

No difference in pain reduction after epidural steroid injections in diabetic versus nondiabetic patients: A retrospective cohort study

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Abstract

Background and Aims: Diabetes affects peripheral and central neurons causing paresthesia, allodynia, hyperalgesia, and spontaneous pain. However, the effect of diabetes on response to epidural steroid injection (ESI) remains unknown. We hypothesized that diabetic patients receiving ESI will have different pain scores compared to nondiabetic patients. We tested a secondary hypothesis that pain reduction differs at different levels of hemoglobin A1c (HbA1c) for patients with diabetes.

Material and Methods: Data from 284 consecutive patients given ESIs for radiculopathy were obtained via a manual review of electronic medical records. We initially compared diabetic and nondiabetic groups with respect to balance on baseline demographic and morphometric characteristics. Next, a linear regression model was developed to evaluate the association between existing diabetes and postinjection reduction in pain scores. And finally, we univariably characterized the association between HbA1c and pain reduction.

Results: After exclusion of nine patients, 275 patients were analysed, including 55 (20%) who were diabetic. Pain reduction after ESI was comparable in diabetic and nondiabetic patients (Wald test $P = 0.61$). The degree of pain reduction generally decreased with the level of HbA1c until reaching HbA1c levels of approximately 7.5%, after which point it stayed fairly constant.

Conclusion: There was no difference in pain reduction after ESIs comparing diabetic with nondiabetic patients; however, for diabetic patients, pain reduction may decrease with uncontrolled diabetes determined by high HbA1c values, thus suggesting pain physicians to take an active role in guiding their patients to have their blood glucose levels better regulated to improve outcomes of their ESIs.

Key words: Diabetes mellitus, epidural, injections, pain

Introduction

The fifth most common cause of patients seeking medical attention is low back pain.^[1] Patients with confirmed radiculopathy secondary to disc herniation or osteophytic

spondylosis are initially offered conservative treatment regimens consisting of: physical therapy, nonsteroidal anti-inflammatory drugs, and anti-convulsants effective in neuropathic pain. If conservative therapy fails, the patients are offered fluoroscopic guided epidural steroid injection (ESI), consisting of local anesthetic and long-acting steroid.

Diabetes mellitus is a life-long chronic disease, affecting 8% of the US population, with 1.9 million new cases diagnosed in 2010. Diabetic patients inevitably develop other comorbidities related to poor glycemic control. An important comorbidity is that diabetics develop central and peripheral neurodegeneration. Peripheral diabetic neuropathy (PDN) affects significant percent of diabetic patients.^[2,3] Patients with PDN encounter abnormal sensations like allodynia, hyperalgesia, paresthesia, and spontaneous pain.^[4] In previous studies incidence of pain in diabetic patients with PDN varied

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from 40 to 50%.^[5] PDN changes vibration and thermal perception and leads to sensory loss, due to degeneration of the peripheral nerves.^[6] There are few studies on co-occurrence of pain and diabetes. Little is known about the influence of pain, on diabetes and glycemic control.^[7]

A growing proportion of the diabetic population suffers from chronic low back pain secondary to nerve radiculitis. However, it is not known if diabetes or poor glycemic control can affect pain-related outcomes after ESI. Neuropathic pain in diabetics has primarily been attributed to widespread peripheral mechanisms and recently by central mechanisms as well.^[6] Various cellular and molecular changes associated with prolonged hyperglycemia in diabetics producing pain may also affect negatively the clinical responsiveness to the anti-inflammatory processes attributed to ESI. However, there are no studies evaluating the effect of diabetes on response to ESIs.

Thus, we tested the primary hypothesis that diabetic patients receiving ESI will have different pain scores (measured by Verbal Rating Scale [VRS]) compared to nondiabetic patients. Secondly, we tested the hypothesis that patients with uncontrolled diabetes (determined by level of hemoglobin A1c [HbA1c]) have higher pain scores after ESI.

Material and Methods

After institutional review board approval, data from 284 consecutive patients receiving ESIs (3 ml of lidocaine 0.5% and 40 mg of triamcinolone) for radiculopathy at our institution between January and October 2010 were obtained via a manual review of the electronic medical records from our institution's Optimizing Health Care Decisions Registry (a clinical data registry developed from electronic health records). Excluded were non-English speaking patients, patients with recent (3 months) non-epidural intervention or regional block, and new trauma/inciting event. We further omitted patients with missing pre- or post-ESI pain scores (within 3 months of the intervention). We included patients into the diabetic group if he or she received oral or insulin therapy or had an HbA1c measurement over 6.5%.

To account for potential confounding due to systematic differences between study groups, we initially compared diabetic and nondiabetic groups with respect to balance on baseline demographic and morphometric characteristics. Balance was assessed using standard univariable summary statistics, as well as standardized difference scores. The standardized difference score is an index that measures the magnitude of difference between groups on baseline variables;

it is calculated as the difference in means, mean rankings, or proportions divided by a common measure of standard deviation across the two groups.

Next, a linear regression model was developed to evaluate the association between existing diabetes and postinjection reduction in pain scores. Any imbalanced baseline demographic and morphometric variables (specifically, those exhibiting a standardized difference score of 0.15^[8] or greater in absolute value) were considered for entry into the model; these variables were retained in the model according to a backward variable selection algorithm (with a selection criteria set conservatively at $P < 0.30$). In addition to these variables, we adjusted for baseline pain score, total epidural steroid dose, the time interval between ESI and documented postprocedure pain score, and the number of ESI's received within 3 months after the intervention.

As for the secondary hypothesis, we first removed data on 18 patients (33% of total analyzed sample) due to missing values of HbA1c. Since the lack of available HbA1c values might not occur at random, and since the limited number of diabetic patients with available HbA1c values made it difficult to adjust for all potential confounders, we therefore restricted analysis of the association between HbA1c and pain reduction to univariable methods. This was done graphically with a scatterplot containing an overlaid loess regression curve (locally weighted regression curve)^[9] and numerically by estimating a linear regression coefficient.

We collected data on consecutive ESI patients, beginning January 1, 2010, until we obtained a predetermined number of diabetic patients that would provide enough power to determine a clinically significant difference in pain reduction between diabetic and nondiabetic groups if it exists. Along these lines, we estimated that data on at least 50 diabetics would be sufficient to provide >90% power at the 0.05 significance level to detect a difference in pain reduction of one point on the VRS or greater (assuming a two-point within-group standard deviation of difference in pain scores.^[10] With an anticipated diabetes incidence of roughly 20%, we estimated prior to data collection that a total of 250 patients would be required to obtain full data on 50 diabetics.

The Wald test for regression model coefficients was employed to test for significance for regression coefficients with a Type I error rate set at 5%. R statistical software version 2.15.2 for 64-bit Unix operating system (The R Foundation for Statistical Computing, Vienna, Austria) was used for all analyses.

Results

We obtained data from 284 patients; after applying exclusion criteria, 275 patients remained in the study including 55 (20%) diabetic patients. ESIs were done by pain physicians having more than 10 years of experience in the field.

Comparisons between diabetic and nondiabetic patients on baseline and intraoperative characteristics are shown in Table 1. Sampled diabetic patients were older, had higher body mass index and slightly higher baseline pain score, were more likely to have documented psychiatric disease and less likely to have chronic pain complications. Diabetic patients also were different from nondiabetic patients in terms of ESI's type and level. We therefore considered all these factors for statistical adjustment for our primary analysis.

As for the primary analysis, backward variable selection led to a final multivariable model with the following variables: baseline pain score, total dose of ESI, time interval between ESI and postprocedure pain score measurement and number of ESI's received within 3 months of the intervention. Adjusting for these variables, we did not find that the pain reduction was significantly different for diabetic and nondiabetic patients (Wald test $P = 0.61$). Adjusted mean (95% confidence interval) pain reduction was 1.2 (0.5, 1.9) and 1.0 (0.7, 1.3) units in VRS scale for the diabetic and nondiabetic groups, respectively, and the corresponding difference in mean (95% confidence interval) pain reduction was estimated at 0.2 (-0.6, 0.9).

As for the secondary hypothesis, estimated pain score reduction as a function of HbA1c level is shown in Figure 1. Based on the loess curve in the figure, the degree of pain reduction (change in VRS pain score after ESIs) generally

decreased with the level of HbA1c until reaching HbA1c levels of approximately 7.5%, after which point it stayed fairly constant and appeared to be mostly negative (pain score even increased after ESIs). The regression coefficient (95% confidence interval), corresponding to the overall linear trend, suggested that with each additional 1% of HbA1c, the mean pain reduction decreased by 1.1 (0.5, 1.7) units. The regression coefficient was adjusted for baseline pain score. Patients were followed for 1 year. None of the patients included in the study required surgery during this time period. The patients' diabetic medications were organized by their primary care physician throughout the period.

Discussion

Our study did not find a difference in response to ESI between diabetic or nondiabetic patients. However, uncontrolled

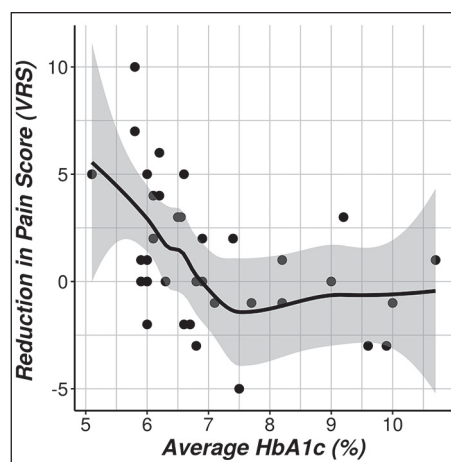


Figure 1: Loess curve describing locally weighted mean pain score reduction (change in VRS pain score after epidural steroid injections) as a function of HbA1c level with approximately 95% confidence interval. VRS = Verbal Rating Scale

Table 1: Summary of demographic and baseline patient characteristics for the groups

Factor	Nondiabetic* (n = 220)	Diabetic* (n = 55)	Standardized difference score
Female gender (vs. male)	135 (61)	33 (60)	-0.03
Age (years)†	56±17	66±11	0.66
BMI (kg/m ²)†	28 (25, 33)	30 (26, 34)	0.29
Smoking status (yes)	50 (23)	13 (24)	0.02
Opioid pain medication (yes)	159 (72)	41 (75)	0.05
Nonopioid pain medication (yes)	196 (89)	48 (87)	-0.06
Chronic pain complications (yes)†	129 (59)	27 (49)	-0.19
Documented psychiatric disease (yes)†	55 (25)	18 (33)	0.17
Baseline pain score (VRS scale)†	6.6±2.0	7.0±2.0	0.20
ESI type/level†			
Interlaminar lumbar	75 (34)	24 (44)	0.31
Interlaminar cervical	59 (27)	9 (16)	
Caudal	54 (25)	16 (29)	
Others	32 (15)	6 (11)	

*Summary is given as "mean±SD," "median (1st quartile, 3rd quartile)," or "n (%)," as appropriate. †These factors were used for adjustment in the primary analysis. ESI = Epidural steroid injection, VRS = Verbal rating scale, BMI = Body mass index, SD=Standard deviation

diabetes determined by high HbA1c values showed some evidence for the association with a decrease in pain after ESI. This result suggests that the effect of diabetes and the related effect on neurons does not significantly alter the beneficial treatment effect of ESI unless the diabetes is uncontrolled. Another way to interpret these results will be to say that if diabetes is well controlled then the response to ESI would be more prominent, thus suggesting pain physicians to take an active role in guiding their patients to have their blood glucose levels better regulated to improve outcomes of their ESI's.

In animal models of diabetes, peripheral glucose concentration in nerves is increased, and related oxidative stress in the neurons is accepted as the mechanism responsible for peripheral neuropathy. Effect of local anesthetics and steroids in diabetic patients are missing in the literature especially when neuraxial blocks are considered. In diabetic animal models for peripheral nerve blocks, Kroin *et al.* demonstrated that local anesthetic nerve block duration was prolonged in the chronic hyperglycemic state.^[5] Human studies in ESIs and effect on diabetic patients are also lacking; however, peripheral nerve blocks in diabetic patients have been previously investigated.^[11,12] Sertoz *et al.*^[11] have demonstrated that peripheral nerve block performance and sensory block regression times were longer in diabetic patients with poor glycemic control and concluded that this should be taken into consideration when peripheral nerve blocks are performed. Gebhard *et al.*^[12] also reported "higher block success" in diabetics receiving the same local anesthetic as nondiabetic patients for supraclavicular blocks. This result in a way supports and contradicts our findings; contradicts because we were unable show any difference in pain decrease between diabetic and nondiabetic patients, although this may be related to our indication and type of block, which were completely different. However, it supports our results because decreased pain relief in uncontrolled diabetic patients with ESI suggests diabetic neuropathy, which is more often seen in uncontrolled diabetes suggesting modification to the response to steroid injections. Animal studies support this where sustained glycemic control causes return of nerve block duration to the nondiabetic baseline after the use of local anesthetics, suggesting adequate glucose control can change the response to certain perineural medications.

Furthermore, there are worries regarding perineural injection of local anesthetics or adjuvants in diabetic patients influencing neurotoxicity; however, steroids in multiple studies have been shown to be a viable and safe agent. Similarities in pain scores on long term follow up in diabetic and nondiabetic patients does support this although we do not have long-term outcomes of these patients. Another

important factor is the effect of steroid injections and outcomes, the studies in the literature are controversial. A recent study^[13] in spinal stenosis patients demonstrated no benefit. However, steroid injections are accepted as part of multimodal analgesia regimen in treating low back pain. Concordant provocation is accepted as a positive prognostic sign.^[14] This has not been evaluated in our study as data are absent.

There are multiple limitations of the current study. One limitation of the study is its small sample size that leads to a potential lack of power to detect a clinically relevant effect of HbA1c level on pain reduction for the secondary hypothesis. Another is the fact that we had a high proportion of missing values of HbA1c; this might cause a potential selection bias. Further, the small number of patients specifically for the HbA1c analysis made it impossible for us to adjust for potential confounders. Another important limitation is that we don't have information regarding the duration of diabetes and control. Finally, like all retrospective studies, our study is subject to potential biases attributable to the influences of external variables not measured.

Conclusion

We did not find a significant difference in pain reduction after ESIs between diabetic and nondiabetic patients. Pain reduction may generally decrease with increase of the HbA1c level and becomes stable and negative for patients with high HbA1c values. However, further investigation is necessary in order to confirm the last claim.

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