Health Policy Review

# Randomized Trial of Epidural Injections for Spinal Stenosis Published in *The New England Journal of Medicine*: Further Confusion Without Clarification

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Disclaimer: There was no external funding in the preparation of this manuscript.
Conflict of Interest: Dr. Benyamin is a consultant and lecturer for Boston Scientific and Kimberly Clark. Dr. Kaye is a speaker for Depomed, Inc. Dr. Falco is a consultant for St. Jude Medical Inc. and Joimax Inc.

Manuscript received: 07-09-2014
Accepted for publication: 07-11-2014

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Randomized controlled trials are considered the hallmark of evidence-based medicine. This conveys the idea that up-to-date evidence applied consistently in clinical practice, in combination with clinicians' individual expertise and patients own preference/expectations are enjoined to achieve the best possible outcome. Since its inception in 1990s, evidence-based medicine has evolved in conjunction with numerous changes in the healthcare environment. However, the benefits of evidence-based medicine have not materialized for spinal pain including surgical interventions. Consequently, the debate continues on the efficacy and medical necessity of multiple interventions provided in managing spinal pain.

Friedly et al published a randomized controlled trial of epidural glucocorticoid injections for spinal stenosis in the July 2014 edition of the highly prestigious *New England Journal of Medicine*,. This was accompanied by an editorial from Andersson. This manuscript provided significant sensationalism for the media and confusion for the spine community. This randomized trial of epidural glucocorticoid injections for spinal stenosis and accompanying editorial concluded that epidural injections of glucocorticoids plus lidocaine offered minimal or no short-term benefit as compared with epidural injections of lidocaine alone, with the editorial emphasizing proceeding directly to surgical intervention. In addition media statements by the authors also emphasized the idea that exercise or surgery might be better options for patients suffereing from narrowing of the spinal canal.

The interventional pain management community believes that there are severe limitations to this study, manuscript, and accompanying editorial. The design, inclusion criteria, outcomes assessment, analysis of data and interpretation, and conclusions of this trial point to the fact that this highly sophisticated and much publicized randomized trial may not be appropriate and lead to misinformation.

The design of the trial was inappropriate with failure to include existing randomized trials, with inclusion criteria that did not incorporate conservative management,or caudal epidural injections. Simultaneously, acute pain patients were included, multilevel stenosis and various other factors were not identified. The interventions included lumbar interlaminar and transforaminal epidural injections with highly variable volumes of medication being injected per patient. Outcomes assessment was not optimal with assessment of the patients at 3 and 6 weeks for a procedure which provides on average 3 weeks of relief and utilizing an instrument which is more appropriately utilized in acute and subacute low back pain. Analysis of the data was hampered by inadequate subgroup analysis leading to inappropriate interpretation. Based on the available data epidural local anesthetic with steroids was clearly superior at 3 weeks and potentially at 6 weeks. Further, both treatments were effective considering the baseline to 3 week and 6 week assessment, appropriate subgroup analysis seems to have yielded significant superiority for interlaminar epidural injections compared to transforaminal epidural injections with local anesthetic with or without steroids specifically with proportion of patients achieving greater than 50% improvement at 3 and 6 week levels.

This critical assessment shows that this study suffers from a challenging design, was premised on the exclusion of available high-quality literature, and had inadequate duration of follow-up for an interventional technique with poor assessment criteria and reporting. Finally the analysis and interpretation of data has led to inaccurate and inappropriate conclusions which we do not believe is based on scientific evidence.

**Key words:** Chronic low back pain, central spinal stenosis, epidural injections, local anesthetics, steroids, randomized trials, outcomes assessment

**Pain Physician 2014; 17:E475-E487**

The recent publication of Friedly et al's randomized trial of epidural glucocorticoid injections for spinal stenosis in the New England Journal of Medicine (1) accompanied by an editorial by Andersson (2) provided sensationalism for the media and confusion for the spine community. (3-8). The payers will no doubt be emboldened to justify denials potentially resulting in increased surgical interventions and other alternative treatments such as physical and exercise therapy. Interventional pain physicians and the spinal stenosis patients they care for with epidural injections have reason for concern. Of interest, IPM providers are often involved, specifically after the failure of an exercise program, physical therapy, drug therapy, surgery, and for those who are not candidates for surgery. An inordinate importance is provided to this manuscript as it was published in the New England Journal of Medicine.

In fact, randomized trials, the hallmark of evidence-based medicine (EBM) have been considered as the savior (9-11) for anecdotal medicine. EBM conveys the idea that up-to-date evidence can be applied consistently in clinical practice, in combination with the clinicians' individual expertise and the patients' own preferences and expectations to achieve the best possible outcomes. EBM has become widely disseminated among medical practitioners since the 1990s, which by some is regarded as a major advance in medico-scientific care (12,13). However, EBM has entered maturity, with numerous changes in the health care environment resulting in dramatic changes to coverage policies. Not only have the benefits of EBM not materialized for spinal pain, the debate continues on multiple fronts with guidance on hypertension, cholesterol management, and diabetes to mention a few (14-54). Despite a multitude of guidelines and controversies a large proportion of Americans face inadequate control of their conditions, whereas some face too much control of their health (55-60).

Proponents of randomized controlled trials often refuse to acknowledge other sources of valid data about outcome interventions (61). Further, some may even refuse to acknowledge high-quality randomized trials already published if they do not agree with their opinions or zeitgeist (1,2,62-66).

Case in point – a randomized trial of epidural glucocorticoid injections for spinal stenosis and accompanying editorial concluding that epidural injections of glucocorticoids plus lidocaine offered minimal or no short-term benefit as compared with epidural injection of lidocaine alone, with the editorial emphasizing lack of benefit of these procedures and directly proceeding to surgical interventions. The media statements by the authors also emphasized exercise or surgery might be better options for narrowing of the spinal canal based on this research (3).

The New England Journal of Medicine rejects an overwhelming proportion of manuscripts and correspondence. It purports to exclusively publish high-quality research to advance the science. Bearing that in mind, the authors believe that there are severe limitations to this study and manuscript. The influence of previous publications on facet joint intraarticular injections (67), and blind interlaminar epidurals (68) has focused attention on fluoroscopically performed interventional procedures. One could argue that the resultant substitution of intraarticular injections by facet joint nerve blocks and radiofrequency neurotomy with double digit annual increases of utilization (69-71). Further, despite enormous opposition to Zohydro approval, a manuscript in the New England Journal of Medicine supported Zohydro approval and even suggested using it to assist to tackle the opioid overdose epidemic (72-74). In fact, Zohydro approval was based on an the data from Institute of Medicine (IOM) (75) report which was derived from Gaskin and Richard/John's Hopkins Researchers (76). It has recently been reported that there were significant conflicts of interest (77) associated with this IOM report. We, the authors of this manuscript have published our analysis of severe pain

existing in 22.6 million persons and moderate pain in 22.3 million persons costing approximately $100 billion a year in the U.S. This analysis is in concordance with other reports (78,79). This contrasts with the IOM report of 100 million people suffering with costs $650 billion per year (75,76).

The study essentially shows that even when published in the New England Journal of Medicine, such trials may prove to be inadequately planned, conducted and interpreted. This further increases the controversy surrounding pain management.

This present paper considers the tensions that arise because of the different perceptions gleaned from the NEJM study regarding the value, quality, and interpretation of clinical and research evidence. This has implications for pain medicine in particular and the applicability of EBM in general.

## Analysis of the Randomized Trial

The issues related to this randomized trial of epidural glucocorticoid injections for spinal stenosis are design, inclusion criteria, interventions, outcomes assessment, analysis of the data, interpretation of results, and final conclusions.

### Design

The study protocol was published in 2012 (62) entitled "Lumbar Epidural Steroid Injections (ESI) for Spinal Stenosis (LESS): A Double-Blind Randomized Controlled Trial of Epidural Steroid Injections for Lumbar Spinal Stenosis Among Older Adults." In contrast to the protocol (62), the manuscript (1) included 30 authors with a total of 20 investigators. The protocol explained that there was only one RCT of fluoroscopically guided ESI compared to injections with local anesthetic alone (80). We are very familiar with this study as it was performed by the lead author. This was a preliminary report published in 2008. They also added that this study (80) while showing improvement in each group, found no advantage of the steroid injection or an injection of local anesthetic alone which we acknowledge is an accurate interpretation of the data. However, they mischaracterized the study by describing significant methodological limitations including lack of statistical power, no primary outcome measure, unblinding of patients and researchers, and a high dropout rate (21 of 60 patients). In our opinion, these comments indicate the authors' misinterpretation of the data. The authors failed to correct this misinterpretation of the data despite a letter to the editor published in 2012 (63). Manchikanti et al (63) in their letter described that the authors have demonstrated a seemingly superficial approach with what is potentially a misinterpretation of the previously available research. In reference to the previous available research, the authors have quoted a preliminary article by Manchikanti et al (80) published in 2008; however, they have ignored multiple other publications in reference to one year follow-up and the complete manuscript of the 2008 publication (81), as well as lumbar interlaminar epidural injections for spinal stenosis by the same authors (82) and multiple other manuscripts (83-86). The letter also showed Friedly's assumptions were inaccurate as the included assessment (62) and the one which was not considered (82) have explicitly included the primary outcome measure, statistical power was calculated for the full report rather than the preliminary report, inaccurate reporting of high dropout rate of 21 of 60 patients, which showed number of patients considered for inclusion. Finally there was no unblinding of the patients or the providers. Even then, Friedly et al failed to respond to the letter or to provide corrections which we consider surprising and unjust. The misinterpretation of the data also was exemplified by a systematic review which was published in 2012 by Bresnahan et al with Friedly as the senior author (64). Several of the authors of this manuscript commented on (65) the seemingly inappropriate search criteria. They failed to include all the manuscripts, which they have previously been made aware of missed 3 systematic reviews (83-85), and multiple randomized, double-blind controlled trials. Finally, in the face of those omissions, the authors included low quality trials (86-92). However, in their reply (93), they stated that their manuscript did not indicate that there were no effectiveness data for ESIs and spinal stenosis or that ESIs are not cost-effective in spinal stenosis population. They also denied that they made any specific claims to cost-effectiveness of ESI and they found no published evidence in which the authors assessed the incremental cost-effectiveness of ESIs for patients with lumbar spinal stenosis. They also justified their search methodology even though they missed multiple manuscripts along with methodologic quality assessment which we believe was inadequate.

Regrettably, the manuscript published in 2014 (1) repeats the same errors with a statement stating that uncontrolled studies suggest that epidural injections provide short-term pain relief for at least some patients with spinal stenosis. They opine that effectiveness and safety data are lacking from rigorous randomized controlled, quoting only multiple observational studies, and

also lumping the preliminary randomized controlled trial by Manchikanti et al (80) into an observational study based on a systematic review published in 2012 which failed to include high-quality randomized controlled trials (94). In fact, 2 randomized controlled trials that were not included (95,96) studied 100 patients with a caudal approach (95) and 120 patients with an interlaminar approach (96). They showed the efficacy of caudal and lumbar interlaminar injections with local anesthetic alone or with local anesthetic with steroids with no significant difference between both groups.

One of the major flaws of the design appears to be the duration of the follow-up and interventions provided. Any trial of interventional techniques of less than 6 months is considered as non-applicable for chronic, persistent pain in the clinical setting. Pain of long duration cannot be measured with improvement in 3 months. In fact, multiple systematic reviews and guidelines do not provide much weight for studies of interventional techniques of less than 6 months (96-101). Even very high quality studies have been excluded from the analysis based on the duration of follow-up in interventional pain management. In fact, in interventional pain management, specific instrument assessing methodologic quality of randomized trials provides very little value for short-term follow-up trials (97). Even opioid drug trials have been criticized for short-term follow-up, the majority of which have been limited to 3 months without long-term follow up (101-104).

The basis for including only interlaminar and transforaminal is not understood. The authors should have included caudal epidural injections too. In fact, caudal epidural steroids have been studied more frequently than transforaminal approaches in managing central spinal stenosis (96-103).

## Inclusion Criteria

The authors included patients with acute pain. Twelve to 20% of the patients had pain levels for less than 3 months, whereas approximately 30% of the patients had pain from 3 to 12 months, indicating that inappropriate inclusion criteria may be present in over 40 to 50% of the patients.

It is essential to recognize the fact that majority of the patients included are on Medicare. CMS has specific regulations along with many other insurers regarding eligibility requirement of epidural injections and spinal stenosis of only after 3 months and after failure of conservative management (104). Thus, the inclusion criteria are not practical when one considers that a substantial segment of these procedures were performed in patients with duration of less than 6 months and without consideration of non-responsiveness to conservative management.

Other criteria include the failure to report the severity of stenosis and chronicity of the patients. These are crucial, important aspects in outcomes assessment of spinal stenosis. It has been demonstrated on multiple occasions that are influenced by severity of stenosis, chronicity, and multi- level involvement (94-98,105,106). It is a well-known fact that the majority of the patients treated with epidural injections are the ones which either do not meet the criteria for surgical interventions, or had surgical interventions performed already, but failed to respond, and those who have failed to respond to conservative management. The descriptions in the manuscript also do not allow one to assess whether these patients may have undergone conservative management prior to the enrollment.

## Interventions

Interventions included were lumbar interlaminar or lumbar transforaminal; either unilateral or bilateral. There is no literature supporting transforaminal epidural injections in central spinal stenosis (93,94,97). Bilateral transforaminal epidural injections are associated with high risk, specifically if they were performed above the L4 level (107). Further, the transforaminal technical approach has not been described, i.e., whether it is supraneural or infraneural, which may subject the patients to increased risk (107).

The volume of the injectate is the same in both groups. Volumes were highly variable ranging from 1 to 3 mL of 0.25% to 1% lidocaine followed by 1-3 mL of triamcinolone (60-120 mg), betamethasone (6-12 mg), dexamethasone (8-10 mg), or methylprednisolone (60-120 mg). The equivalency of these doses and required volume are not proven in this protocol. In addition, a low volume 1 mL of 0.25% lidocaine may not have any therapeutic effect and in fact has been considered as placebo by some reviewers (108,109). In practice, 2 mL volumes are utilized for transforaminal epidural injections per level; whereas, 6-10 mL are utilized for interlaminar epidural injections and over 10 mL are utilized for caudal epidural injections (95-97,110). By the same token, 6 mL of volume on the higher side is almost like performing interlaminar with transforaminal, which may be even increased to 12 or 24 mL if 2 bilateral levels are performed with an inordinately high dose of steroids, if in fact these doses are per level. We men-

tion this because the specifics of what percentage of patients were provided these various injections are not covered in the manuscript.

## Outcomes

The authors measured outcomes at 6 weeks with the Roland Morris Disability Questionnaire (RMDQ) score and average numeric pain score of the past week. The measurement with RMDQ is more appropriate for subacute patients, less so for chronic pain patients (111-116). In addition, the average of the previous week may not reflect the improvement 2 weeks prior to that as during the third week the injection effect will be wearing off, providing inappropriate data.

The authors have repeated the procedures in only a small proportion of patients. In general, the half life of the first epidural injection with or without steroids has been described to be on average of 3 weeks (80,81,95-97). Consequently, the majority of the patients who were assessed at 3 months fell into the period after exhaustion of the relief provided. Thus, outcomes may not correlate with the treatment provided. It is similar to an insulin injection and monitoring the blood sugar after several days or even weeks.

## Analysis of the Data

The authors utilized appropriate statistical analysis; however, the same concern applies in reference to the monitoring of the outcomes assessment at 3 and 6 weeks for the previous week which only reports that week rather than the average pain over a period of 3 weeks or even 6 weeks. Even though the protocol calls for assessing those with 30% and 50% improvement, the proportion of those patients is not indicated in the tables. On closer look at the RMDQ scores, it appears that with an interlaminar approach there was a highly significant difference at 3 weeks between the 2 groups of local anesthetic alone or local anesthetic with steroids with a *P* value of less than 0.001. Similarly for 6 week data, the differences were also significant with a P value of 0.04 with significance below 0.05. The pain rating scale for leg pain with an interlaminar approach showed highly significant improvement at 3 weeks even though at 6 weeks there was no significant improvement with a *P* value of 0.37. In contrast, a transforaminal approach failed to show these differences; however, the authors have reached the same conclusions stating that there was no significant difference. In fact, there was a significant difference between local anesthetic and local anesthetic with steroids at 3 weeks, with overall improvement at 3 weeks with RMDQ scores as well as the numeric rating scale for leg pain. It appears that transforaminal epidural injections provided overall negative results compared to an interlaminar approach. In addition, it appears that there was 30% improvement in the rating of leg pain at 6 weeks in 49.2% and 49.7%, whereas 50% improvement in the rating of leg pain at 6 weeks was shown in 38.3% of the patients in both groups. The authors have not shown the differences between the interlaminar and transforaminal groups in reference to the proportion of patients with greater than 30% and 50% improvement. It appears that separation of the data may show 30% improvement at 6 weeks with leg pain in over 60% of the patients and almost in 50% of the patients with 50% improvement at 6 weeks. The authors also have not shown separate data for the duration of chronicity of pain among interlaminar and transforaminal approaches.

The complications described are inordinately high with 3% of patients suffering with fever, infection, or both with 5% in patients receiving glucocorticoids/lidocaine. All other complications including leg swelling and cardiovascular problems seem to be high with serious adverse events leading to hospitalization, surgery or both with 9 patients in the study. The data in reference to the complications is also confusing with supplementary appendix and the table published in the text. A great proportion of patients, over 50% in the lidocaine group and 42% in steroid group, underwent bilateral injections and many of them also underwent multilevel injections. These may raise questions in reference to the selection criteria, as well as ignoring the risk of transforaminal injections, specifically when performed bilaterally at multiple levels.

## Conclusion

The authors had to correct their conclusion before the paper was published. Of note it was not corrected in the hard copy version, but was corrected in the electronic version of the manuscript (117). They concluded that in the treatment of lumbar spinal stenosis, epidural injections of glucocorticoids plus lidocaine offered minimal or no short-term benefit as compared with epidural injection of lidocaine alone. This appears to be an inaccurate conclusion based on the available data. Further, they also have not assessed the proportion of patients in each group. There appears to be significant improvement in each group compared to baseline to 3 and 6 weeks. The analysis of this data is not available

as it is not included in the manuscript. Consequently, based on the above the paper's conclusion is inaccurate and in our opinion misleading. Essentially the data of this trial provides the information that epidural injections with local anesthetic with or without steroids are effective at 3 weeks and potentially at 6 weeks – the duration of effect of the first epidural injection.

### Conflicts of Interest

While some believe that conflict of interest only exists among clinical practitioners, it is clear that they exist in all environments including the IOM and amongst investigators in government funded trials. Conflicts of interest from non-physicians involved in the trial occur at various levels (77,98,116,118,119). In fact, this study includes 7 non-physicians who are listed among the initial authorship and 3 physicians who did not participate in the actual performance of the trial though neither is necessarily inappropriate. Multiple authors had conflicts of interest. Even though, statements in favor of exercise and surgery have been made we point out that these have not been shown to be effective (119-130).

## Comments on the Editorial

Andersson (2) provided an accompanying editorial which essentially advises not to perform any epidural injections for spinal stenosis and sends the patients directly to surgery. The press has reported (3) either patients should go through exercises or surgical interventions. They stated that even though many injections are used for indications other than spinal stenosis, epidural injections have become almost an expected part of a comprehensive, non-operative treatment protocol in patients with this condition. Unfortunately, Andersson also missed the existing high-quality literature similar to the authors of the original manuscript. He refers to the recent Cochrane review of nonsurgical treatment for spinal stenosis with neurogenic claudication, concluding that supportive evidence for glucocorticoid injections was limited to "low-quality evidence" (131) with incomplete review of the available literature reaching inappropriate conclusions. Similarly, another reference Andersson used belonged to a surgical organization with guidance prepared by the North American Spine Society (NASS) in reference to a lumbar transforaminal epidural steroid injections review and recommendations statement which focuses mainly on disc herniation and serves as a warning in performing these injections (132). Further, the patients described in comprehensive approaches in the editorial (2) are not the typical patients presenting with spinal stenosis to interventional pain management. Patients presenting to interventional pain management settings generally have failed conservative management or even surgery, and have mild to moderate stenosis, and generally are not candidates for surgery. Thus, these results are not applicable to clinical settings (2). It is rather surprising that Andersson, while promoting surgical intervention, seems to have has not carefully reviewed the literature on spinal surgery and other modalities and also has not looked at this study carefully. Andersson has written in the past along with others, favorable manuscripts for surgery and intradiscal electrothermal therapy despite controversies (101,133-150). It is noteworthy that Andersson was a staunch supporter of intradiscal electrothermal therapy (IDET) which has essentially been eliminated from use in the United States (101,133-136). The author also quotes that many insurances require epidural injections as part of non-surgical treatment before surgery is approved which is not based on evidence. We consider it obvious that if a patient does not respond, there is no need to perform these procedures. Manchikanti et al (95,96) have shown that 26% of the patients in the caudal group and 26% of the patients in interlaminar group were non-responsive with the first 2 injections and did not receive any further injections. Majority of the patients in spinal stenosis management are on Medicare. Medicare has no such requirements as epidural injections prior to surgical interventions. In fact, Medicare considers it as fraud and abuse and not medically necessary if a patient does not respond with initial injections to provide any further repeat injections after the first 2.

## Discussion

The randomized trial and accompanying editorial published in the NEJM (1,2) appear inappropriately biased against the practice of pain management, and may impair patient access to epidural injections, which are actually supported by high quality studies in the current literature. The NEJM trial has significant design challenges and the data is improperly interpreted. The authors failed to consider high-quality publications available on the topic. Rather than clarifying issues regarding the effectiveness of epidural steroids for spinal pain, the NEJM articles add further controversy surrounding the therapeutic value of epidural injections for pain management, while suggesting alternate therapies of unproven benefit

These recommendations are in contrast to even

the evidence published for medical therapy. A recent manuscript of JAMA Clinical Evidence Synopsys by Moore et al (151) showed that with at least 8 weeks of treatment, gabapentin or pregablin alone compared with placebo are associated with a greater proportion of patients achieving 50% pain reduction: 9% to 17% among patients with painful diabetic neuropathy; 13% to 25% among patients with post herpetic neuralgia; and 7% to 11% for pregablin alone among patients with fibromyalgia. These response rates are less than placebo response of 30%. Further, the number needed to treat to achieve a pain reduction of 50% or greater was 6 for gabapentin and pregablin for patients with painful diabetic neuropathy; 8 for gabapentin and 4 for pregabalin among patients with post herpetic neuralgia; 6 for pregabalin among patients with central neuropathic pain and 10 for pregabalin among patients with fibromyalgia. In this well performed evidence synopsis as published in a high prestigious journal the authors reached conflicting conclusions that outcomes trial data may have been overstated, but they conclude that these results supported the recommendations of Neuropathic Pain Special Interest Group of the International Association for the Study of Pain (IASP) (152), and more importantly the National Institute for Health and Care Excellence (NICE) (153), recommending gabapentin and pregabalin as the first-line treatments for neuropathic pain, a "gold-standard or gold-plated" approval. Further, this review also showed that antidepressants and topical capsaicin have similar effect sizes compared with gabapentin and pregabalin (154,156). Above all a great proportion of studies where this evidence is derived from Cochrane reviews as well as others is based on industry sponsorship (157,158). Above all, the sales of gabapentin and pregabalin are exceeding $4 billion per year with these companies also paying substantial fines for illegal promotion of off-label drug uses. Multiple side effects and complications also have been described with these drugs including euphoria, dependency, and obesity with pathology induced in the brain (156,159-162). These drugs may be abused and also may cause multiple side effects including euphoria, obesity, memory loss and suicide.

Based on the available research it appears that while a drug which may have more side effects than epidural injections and are also more expensive is approved by prestigious agencies with less than 50% of success rate, yet, procedures like epidural injections are being criticized with an unattainable high standards being applied.

It is time to apply the same principles for surgery, interventional techniques and non-interventional techniques, and drug therapy irrespective of the sponsor of the trial and irrespective of the journal where it is published.

## Acknowledgments

The authors wish to thank Vidyasagar Pampati, MSc, for statistical assistance, and Tom Prigge, MA, for manuscript review, and Tonie M. Hatton and Diane E. Neihoff, transcriptionists, for their assistance in preparation of this manuscript.

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