminal approach compared with the IL approach. A prospective trial comparing fluoroscopically guided TFESIs to fluoroscopically guided IL corticosteroid injections was recently reported [14]. This study demonstrated statistically significant benefit in the transforaminal group. Additionally, three of the other four trials that compared the two approaches reported better results from the TFESIs [13,15,16]. The one trial that showed no difference between the two approaches is limited by significant flaws in its study design [17] (15% of the patients in the IL group received a TFESI after not obtaining 50% improvement from the IL injection; the steroid was combined in the syringe with contrast, thereby preventing the interventional spine physician from delivering the entire dose of steroid to the nerve root if a radiculogram was not obtained on the first attempt; and postprocedure treatment—inpatient hospital bed rest for 7 days—is not current standard of care in most interventional spine centers).

Given the information presented above, this article will only examine the four prospective, double-blind, randomized controlled trials of fluoroscopically guided transforaminal lumbosacral epidural corticosteroid injections [13,18–20]. Three of these studies were considered to be placebo controlled [18–20]. The other compared fluoroscopically guided TFESIs to blind IL corticosteroid injections [13]. This non–placebo-controlled trial was included in the current review of the PDBRPCTs because a difference was demonstrated between the two treatment groups. If a study compares two treatments groups and demonstrates positive results, but there is no difference between treatment A and treatment B, then no conclusion can be drawn (because it was not placebo controlled). However, if treatment A is shown to be more effective than treatment B (assuming that treatment B is not detrimental), then a conclusion can be drawn—not only does it show that treatment A is effective, but it is more effective than treatment B (and by inference, it is more effective than placebo). Therefore, this non–placebo-controlled study was included in the current article because it compared two treatments (fluoroscopically guided TFESIs vs. blind IL corticosteroid injections) and showed benefit of one treatment over the other [13].

Because non–image-guided injections are so frequently outside the epidural space [2–12], non–image-guided injections have worse outcomes than image-guided injections [13], and because the transforaminal route is more effective

<table>
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<tr>
<td>Number of prospective, double-blind, randomized, placebo-controlled trials</td>
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<td>Fluoroscopically guided lumbosacral transforaminal epidural corticosteroid injections for lumbosacral radiculopathy</td>
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than the IL route [13–16], the older PDBRPCTs on non–image-guided IL injections will not be included in the current article.

- **Riew. JBJS 2000**
  Fifty-five patients with lumbar radicular pain and corresponding magnetic resonance imaging who had requested surgery were randomized to fluoroscopically guided selective nerve root injections (similar to TFESIs) of either corticosteroid or bupivacaine. The primary outcome measure showed fewer patients in the corticosteroid group going on to surgery at 13 to 28 months (32% vs. 71%, p<.004). Overall, 29/55 of the patients involved in the study avoided surgery, including 68% of the patients who had repeat injections (two to four total) [20].

- **Karppinen. Spine 2001**
  One hundred and sixty patients with lumbosacral radiculopathy of 1- to 6-month duration were randomized to one fluoroscopically guided transforaminal epidural injection of either corticosteroid or saline. At 2 weeks, there was significant improvement in the corticosteroid group over the saline group in leg pain (steroid 7.1 → 3.9 vs. saline 7.5 → 5.4, p=.02) straight leg raise pain, lumbar flexion, and patient satisfaction. At 4 weeks, there were no significant differences between groups. At 3 months, there was significant improvement in the saline group in back pain (steroid 5.3 → 2.6 vs. saline 6.0 → 2.3, p=.03). At 6 months, there was significant improvement in the saline group in back and leg pain (steroid 7.1 → 3.1 vs. saline 7.5 → 2.2, p=.003). At 12 months, there were no significant differences between groups [18].

- **Thomas. Clin Rheumatol 2003**
  Thirty-one patients with “discal radicular pain” of less than 3 months duration were randomized to either fluoroscopically guided TFESI or blind IL epidural corticosteroid injection. All procedures were done in the fluoroscopy suite, and blindling was maintained with sedation. Significant improvements were obtained in the TFESI group at Day 6 in Schober’s index, finger-to-floor distance, daily activities, and leisure and work activities. There was a trend in pain relief (TFESI 7.4 → 3.0 vs. IL 7.2 → 4.2). At Day 30, there was significant improvement in the TFESI group in pain relief (TFESI 7.4 → 1.7 vs. IL 7.2 → 3.1, p=.04). Between 1 and 6 months, 5 out of 15 in the TFESI group and 4 out of 16 in the IL group (not significantly different) underwent surgical discectomy for reasons not reported. These patients were excluded from the 6-month follow-up data. At 6 months, there was significant improvement in pain relief in the TFESI group (TFESI 7.4 → 2.2 vs. IL 7.2 → 4.4, p=.04), in addition to improvements in daily activities, leisure and work activities, anxiety and depression, and quality of life [13].

  Reviewing the raw data presented above, the blind IL epidural corticosteroid injections were clearly not a detrimental intervention. Therefore, not only did this study demonstrate efficacy of TFESIs, but it demonstrated efficacy over another active treatment [13].

- **Ng. Spine 2005**
  Eighty-six patients with chronic radicular pain (mean 12–17 mo) were randomized to one fluoroscopically guided transforaminal epidural injection of either corticosteroid or bupivacaine. Both groups improved modestly (visual analog scale leg pain improved from about seven to five in each group), but there were no significant differences between groups at follow-up of 2 to 12 weeks [19].

**Evidence-based conclusions on fluoroscopically guided transforaminal lumbar epidural corticosteroid injections in the treatment of lumbosacral radiculopathy**

- They are more effective than blind IL epidural corticosteroid injections, and by inference, placebo, from Day 6 to 1 month in patients with radicular symptoms of less than 3-month duration [13].
- They are more effective than epidural saline injections at 2 weeks in patients with radicular symptoms of 1- to 6-month duration [18].
- They may be more effective than blind IL epidural corticosteroid injections, and by inference, placebo, at 6 months in patients with radicular symptoms of less than 3-month duration [13].

  o The validity of this conclusion is unclear because of the patient dropout after 1 month.

- They are more effective than epidural bupivacaine injections, and by inference, placebo, in decreasing the number of patients going on to surgery at 13 to 28 months [20].
- One injection is not more effective than one transforaminal epidural saline injection at 1, 3, 6, or 12 months in patients with radicular symptoms of 1- to 6-month duration [18].
- One injection is not more effective than one transforaminal epidural bupivacaine injection at 2 to 12 weeks in patients with chronic radicular symptoms [19].

**Epidural corticosteroid injections in the treatment of cervical radiculopathy**

One PDBRPCT has been reported [21]. This trial used fluoroscopically guided TFESIs.

- **Anderberg. Eur Spine J 2007**
  Forty patients with chronic cervical radicular pain (mean 31 mo) and a corresponding magnetic
Evidence-based conclusions on cervical epidural corticosteroid injections in the treatment of cervical radiculopathy

- Fluoroscopically guided cervical transforaminal epidural corticosteroid injections are not more effective than fluoroscopically guided cervical transforaminal mepivacaine/saline injections at 3 weeks in patients with chronic radicular pain resulting from “hard disc” pathology [21].

**Evidence-based conclusions on intra-articular lumbosacral zygapophysial joint corticosteroid injections**

- When patients are selected with one diagnostic 2-cc intra-articular lumbosacral zygapophysial joint injection, and when successful medication placement is obtained 84% of the time, 2-cc corticosteroid injections are no more effective than placebo at 1 or 3 months [32].

**Lumbar medial branch nerve corticosteroid or Sarapin injections**

One PDBRPCT has been reported [33].


These are the preliminary results of 60 patients (randomly selected from the 120 patients enrolled in the trial) with low back pain of at least a 6-month duration who had greater than or equal to 80% improvement on the numeric pain rating score with comparative diagnostic medial branch blocks (1st with lidocaine, 2nd with bupivacaine.) The patients were randomized into four groups and received the following injections on the lumbar medial branch nerves: bupivacaine only, bupivacaine plus Sarapin (High Chemical Company, Levittown, PA, USA), bupivacaine plus steroid, or bupivacaine plus Sarapin plus steroid. At 3, 6, and 12 months, there were improvements in all four groups, but there were no statistically significant differences between any of the groups [33]. The authors of this study do not consider it to be a placebo-controlled trial. The inclusion of...
this study in the current review article, and the reason for considering lumbar medial branch nerve injections with bupivacaine to be equivalent to placebo when it comes to long-term follow-up, will be explained in the Discussion section.

Evidence-based conclusions on lumbar medial branch nerve corticosteroid or Sarapin injections

They are no more effective than placebo in the treatment of patients with chronic lumbar zygapophysial joint pain [33].

Cervical intra-articular zygapophysial joint corticosteroid injections when using at least one diagnostic injection for patient selection

One PDBRPCT that used at least one diagnostic injection has been reported [34].

- Barnsley. NEJM 1994
  Forty-one patients with chronic neck pain (mean 39 mo) after a whiplash automobile injury had complete or definite pain relief from one cervical medial branch block with lidocaine, and to a subsequent medial branch block with bupivacaine. They were then randomized to 1-cc intra-articular cervical zygapophysial joint injections of either steroid or bupivacaine. There were no outcome differences between the two groups [34].

Evidence-based conclusions on intra-articular cervical zygapophysial joint corticosteroid injections

- They may be no more effective than placebo in treating patients with chronic cervical zygapophysial joint pain after a whiplash automobile injury [34].
  - The validity of this conclusion is unclear because only one level was treated despite the diagnosis of multiple joint pain in 37% of patients.
  - No conclusions can be reached about patients with degenerative cervical zygapophysial joint arthropathy.

Cervical medial branch nerve corticosteroid or Sarapin injections

One PDBRPCT has been reported [35].

- Manchikanti. Pain Physician 2006
  These are the preliminary results of 60 patients (randomly selected from the 120 patients enrolled in the trial) with neck pain of at least 6-month duration who had greater than or equal to 80% improvement on the numeric pain rating score with comparative diagnostic medial branch blocks (first with lidocaine and second with bupivacaine). The patients were randomized into four groups and received the following injections on the cervical medial branch nerves: bupivacaine only, bupivacaine plus Sarapin, bupivacaine plus steroid, or bupivacaine plus Sarapin plus steroid.

At 3, 6, and 12 months, there were improvements in all four groups, but there were no statistically significant difference between any of the groups [35]. The authors of this study do not consider it to be a placebo-controlled trial. As noted above, the inclusion of this study in the current review article, and the reason for considering cervical medial branch nerve injections with bupivacaine to be equivalent to placebo when it comes to long-term follow-up, will be explained in the Discussion section.

Evidence-based conclusions on cervical medial branch nerve corticosteroid or Sarapin injections

- They are no more effective than placebo in the treatment of patients with chronic cervical zygapophysial joint pain [35].

Percutaneous radiofrequency lumbar medial branch neurotomy for the treatment of lumbosacral zygapophysial joint pain when using at least one diagnostic injection for patient selection

Five PDBRPCTs that used one diagnostic injection have been reported [36–40]. None that used two diagnostic injections have been reported.

  Sixty patients with low back pain of greater than a 3-month duration underwent one diagnostic bupivacaine (and corticosteroid?) injection “in and around the appropriate painful joints.” Forty-one patients had a good [30] or equivocal [11] response and were randomized to percutaneous radiofrequency lumbar medial branch neurotomy at 80°C for 90 seconds (using the technique described by Shealy [41]) versus a sham procedure. Of the patients who had a good response to the diagnostic block, there was statistically significant improvement at 1 and 6 months in the medial branch neurotomy group. Of the patients with an unequivocal response to the diagnostic block, there were no outcome differences between the two groups. The authors of this article incorrectly stated that the L4–L5 zygapophysial joint is innervated by the medial branch of L4 and the dorsal ramus of L5 (the true innervation of the L4–L5 zygapophysial joint is the medial branches of L3 and L4), so it is unclear if neurotomy was performed on the proper medial branches in this study [36].

- van Kleef. Spine 1999
  Ninety-two patients with low back pain of greater than a 12-month duration underwent one diagnostic block of the L3 and L4 medial branches and the L5 dorsal ramus requiring greater than or equal to 50% improvement to be considered as a positive response. Thirty-one patients with positive responses were then randomized to percutaneous radiofrequency...
neurotomy of the L3 and L4 medial branches and the L5 dorsal ramus at 80°C for 60 seconds versus a sham procedure. The technique used in this study has been criticized for placing the radiofrequency needle perpendicular to the target nerve [42]; however, it has also been praised as being superior to the technique used in the other three PDBRPCtS reported before 2007 [43]. There was statistically significant improvement in the medial branch neurotomy group at 8 weeks, 3, 6, and 12 months. Higher success rates were reported from the medial branch neurotomy in the patients who were pain free after the diagnostic medial branch block [38].

- Leclaire. Spine 2001

Seventy patients with low back pain of greater than a 3-month duration experienced “significant relief” for at least 24 hours during the week after one intra-articular zygapophysial joint corticosteroid/anesthetic injection. They were randomized to percutaneous radiofrequency lumbar medial branch neurotomy at 80°C for 90 seconds versus a sham procedure. At 4 weeks, there was improvement in the Roland-Morris score in the medial branch neurotomy group, but no difference in the Oswestry disability score or the VAS pain score between groups. At 12 weeks, neither group showed improvement [37].


Four hundred and sixty-two patients with low back pain of greater than a 6-month duration were screened with one intra-articular zygapophysial joint lidocaine block. Eighty-one experienced greater than or equal to 50% improvement and were randomized to one diagnostic medial branch neurotomy at 80°C for 60 seconds versus a sham procedure. There were no differences in the number of successes between groups at 3 months. There was significant improvement in the Global Perceived Effect and a significantly better cost benefit in the medial branch neurotomy group at 3 months [39].


Sixty patients with low back pain of greater than a 6-month duration demonstrated greater than 50% improvement for the expected duration of lidocaine from one medial branch block. They were then randomized into three groups: continuous percutaneous radiofrequency lumbar medial branch neurotomy (“CRF”) at 80°C for 90 seconds versus pulsed percutaneous radiofrequency lumbar medial branch neurotomy (“PRF”) at 2 Hz for 4 minutes at 42°C versus a sham procedure. In the “CRF” group, the authors state that the electrode “was placed parallel to the nerves.” There was a statistically significant improvement in the Oswestry disability score, VAS pain score, patient satisfaction, and the number of patients requiring analgesics in the “CRF” group versus the sham group at 6 months and 1 year. There was better patient satisfaction and fewer patients requiring analgesics in the “PRF” group versus the sham group at 1 year [40].

Evidence-based conclusions on percutaneous radiofrequency lumbar medial branch neurotomy for the treatment of lumbosacral zygapophysial joint pain (in studies that used one diagnostic injection)

- Radiofrequency using 80°C for 60 seconds
  - It is more effective than placebo in the short term (8 wk) and long term (3–12 mo) in patients with greater than or equal to 50% improvement from one diagnostic medial branch block [38].
  - When using a perpendicular approach to the target nerve, it is not more effective than placebo (other than Global Perceived Effect and cost) at 3 months in patients with greater than or equal to 50% improvement from one diagnostic intra-articular zygapophysial joint block [39].

- Radiofrequency using 80°C for 90 seconds
  - When using a perpendicular approach to the target nerve, it is more effective than placebo at 1 and 6 months in patients with a good response to one diagnostic injection “in and around” the zygapophysial joint [36].
  - When using a perpendicular approach to the target nerve, it shows some functional benefit over placebo at 4 weeks, but no benefit at 12 weeks, in patients with “significant relief” for at least 24 hours during the week after one intra-articular zygapophysial joint corticosteroid/anesthetic injection [37].
  - When placing the electrode parallel to the target nerve, it is more effective than placebo at 6 months and 1 year in patients with greater than 50% improvement from one diagnostic medial branch block [40].

- Pulsed radiofrequency at 2 Hz for 4 minutes at 42°C
  - It is more effective than placebo in patient satisfaction and analgesic requirements at 1 year in patients with greater than 50% improvement from one diagnostic medial branch block [40].

- No conclusions can be reached about percutaneous radiofrequency lumbar medial branch neurotomy for the treatment of lumbosacral zygapophysial joint pain when patients are selected using two separate diagnostic injections.

*Note: Most interventional spine physicians consider the study by Dreyfuss et al. to be the highest quality study on percutaneous radiofrequency lumbar medial branch neurotomy for the treatment of lumbosacral zygapophysial joint pain
However, because this study was not placebo controlled, it was not included in the current article.

Percutaneous radiofrequency cervical medial branch neurotomy for the treatment of cervical zygaphysial joint pain when using at least one diagnostic injection for patient selection

One PDBRPCT that used at least one diagnostic injection has been reported [45].

- Lord. NEJM 1996
  Twenty-four patients with chronic C3–C4 to C6–C7 zygaphysial joint pain (mean 34 mo) after a whiplash automobile injury experienced complete pain relief from two blinded diagnostic local anesthetic medial branch blocks (one with lidocaine, one with bupivacaine) and no pain relief from a blinded medial branch saline injection. They were randomized to percutaneous radiofrequency cervical medial branch neurotomy at 80°C for 90 seconds versus a sham procedure. Although 29% of patients were diagnosed with pain emanating from more than one joint, only one joint was treated in each patient. Surprisingly, each procedure lasted approximately 3 hours. There was statistically significant improvement in the percutaneous radiofrequency cervical medial branch neurotomy group (time from treatment to a 50% return of pain was 263 versus 8 days, p=.04) [45].

Evidence-based conclusions on percutaneous radiofrequency cervical medial branch neurotomy for the treatment of cervical zygaphysial joint pain

- It is more effective than placebo in patients with chronic C3–C4 to C6–C7 zygaphysial joint pain after a whiplash automobile injury when selected via a triple block (including one placebo) algorithm [45].
- No conclusions can be reached about patients with degenerative cervical zygaphysial joint arthropathy.

Intra-articular sacroiliac joint corticosteroid injections

One PDBRPCT has been reported, and it did not use any diagnostic injections [31].

- Maguars. Br J Rheumatol 1996
  Ten patients (13 joints) with spondyloarthropathy and low back pain were randomized to a fluoroscopically guided sacroiliac joint corticosteroid versus saline injection. No diagnostic injections were performed. At 1 month, there was statistically significant improvement in the corticosteroid group (5/6 vs. 0/7 with very good or good improvement, p<.05; dolorimetry improvement from 6.8 to 1.3 corticosteroid group vs. 7.0 to 5.2 placebo group, p<.005) [31].

Evidence-based conclusions on intra-articular sacroiliac joint corticosteroid injections

- Fluoroscopically guided SI joint corticosteroid injections are more effective than placebo at 1 month in patients with spondyloarthropathy and low back pain [31].

Sacroiliac joint percutaneous radiofrequency denervation

No PDBRPCTs have been reported.

Evidence-based conclusions on sacroiliac joint percutaneous radiofrequency denervation

No conclusions can be reached.

Discogenic pain

Currently, there is no universally accepted gold standard diagnostic test for discogenic pain. To attempt to reliably diagnose pain emanating from the intervertebral disc, provocative discography has been studied exhaustively. Although a consensus has not been reached regarding the utility of discography, it is clear that history, physical exam, and imaging without provocative discography, cannot reliably diagnose discogenic pain. This is clearly demonstrated in the results of the three prospective, randomized controlled trials on surgical fusion, none of which used provocative discography as a diagnostic tool. One trial showed no benefit of fusion over intense cognitive intervention and exercises [46], another showed only mild, clinically insignificant benefit of fusion over intense re-habilitation in Oswestry Disability Index [47], and although the third trial showed benefit of fusion over continued failed 1990s physical therapy at 2 years [48], this benefit was lost at 5 years [49]. Whether this lack of efficacy of fusion over conservative treatment was because of the absence of discography in patient selection, the ineffectiveness of surgical fusion, or some other unknown reason, remains to be proven.

Multiple studies have demonstrated that when performed without strict criteria for interpretation of results, discography is not a valid diagnostic screen for discogenic pain [50–54], and it does not predict which patients will succeed with treatment [55,56]. However, several studies have shown that when performed with strict criteria, including concordant pain of greater than or equal to 7 out of 10 on aVAS at low pressure (under 15 psi above opening pressure) with negative control discs, discography is a useful diagnostic tool [57–60]. Two PDBRPCTs, which used some (but not all) of the strict discography criteria, have demonstrated that it does reliably diagnose patients who benefit from treatment [61,62]. This clearly demonstrates that discography can be used diagnostically to predict outcomes when done (at least partially) correctly. Therefore, any study that reports negative results without using discography with strict criteria should be interpreted with scrutiny. The 2004 International Spine Intervention Society (ISIS) guidelines for “unequivocal,” “definite,” and “probable” discogenic pain (see Table 2) take into
Intradiscal electrothermal therapy (IDET) for discogenic pain

Intradiscal electrothermal therapy (IDET) for the treatment of discogenic pain has yet to be done. Although some recent studies have reported definite discogenic pain selected by the discography criteria of concordant pain at “low pressure” who had failed conservative treatment and IDET underwent a diagnostic block of the ramus communicans after zygapophysial joint pain had been excluded with negative L3 and L4 medial branch and L5 dorsal ramus blocks. Forty-nine patients had greater than or equal to 50% temporary pain relief and were randomized to percutaneous radiofrequency neurotomy group in VAS pain procedure. At 4 months, there was significant benefit when using the 2004 ISIS Practice Guidelines for discography interpretation [63] for patient selection.

Percutaneous radiofrequency neurotomy of the ramus communicans for discogenic pain

One PDBRPCT has been reported [61].


Sixty-three patients with a positive discogram (concordant pain at “low pressure”) who had failed conservative treatment and IDET underwent a diagnostic block of the ramus communicans after zygapophysial joint pain had been excluded with negative L3 and L4 medial branch and L5 dorsal ramus blocks. Forty-nine patients had greater than or equal to 50% temporary pain relief and were randomized to percutaneous radiofrequency neurotomy group in VAS pain procedure. At 4 months, there was significant benefit in the radiofrequency neurotomy group in VAS pain (7.1 → 3.8 vs. 7.0 → 6.3, p < .05) SF-36 bodily pain (29.2 → 43.7 vs. 28.8 → 32.4, p < .05), and SF-36 physical function (43.7 → 58.9 vs. 44.1 → 46.5, p < .05). Seventy-seven percent of patients in the percutaneous radiofrequency neurotomy group discontinued or decreased analgesic medication consumption. Fifty-eight percent of patients in the percutaneous radiofrequency neurotomy group were highly satisfied and 23% were moderately satisfied [61].

Evidence-based conclusions on IDET for the treatment of discogenic pain

- It is modestly more effective than placebo at 6 months in patients with less than 20% disc height loss selected by the discography criteria of concordant pain multiple times at a similar PSI with negative control discs [62].
- It may not be more effective than placebo at 6 months in patients with less than 50% disc height loss selected by the discography criteria of “one- or two-level symptomatic disc degeneration with an adjacent asymptomatic control disc” [55].
- The validity of this conclusion is unclear because this study failed to reach the intended number of patients required by the power analysis, there may have been baseline differences between the two groups, and 90% of patients had abnormal reflexes [55].
- No conclusions can be drawn about long-term outcomes.
- No conclusions can be drawn about the utility of IDET when using the 2004 ISIS Practice Guidelines for discography interpretation [63] for patient selection.

Table 2

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<thead>
<tr>
<th>Pain description</th>
<th>PSI requirements</th>
<th>Control discs</th>
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<tbody>
<tr>
<td>Unequivocal discogenic pain</td>
<td>Concordant pain ≥7/10</td>
<td>Two pain-free control discs</td>
</tr>
<tr>
<td>Definite discogenic pain</td>
<td>Concordant pain ≥7/10</td>
<td>One pain-free control disc</td>
</tr>
<tr>
<td>Definite discogenic pain</td>
<td>Concordant pain ≥7/10</td>
<td>Two pain-free control discs</td>
</tr>
<tr>
<td>Probable discogenic pain</td>
<td>Concordant pain ≥7/10</td>
<td>One pain-free disc and one disc with nonconcordant pain at &gt;50 PSI</td>
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Intradiscal electrotherapy (IDET) for discogenic pain

Two PDBRPCTs have been reported [55,62].

- Pauza. Spine J 2004

After 4,523 inquiries for participation in this study, 1,360 patients were eligible after a telephone interview, and 260 with less than 20% disc height loss were eligible after evaluation of the patients. These patients had discography, and 64 met criteria for a positive discogram (concordant pain multiple times at a similar PSI with negative control discs). These patients were randomized to IDET versus a sham procedure. At 6 months, statistically significant benefit was demonstrated in the IDET group in VAS pain (6.6 → 4.2 vs. 6.5 → 5.4, p = .045) and Oswestry Disability Index (31 → 20 vs. 33 → 28, p = .050). A trend was seen in the SF-36 Bodily Pain subscale (36 → 53 vs. 35 → 44, p = .086). Although statistically—and clinically—significant benefit was demonstrated, the results were modest. Approximately two out of five patients experienced greater than or equal to 50% pain relief, and approximately one out of five experienced greater than or equal to 75% pain relief [62].

- Freeman. Spine 2005

Less than 200 patients with less than 50% disc height loss underwent discography and 57 met criteria for a positive discogram (one- or two-level symptomatic disc degeneration with an adjacent asymptomatic control disc) and were randomized to IDET versus a sham procedure. At 6 months, no patients in either group met the predefined criteria for a successful outcome (no neurologic deficit, greater than seven-point improvement on the Low Back Outcome Score, and greater than 1 standard deviation improvement in the SF-36 physical function and bodily pain subscales) [55].

Evidence-based conclusions on IDET for the treatment of discogenic pain

- It is modestly more effective than placebo at 6 months in patients with less than 20% disc height loss selected by the discography criteria of concordant pain multiple times at a similar PSI with negative control discs [62].
Evidence-based conclusions on percutaneous radiofrequency neurotomy of the ramus communicans for the treatment of discogenic pain

- It is more effective than placebo at 4 months in patients with chronic low back pain who have positive discography (defined by concordant pain at “low pressure”), greater than or equal to 50% temporary improvement after a diagnostic block of the ramus communicans, and the exclusion of zygapophysial joint pain with negative L3 and L4 medial branch and L5 dorsal ramus blocks [61].
- No conclusions can be drawn about long-term outcomes.

Intradiscal corticosteroid injections for discogenic pain

Two PDBRPCTs have been reported [64,65].

- Simmons. Spine 1992
  Twenty-five patients with one-level “intervertebral disc disruption” with or without sciatica and a one-level “positive pain response on discography” were randomized to an intradiscal corticosteroid injection versus an intradiscal bupivacaine injection. At 2 weeks, there were no significant differences between the two groups [65].

- Khot. Spine 2004
  One hundred twenty patients with chronic low back pain and concordant pain on discography were randomized to an intradiscal corticosteroid injection versus an intradiscal saline injection. At 1 year, there were no significant differences between the two groups [64].

Evidence-based conclusions on intradiscal corticosteroid injections for the treatment of discogenic pain

- They are not more effective than placebo at 2 weeks in patients with radicular or discogenic pain who are selected by the discography criteria of a one-level “positive pain response” [65].
- They are not more effective than placebo at 1 year in patients selected by the discography criteria of concordant pain [64].
- No conclusions can be drawn about the utility of intradiscal corticosteroids when using the 2004 ISIS Practice Guidelines for discography interpretation [63] for patient selection.

Summary of evidence-based conclusions

- Fluoroscopically guided lumbosacral transforaminal epidural corticosteroid injections are effective in the short term, and possibly at 6 months, in treating acute/subacute lumbosacral radicular pain [13,18].
- Fluoroscopically guided lumbosacral transforaminal epidural corticosteroid injections are more effective than placebo at preventing future surgeries [20].
- One-level intra-articular cervical zygapophysial joint corticosteroid injections are not more effective than placebo in treating patients with chronic cervical zygopophysial joint pain after whiplash injury [34].
- Corticosteroid or Sarapin injections on the cervical or lumbosacral medial branch nerves are not more effective than placebo in treating patients with chronic cervical or lumbosacral zygapophysial joint pain [33,35].
- When using a technique that is superior to the technique used in the other randomized controlled trials, percutaneous radiofrequency lumbar medial branch neurotomy in patients with chronic lumbosacral zygapophysial joint pain is more effective than placebo [38,40].
- Percutaneous radiofrequency cervical medial branch neurotomy is more effective than placebo in treating patients with chronic cervical zygapophysial joint pain after whiplash injury [45].
- Sacroiliac joint corticosteroid injections are more effective than placebo in treating patients with spondyloarthropathy and low back pain [31].
- IDET is modestly more effective than placebo at 6 months in treating patients with less than 20% disc height loss who are diagnosed with discogenic pain via the discography criteria of concordant pain multiple times at a similar PSI with negative control discs [62].
- Percutaneous radiofrequency zygapophysial joint neurotomy is more effective than placebo at 4 months in treating discogenic pain [61].
- Because of the lack of PDBRPCTs or the significant methodologic flaws in the existing PDBRPCTs, no firm conclusions can be drawn about: lumbosacral epidural corticosteroid injections for the treatment of chronic radicular pain, cervical epidural corticosteroid injections for the treatment of acute or chronic radicular pain, lumbosacral or cervical zygapophysial joint corticosteroid injections for the treatment of degenerative zygapophysial joint pain, percutaneous radiofrequency cervical medial branch neurotomy for the treatment of degenerative zygapophysial joint pain, sacroiliac joint corticosteroid injections in patients without spondyloarthropathy, percutaneous radiofrequency denervation of the sacroiliac joints, or intradiscal corticosteroid injections for the treatment of discogenic pain.

Discussion

The current article reviews the PDBRPCTs in the interventional spine literature with strict interpretation of their results. As physicians, it is our job to understand how to properly translate this raw data into accurate and clinically relevant information. To do this, one must know how to properly evaluate medical literature.

In outcome studies, there are two potential results—positive (meaning that the treatment is statistically better...
than the control group) or negative (meaning that no difference was demonstrated between groups.) As with diagnostic tests, a positive study can be a true positive or a false positive, and a negative study can be a true negative or a false negative. As clinicians, it is our duty to attempt to recognize false positive and false negative studies so that the conclusions of these studies are not misinterpreted.

In the interpretation of medical literature, the design of negative studies deserves closer evaluation than that of positive studies. As William Cowper said, “absence of proof is not proof of absence.” A negative study may be negative because the treatment is ineffective. However, if serious flaws in study design exist, the negative results are in question. Because proof of absence is much more difficult to demonstrate than proof of presence, negative studies should receive strict scrutiny to determine if the results are truly negative. Positive studies are different. Assuming that the randomization process has equalized baseline data between groups, and that the control group does not receive a detrimental treatment, then positive results should be accepted for what they are—statistically (although not necessarily clinically) significant proof that a true difference exists between the treatment and control groups. Of course, when interpreting positive results, one must consider that the defined medical convention is to accept a 5% false positive rate (p value of .05). With that in mind, positive results are positive. Negative results, however, require greater scrutiny to determine if the treatment is truly ineffective.

This is best demonstrated with an exaggerated example. In this hypothetical example, let us evaluate if IV hydromorphone is effective in treating the pain from a mild paper cut. In designing this study, one should compare IV saline to IV hydromorphone. However, what if the control group received IV morphine instead? If negative results were obtained (ie, if there was no statistically significant difference between IV hydromorphone and IV morphine), should we conclude that IV hydromorphone is ineffective at treating the pain from a minor paper cut? Of course not—a major flaw in the design of the trial explains the negative results (the control group received an active treatment instead of a true placebo). Now, what if the results were positive (ie, IV hydromorphone was shown to be significantly more effective than IV morphine)? In this case, despite the significant flaw in study design, IV hydromorphone was shown to be an effective treatment. It would be reasonable to conclude that IV hydromorphone is more effective than placebo, and even more impressively, that it is more effective than another active treatment—IV morphine. Lastly, let us examine a final example. Instead of comparing IV hydromorphone to IV saline or IV morphine, consider a study in which the control group received IV cyanide. One would expect positive results from the hydromorphone compared with the cyanide. However, because IV cyanide would be expected to be a detrimental treatment, these positive results would not truly tell us if IV hydromorphone is more effective than placebo. In the above review of the PDBRPCTs in the interventional spine literature, none of the control groups received a treatment that can reasonably be expected to be of detriment.

This exaggerated example is similar to a situation that is present in the fluoroscopically guided TFESI literature. Five of the trials presented in the body of the current manuscript compared fluoroscopically guided TFESIs to potentially effective treatments (either blind IL epidural corticosteroid injections [13], fluoroscopically guided transformaminal epidural local anesthetic injections [19–21], or fluoroscopically guided transformaminal epidural saline injections [18]). The potential efficacy of epidural saline injections is supported by non-PDBRPCTs that show benefit in 70% to 92% of patients who receive epidural saline injections [66,67]. Also, local anesthetic has proven anti-inflammatory [68–70] and neuroprotective [71,72] benefits. In fact, when compared with no treatment, although a recent animal study demonstrated significant improvement from nerve root injections with lidocaine, dexamethasone, and lidocaine plus dexamethasone, there were no significant differences between the treatment groups [73]. Therefore, control groups in the epidural corticosteroid injection literature that receive an epidural injection of either local anesthetic or saline may in fact be receiving a beneficial treatment, and may not truly represent a placebo group. Negative results from such studies are in question, because although they may demonstrate lack of benefit of corticosteroid over saline/local anesthetic, they do not necessarily demonstrate lack of benefit of the injection. Despite this flaw in study design, two of the five PDBRPCTs concluded with positive results [13,20], and a third demonstrated positive short-term results [18].

In addition to the control group receiving a potentially beneficial treatment, several other flaws in study design were present in the fluoroscopically guided TFESI literature. First, one needs to consider the appropriate time period to measure outcomes from a TFESI. If patients are given one injection that is not repeated, it is this author’s belief that it is reasonable to expect the corticosteroid injection to last for several weeks, and possibly for several months, but it is unlikely that the benefits from the injection itself will last beyond this time period. However, this does not mean that the patient will not do well clinically in the long term. Radiculopathy has a favorable natural history. Forty-one percent of patients improve significantly within 5 months of symptom onset [74], and 86% to 90% of patients obtain good-to-excellent results and avoid surgery at 1 to 2.5 years [75,76]. Therefore, this author believes that outcome measures past 4 to 6 months post-injection are simply a measure of natural history, and would be expected to be similar between treatment and placebo groups if the injection is not repeated. When patients in a research study receive one TFESI, outcome measures should ideally be drawn in the short term to truly evaluate if the treatment is effective. In clinical practice, it should be explained to patients that the purpose of the injection (which can be repeated) is to provide short-term relief to allow the favorable
natural history of radiculopathy to run its course so that patients can avoid more invasive surgical treatments.

The interventional zygapophysial joint literature also is filled with flaws that bias studies toward negative outcomes. The most striking flaw is the use of a single diagnostic injection in most trials [32,36–40]. One can make the argument that in clinical practice, given the minimally invasive nature of intra-articular corticosteroid injections and percutaneous radiofrequency medial branch neurotomy, the improved sensitivity from the use of a single diagnostic block over comparative diagnostic blocks makes up for the increased false positive rate from just one diagnostic injection. However, the 22% to 32% false positive rate of diagnostic injections, which corresponds to 41% to 69% of positive diagnostic blocks being falsely positive [28–30], is unacceptably high for research, particularly if one is attempting to demonstrate proof of absence in a negative trial.

The intra-articular lumbosacral zygapophysial joint corticosteroid injection literature is very limited. In the only trial reviewed in the current article [32], the single diagnostic injection consisted of a 2-cc injection of lidocaine. It is recommended that no more than 1 cc be injected into a lumbosacral zygapophysial joint because larger volumes lead to extra-articular extravasation of injectate, thereby decreasing the specificity of the diagnostic block [77]. Additionally, only 84% of the zygapophysial joints were reported as being successfully injected. Therefore, only limited information can be obtained from this study [32].

The intra-articular cervical zygapophysial joint corticosteroid injection literature is stronger. In the one trial reviewed in the current article, two controlled diagnostic injections were used for patient selection. Despite this excellent inclusion criteria, negative results were obtained. This gives greater credence to the idea that the procedure may in fact be ineffective (proof of absence) in the population that was studied (whiplash injury after a motor vehicle collision). However, one significant flaw in study design did exist. Although 37% of patients were diagnosed with pain emanating from more than one joint, only one joint was treated in each patient, which may—or may not—explain the lack of efficacy from the treatment [34].

The percutaneous radiofrequency lumbar medial branch neurotomy literature has two significant flaws. All five PDBRPTs used just one diagnostic injection [36–40], and the technique used in at least three of the trials was flawed [36,37,39]. This technique, a modification of that described by Shealy [41], has been criticized for placing the radiofrequency needle perpendicular, instead of parallel, to the medial branch nerves [43,78–80]. It has been shown that the radiofrequency lesion does not extend to a significant degree distal to the tip of the radiofrequency needle (it extends radially in a spheroid shape) and therefore, to obtain a successful neurotomy, the needle must be placed parallel to the target nerve [81–83]. The study that appears to have used the best technique demonstrated positive results, despite using just one diagnostic injection [40].

The one PDBRPT on percutaneous radiofrequency cervical medial branch neurotomy used excellent patient selection—three blinded diagnostic blocks [45]. By performing three diagnostic injections, the sensitivity of the diagnosis is decreased while the specificity is increased. Although this degree of patient selection may not be practical in clinical medicine, it is important in clinical research. This trial demonstrates that in well-selected patients, the procedure is effective. It is the role of the interventional spine physician to determine what level of sensitivity and specificity from diagnostic injections is appropriate in clinical practice to treat as many patients who have the disease process as possible without sacrificing the positive results that were obtained in this study.

Another popular treatment for lumbar and cervical zygapophysial joint pain is a corticosteroid injection directly on the medial branch nerves. However, the rationale for performing this injection is flawed. Unlike radiculopathy, where the site of pathology is the nerve itself, zygapophysial joint pain is merely transmitted through the medial branch nerve. The site of pathology is the joint. Therefore, it does not make logical sense to inject corticosteroid on a nerve that is not pathologic. Patients with zygapophysial joint pain have zygapophysial joint arthritis or arthropathy, not medial branchitis or medial branchopathy. In radiculopathy, a local anesthetic injection, or even a saline injection, on the pathologic nerve itself may be expected to result in prolonged benefit. However, injection of local anesthetic on the medial branch nerve in patients with zygapophysial joint arthritis/arthropathy can only be expected to provide pain relief for the duration of the local anesthetic (with the possibility of mildly longer relief from relaxation of tight multifidus muscles—which are innervated by the medial branch nerves—that have been contracting to protect the inflamed joint). Pain relief that lasts greater than this expected time period is likely due either to relief through natural history, or more likely, to placebo effect. In the two trials on this topic that were reviewed in the current article, the authors did not consider their trials to be placebo-controlled studies [33,35]. However, given the information listed above, it is reasonable to view the 3-, 6-, and 12-month results from local anesthetic injections on the medial branch nerves as placebo injections. This was the rationale for the inclusion of these trials in the current article, and the rationale for the conclusion that corticosteroid injections on the medial branch nerves are no better than placebo.

The literature on interventional sacroiliac joint treatments is quite limited. In the only PDBRPT presented in the current article, significant benefit was demonstrated from intra-articular sacroiliac joint corticosteroid injections in patients with spondyloarthropathy and low back pain [31]. No PDBRPTs on interventional sacroiliac joint treatments in patients without spondyloarthropathy have been reported. Such studies are long overdue.
The IDET PDBRPCTs present an interesting opportunity in the interpretation of interventional spine literature—one PDBRPCT demonstrates (modest) benefit, whereas the other does not. The two most likely explanations for this are that either the Pauza et al.’s study [62] is one of the 5% of medical studies that our conventional p value of .05 leads us to incorrectly accept as positive, or the Freeman et al.’s study [55] had significant flaws that predisposed it to negative results. Examination of the Freeman et al.’s study in closer detail suggests that the latter is more likely. This study fell 18 patients short of the 75 that the power analysis required, and there appear to have been baseline differences between the two groups; however, it was not stated whether or not these differences were statistically significant. The study did not use strict discography criteria (no manometry, no concordance requirement, no severity requirement). Lastly, 90% of the patients had abnormal reflexes (suggesting that several patients with radiculopathy, and not discogenic pain, may have been treated) [55]. Although the Pauza et al.’s study demonstrated only modest benefit, and only two out of five patients obtained at least 50% pain relief, it does appear that the appropriate interpretation of the IDET PDBRPCTs is that the treatment is modestly effective in well-selected patients.

Because the IDET literature demonstrates only modest benefit, a potentially interesting alternative for the treatment of discogenic pain is percutaneous radiofrequency neurotomy of the ramus communicans. The one PDBRPCT on this topic demonstrated statistically and clinically significant benefit [61], suggesting that this may be a reasonable treatment option for patients with discogenic low back pain, who in the past, have often been offered surgical fusion.

Lastly, the intradiscal corticosteroid literature is quite limited. Neither of the two PDBRPCTs used strict discography criteria (no manometry, no concordance requirement, and no severity requirement in the Simmons et al.’s study [65], and no manometry, no severity requirement, and no negative control discs in the Khot et al.’s study [64]). Additionally, in the Khot et al.’s study, the outcomes were measured at an inappropriate time period [64]—it is unreasonable to expect one corticosteroid injection to provide 1 year of benefit.

Conclusions

The PDBRPCT study design is essential in the interventional spine literature. The proper interpretation of the results of these studies is just as important. To provide the best care to patients, interventional spine physicians should familiarize themselves with this literature and interpret it correctly.

References


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