Lumbar Transforaminal Epidural Dexamethasone

A Prospective, Randomized, Double-Blind, Dose-Response Trial

Farshad M. Ahadian, MD,† Kai McGreevy, MD,‡ and Gerhard Schulteis, PhD*§*

Background and Objectives: Serious adverse events related to particulate steroids have curtailed the use of transforaminal epidural steroid injections for radicular pain. Dexamethasone has been proposed as an alternative. We investigated the efficacy, dose-response profile, and safety of 3 doses of epidural dexamethasone.

Methods: A prospective, randomized, double-blind, dose-ranging design was used. A total of 98 subjects were randomized to transforaminal epidural dexamethasone 4 mg (n = 33), 8 mg (n = 33), or 12 mg (n = 32). The primary outcome measure for this study was reduction in radicular pain according to the visual analog scale from baseline, with 30% reduction or higher considered clinically meaningful. Secondary measures included the Oswestry Low Back Disability Scale, Subject Global Impression of Change, Subject Global Satisfaction Scale, and adverse events. Outcomes were assessed at 1, 4, 8, and 12 weeks after injection. Outcome measures, sample size, and statistical analysis were defined before enrollment.

Results: Mean radicular pain according to the visual analog scale compared with baseline was reduced 41.7%, 33.5%, and 26.6% at 4, 8, and 12 weeks, respectively, after injection. Oswestry disability ratings declined from "moderate" at baseline to "minimal" at 4, 8, and 12 weeks after injection. There was no statistical difference between groups for either measure (all P values < 0.05, Bonferroni-corrected). Parallel effects were observed in "impression of change" and "satisfaction" measures. No serious adverse events were noted.

Conclusions: Transforaminal epidural dexamethasone provides statistically significant and clinically meaningful improvement in radicular pain at 12 weeks after injection, with parallel improvements in disability, impression of change, and satisfaction measures. There was no difference in efficacy for dexamethasone 4 mg compared with 8 or 12 mg. The optimal dose of epidural dexamethasone may be lower than 4 mg, further increasing the long-term safety and tolerability of this treatment. Current data are reassuring with regard to the safety of dexamethasone for transforaminal epidural steroid injection.

(*Reg Anesth Pain Med* 2011;36: 572–578)

From the *Department of Anesthesiology, University of California, San Diego, La Jolla; †Anesthesia Service, VA San Diego Healthcare System, San Diego; ‡Department of Neurology, University of California, San Diego, La Jolla; and §Research Service, VA San Diego Healthcare System, San Diego, CA.

Accepted for publication August 12, 2011.

Address correspondence to: Farshad M. Ahadian, MD, Department of Anesthesiology, University of California, San Diego, 9300 Campus Point Dr, MC 7651, La Jolla, CA 92037 (e-mail: fahadian@ucsd.edu).

The authors do not have any financial or other relationships that may lead to conflicts of interest. Dr Schulteis was supported by a Research Career Scientist Award from the Department of Veterans Affairs, Office of Research and Development, Biomedical Laboratory Research & Development Program. Dr Ahadian is a consultant for Boston Scientific Corporation and on the speaker's bureau for NeurogesX Corporation.

This is an investigator-originated, unfunded project.

This information was presented, in part, as an abstract at the 2010 Annual ASRA Pain Meeting and was selected as a "Best of Abstracts."

Study registration: ClinicalTrials.gov, NCT01303354.

ISSN: 1098-7339

DOI: 10.1097/AAP.0b013e318232e843

Transforaminal epidural steroid injection (TFESI) has gained popularity since its superiority over placebo was demonstrated in a randomized prospective trial.[1] However, since 2002, 18 reports of serious adverse events (SAEs) after TFESI have been published.[2–13] The serious nature of these SAEs has curtailed the use of TFESI in clinical practice. Seventeen of the reported cases involved injection of corticosteroids resulting in persistent neurologic deficits from spinal cord and brain infarctions or death, and 1 case involved transient neurologic deficit after administration of local anesthetic only. An anonymous survey of pain physicians in 2007 indicates that the incidence of SAEs may be higher than the published literature may suggest.[14]

The evidence regarding the mechanism of these injuries is limited. Dawley et al[15] injected methylprednisolone, dexamethasone (DXM), and saline into the rodent carotid arterial system. Cerebral hemorrhage occurred with high frequency in subjects receiving methylprednisolone. However, no lesions were observed in the DXM or saline groups ($P < 0.01$). In the case reports thus far published, 10 subjects received methylprednisolone, 5 received triamcinolone, and 2 received betamethasone. One subject received local anesthetic only with subsequent resolution of neurologic deficits. To date, no SAEs related to TFESI with DXM have been reported. The evidence for efficacy of DXM for TFESI to date has been limited by 2 key methodological factors, including inadequate power and short follow-up.[16–18]

We present a prospective, randomized, double-blind, dose-response trial to assess the efficacy, dose-response profile, and safety for TFESI using DXM with a 12-week follow-up. We hypothesized that (*a*) DXM provides statistically significant improvement in radicular pain in patients undergoing lumbar TFESI, and (*b*) DXM produces statistically significant dose-dependent relationship with respect to efficacy. The primary outcome measure for this study was reduction in radicular pain according to the visual analog scale (VAS) compared with baseline, with 30% reduction or higher considered clinically meaningful. Additional measures included the Oswestry Low Back Disability Scale (ODI), Subject Global Impression of Change (SGIC), Subject Global Satisfaction Scale (SGSS), and adverse events. Outcome measures, sample size, and statistical analysis were defined before enrollment.

METHODS

Study Design

This study was approved by the institutional review board of the University of California, San Diego (UCSD), and the VA San Diego Healthcare System, the 2 study sites. Written informed consent was obtained before enrollment. Methodology was selected in concordance with IMMPACT recommendations.[19,20]

To date, none of the steroids used for ESI have US Food and Drug Administration approval for this indication, and all are used in a wide range of doses. Dexamethasone has been suggested as the agent of choice for TFESI owing to safety concerns

pending more definitive investigation of its efficacy, dose-response profile, and neurotoxicity.[18,21] We used a prospective, randomized, double-blind design to assess these parameters for 3 doses of DXM administered via a single-level, unilateral, fluoroscopic-guided TFESI. Subjects were recruited from the existing pool of patients at each study site. We selected subjects with persistent distal radicular pain 6 months or longer in duration, who had previously benefited from TFESI using betamethasone 6 to 12 mg with subsequent recurrence of pain, with a VAS score of 50 or higher of 100. This enriched recruitment design was selected to preclude the possibility that changes in outcome measures will be due to the natural evolution of the disease. Subjects were randomized into 3 groups: DXM 4 mg, DXM 8 mg, or DXM 12 mg. Outcomes were assessed at 4, 8, and 12 weeks after injection. Procedure-related adverse events were assessed on the day of injection and 1-week after injection.

Eligibility Criteria

Inclusion criteria were as follows: 18 years or older, unilateral lumbar radicular pain, baseline VAS score for distal lower extremity radicular pain of 50 or higher of 100, and previous favorable response to TFESI. Exclusion criteria were as follows: pregnancy, infection, coagulopathy, uncontrolled diabetes mellitus or hypertension, allergy to iodinated contrast medium, and interventional therapies for pain within 90 days before study enrollment.

Intervention

Transforaminal epidural steroid injection was performed at a unilateral, single level. No sedation was administered. The procedure was performed using an aseptic technique, in the prone position, under fluoroscopic guidance (GE-OEC 9800, GE Healthcare, Waukesha, Wisc), using a dorsal oblique approach. Lidocaine 1% was administered to the skin and soft tissues. A 23-gauge Quincke tip spinal needle (Kimberly-Clark Health Care, Roswell, Ga) was used for the study injection. Iohexol (Omnipaque 240; GE Healthcare, Mississauga, Ontario, Canada) was administered under live fluoroscopy in both anteroposterior and lateral projections. Once epidural spread of contrast was confirmed, 1-, 2-, or 3-mL aliquot of DXM (4 mg/mL) (American Regent, Shirley, NY) was administered according to the randomization assignment.

Outcome Measures

The primary outcome measure for this study was reduction in VAS score for radicular pain from baseline, with 30% reduction or higher considered clinically meaningful.[22,23] Additional measures included the ODI, SGIC, SGSS, and adverse events.[19,20]

Complications

The following procedure-related adverse events were assessed on the day of procedure: positive needle aspiration, radiologic evidence for intravascular spread of contrast, needle repositioning, difficulty rating of procedure, procedure duration, fluoroscopy time, allergic reactions, neurovascular events, pain on injection, paresthesias during procedure, dural puncture, headache, and meningismus.

The following postprocedure adverse events were assessed 1 week after injection: headache, neck pain, arm pain, dysesthesias, worsening of back pain, worsening of leg pain, facial flushing, mania, insomnia, agitation, hypertension, and hyperglycemia. Subjects were asked to report any other adverse events.

Determination of Sample Size

Sample size was based on power analyses using effect sizes and variances estimated from previous work on the University of California, San Diego, and VA San Diego Pain Groups, assuming a standard minimal power of 0.8 and a fixed alpha level of $P < 0.05$ after Bonferroni correction for the number of planned individual means comparisons. The study has specifically been powered to detect a change of 30% or higher in VAS score from baseline. Final sample size selection ensured a power of at least 0.8 for both of our primary hypotheses: (*a*) that 1 dose or more of DXM would significantly decrease VAS scores for pain from before to after treatment and (*b*) that the improvement in VAS score for pain by DXM would be dose dependent (ie, greater change at higher doses of DXM).

Randomization

Subjects were sequentially randomized into 3 groups using a random number generator. Randomization assignments were viewed only by the interventionalist immediately before injection.

Blinding

Subjects were blinded to DXM dose. Data were collected by an investigator blinded to DXM dose. The unblinded interventionalists performing study injections were not involved in data collection.

Statistical Analysis

Before database lockup and unmasking of the randomization, a detailed analysis was performed. Data from all randomized subjects were included in the statistical evaluation. The evaluability criteria included (*a*) subjects who met inclusion/exclusion criteria and (*b*) subjects who had no protocol violations. Before the analysis of the primary outcome variables of interest, all key demographic and diagnostic factors summarized in Tables 1 and 2 (eg, age, sex, comorbid diagnoses, previous medications/interventions, procedural data) were subjected to analysis of variance (ANOVA) for continuous variables, such as age, or to χ^2 analysis of frequency for categorical variables (sex, spinal level of injection, etc). Significant differences across DXM dose groups for 1 or more of these variables resulted in their inclusion as a factor in the analysis of primary outcomes.

Analysis of VAS Scores for Pain and ODI

Initial analysis of pretreatment VAS scores for radicular pain at baseline and across DXM dose groups using a 1-factor ANOVA revealed no differences. Accordingly, VAS scores for radicular pain were analyzed with standard mixed-design ANOVA, with time (baseline versus 4, 8, and 12 weeks after reatment) as a repeated measure and dose of DXM (4, 8, and 12 mg) as the randomized factor. Sex was entered as an additional between-subjects factor because of a significant difference in representation of males and females across the randomized DXM dose conditions. Data of ODI were similarly analyzed with mixed-design ANOVA entering the time, DXM dose, and sex factors. Significant overall main effects or interactions for either VAS or ODI measures were probed further with follow-up analyses of simple main effects or interaction contrasts as appropriate. $P < 0.05$ was interpreted as statistically significant, with a Bonferroni correction applied to all individual means comparisons.

Analysis of Improvement and Satisfaction Scales (SGIC, SGSS)

Ordinal data from all Likert scale instruments were analyzed using rank-order statistics (Friedman ANOVA) to compare

TABLE 1. Baseline Demographics, Diagnostic Characteristics, Analgesic Use Profile and Pain-Related Comorbidities

	DXM 4 mg	DXM 8 mg	DXM 12 mg	*P*
Demographics				
No. subjects	33	33	32	
Age, median (range), y	60 (33–82)	57 (27–84)	58 (35–86)	NS
Male/female	29/4	23/10	17/15	<0.009
White, %	67	70	66	>0.19
African American, %	6	12	13	
Hispanic, %	12	15	16	
Asian, %	9	0	0	
Other, %	0	0	6	
Pain and disability ratings				
VAS score for radicular pain, mean, mm	68	71	73	NS
ODI score, mean	24	24	23	NS
Symptom duration				
>2 y	30	29	29	>0.20
1–2 y	3	4	1	
6–12 mo	0	0	2	
MRI findings				
Subjects with previous MRI	21	23	14	
L3-4 disk abnormality	3	2	1	>0.70
L4-5 disk abnormality	12	15	8	>0.70
L5-S1 disk abnormality	9	13	10	>0.70
Foraminal stenosis	17	17	10	>0.70
Central stenosis	13	13	9	>0.70
Spondylosis	14	11	13	>0.70
Spondylolisthesis	4	4	1	>0.70
Analgesic use profile				
Nonopioids	19	25	16	0.09
Short-acting opioids	19	25	19	>0.20
Long-acting opioids	6	4	6	>0.70
Antiepileptic drugs	13	16	15	>0.70
Antidepressants	12	17	10	>0.20
Antispasmotics	9	10	11	>0.70
Benzodiazepines	6	6	3	>0.70
Pain-related comorbidities				
Postlaminectomy syndrome	1	5	3	>0.20
Facet dysfunction	14	12	10	>0.60
Sacroiliac dysfunction	3	4	3	>0.60
Peripheral neuropathy	0	0	2	>0.60
Nerve entrapment syndrome	1	0	0	>0.60
Regional myofascial pain	0	0	2	>0.60
Fibromyalgia	0	1	0	>0.60

across time after treatment. Again, $P < 0.05$ was interpreted as statistically significant.

RESULTS

Demographics, Diagnostic, and Procedural Characteristics

Of 449 individuals screened for study participation, 351 subjects did not meet eligibility criteria because of poorly controlled diabetes or hypertension, allergy to contrast medium, inability to meet wash-out requirement because of multiple pain interventions, or baseline VAS level for radicular pain less than 50 of 100. Ninety-eight subjects (50 from the University of California, San Diego, and 48 from the VA San Diego Healthcare System) completed the study. Subjects were randomized into 3 groups: DXM 4 mg (n = 33), DXM 8 mg (n = 33), and DXM 12 mg (n = 32). Table 1 compares the baseline demographic and diagnostic characteristics, and Table 2 compares the procedural characteristics and adverse events for each treatment group. There were no statistical differences in baseline demographics, with the exception of sex. Significantly fewer females were randomized to the DXM 4-mg dose condition than to the 8- and 12-mg dose groups ($P < 0.01$); accordingly, sex was entered as a factor into the ANOVAs conducted on VAS and ODI. Diagnostic profiles, preoperative magnetic resonance imaging findings, electrophysiologic studies, comorbidities, and

TABLE 2. Procedure Characteristics and Adverse Events

	DXM 4 mg	DXM 8 mg	DXM 12 mg	*P*
Side and level injected				
Right/left	16/17	22/11	18/14	>0.30
L3-L4	1	1	1	>0.35
L4-5	15	9	16	
L5-S1	17	22	13	
S1	0	1	2	
Procedure and fluoroscopy duration				
Procedure time, mean, min	9	9	10	NS
Fluoroscopy time, mean, s	23	28	26	
Operator's rating of procedure difficulty				
Uncomplicated	28	26	26	NS
Moderately complicated	5	7	5	
Extremely complicated	0	0	1	
No. adverse events				
Aspiration positive for blood	1	0	1	NS
Vascular uptake noted on imaging	1	1	1	
Paresthesia during procedure	1	1	4	
Pain on injection	0	0	1	

intraoperative characteristics of the procedures were not significantly different across dose groups.

VAS Scores for Radicular Pain and ODI Scores

As shown in Figure 1A, there was no significant difference in baseline VAS scores across groups. Three-factor mixed-design ANOVA, including time before/after treatment, dose group, and sex, revealed a significant main effect of time ($P < 0.0001$) but no significant main effect of dose group or sex. None of the interactions among the 3 factors were significant (all P values > 0.125). This pattern of statistical outcome is consistent with a significant reduction of VAS from baseline in all dose groups, with no significant differences in VAS between groups at 4, 8, or 12 weeks after TFESI. Follow-up comparisons of the significant time-dependent change in data collapsed across dose groups revealed a significant reduction in VAS scores for radicular pain from baseline to 4 weeks after TFESI (41.7% reduction); this effect was significantly diminished at 12 weeks (26.6% reduction) but still remained significantly different from baseline (all P values < 0.05, Bonferroni-corrected).

As shown in Figure 1B, in data collapsed across dose groups, there was a significant 24% reduction in ODI at 4 weeks and 18% reduction at 12 weeks relative to baseline. The increase in ODI from 4 to 12 weeks was modest but statistically significant (all P values < 0.05, Bonferroni-corrected). These scores correspond to ODI ratings of moderate disability at baseline, minimal disability at 4 and 8 weeks, and minimal to moderate disability at 12 weeks.

Subject Global Impression of Change

Significant improvement (SGIC ≤ 3/7) after TFESI was reported in 77% of all subjects at 4 weeks, in 70% at 8 weeks, and in 61% at 12 weeks after injection. Friedman ANOVA indicated that this modest time-dependent shift toward lower

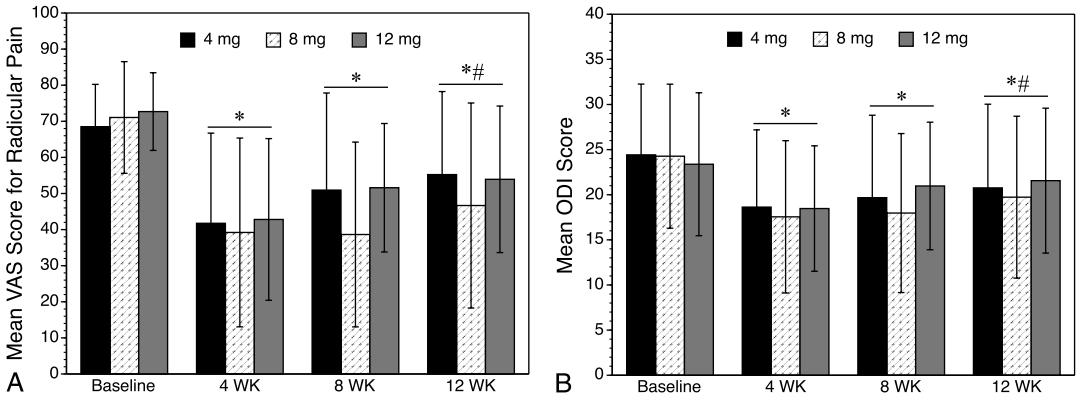

FIGURE 1. Improvement in radicular pain (VAS) and functional status (ODI) from baseline. There was no significant difference in baseline radicular pain VAS scores or ODI ratings across DXM groups. All dose groups experienced a significant improvement in VAS score for pain and ODI ratings from baseline to 4, 8, and 12 weeks after TFESI with no differences between groups (*$P < 0.05$ relative to baseline). There was a modest but statistically significant decrease in improvement from 4 to 12 weeks after TFESI (#$P < 0.05$ relative to the 4-week time point), indicating a gradual return to baseline.

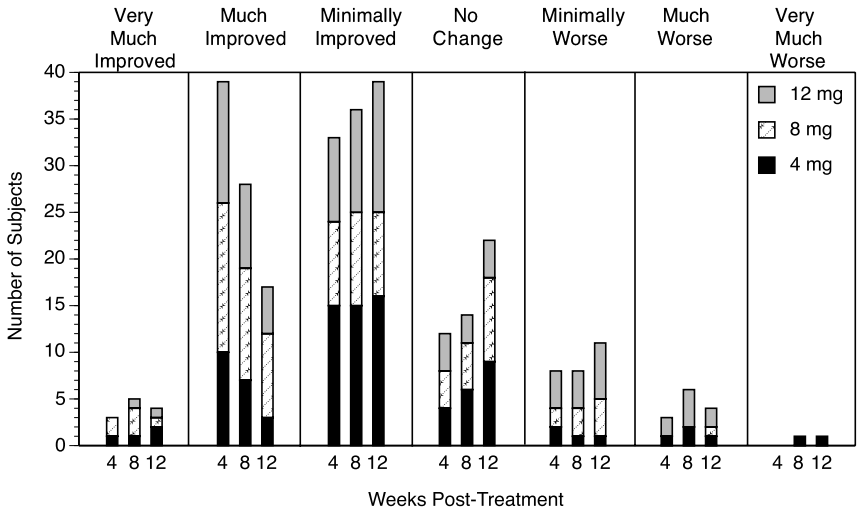

FIGURE 2. Subject global impression of change. Subjects reported a highly favorable clinical response to DXM with SGIC of 3 or lower of 7 in 77% of subjects at 4 weeks, 70% of subjects at 8 weeks and 61% of subjects at 12 weeks after TFESI. As expected, there was a modest but statistically significant shift toward lower ratings over time as responses shifted from ''much improved'' to ''minimally improved'' and ''no change.''

improvement ratings on the SGIC (collapsed across dose groups) was statistically significant ($P < 0.001$). The shift in SGIC across weeks resulted from a reduction in the rating of "much improved," and corresponding increases in rating of "minimally improved" or "no change" from 4 to 12 weeks, indicating a gradual return to baseline (Fig. 2).

Subject Global Satisfaction Scale

Most subjects expressed satisfaction (SGSS $\geq$ 2/5) with their treatment at all points of observation (87%, 85%, and 89% at 4, 8, and 12 weeks, respectively). Again, Friedman ANOVA indicated a modest but significant ($P < 0.0001$) time-dependent shift toward lower satisfaction ratings (collapsed across dose groups). This was accounted for by a reduction in subjects reporting "moderately satisfied" and a corresponding increase in subjects reporting "mildly" or "minimally satisfied" from 4 to 12 weeks. Importantly, only 2 subjects changed their rating from "mildly satisfied or better" to "not satisfied" (Fig. 3).

Adverse Events

No SAEs were noted throughout this study. Paresthesias occurred in 6 subjects (6%), all of which was resolved before discharge. There were no reports of dysesthesia after injection. One subject complained of significant pain on injection (1%), which was resolved without sequelae. Vascular cannulation was detected in 5 subjects (5%). Needle aspiration was positive for blood in 2 subjects. In another 3 subjects, intravascular spread of contrast was detected on radiographic examination despite negative aspiration. There were no adverse events noted at 1 week after study injection (Table 2).

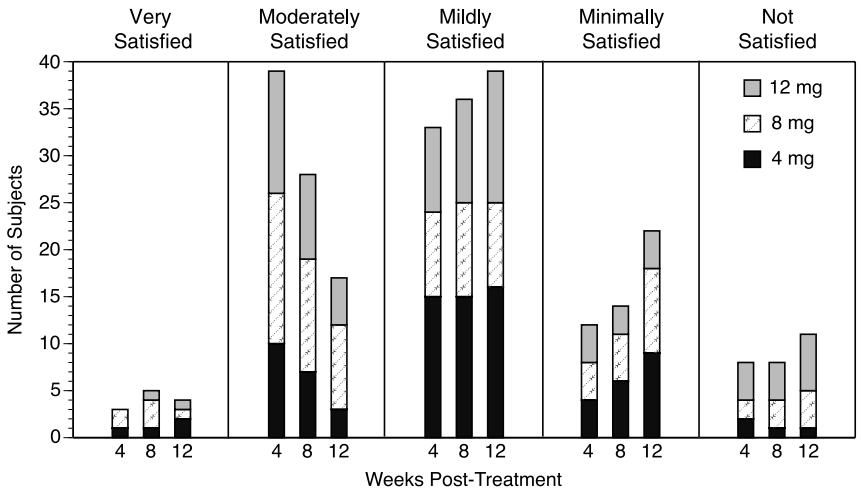

FIGURE 3. Subject Global Satisfaction Scale. Participants were highly satisfied with their response to DXM. Of all subjects, 87%, 85%, and 89% reported SGSS of 2 or higher of 5 at 4, 8, and 12 weeks after TFESI, respectively. As expected, there was a modest but statistically significant time-dependent shift from ''moderately satisfied'' to ''mildly'' or ''minimally satisfied'' responses. Notably, only 2 subjects changed their rating from ''mildly satisfied'' or better to ''not satisfied'' from 8 to 12 weeks after TFESI.

DISCUSSION

To our knowledge, this is the first adequately powered clinical trial to address the efficacy of epidural DXM. The results support our primary hypothesis that TFESI with DXM provides statistically significant improvement in moderate to severe radicular pain, as demonstrated in subjects refractory to conservative, multidisciplinary management, who had previously benefited from TFESI using betamethasone. Improvements in pain and disability peaked by 4 weeks and gradually approached baseline during 3 months. If the duration of effect for betamethasone is assumed to be similar to that of DXM, as confirmed by clinical observations, then the magnitude of the reported outcomes might be underestimated because the duration of effect seems to extend beyond the 90-day wash-out period for this study, leading to lower baseline values.

However, the results refute our secondary hypothesis that DXM produces a statistically significant dose-dependent relationship with respect to efficacy. We chose DXM 12 mg as the highest dose based on prior published data,[18] clinical practice, and dose-equivalency tables. We hypothesized that a 3-fold difference in dose range between groups would yield a clinically relevant dose-response profile. However, we did not find any difference in outcome measures between groups at any point of observation. Results indicate that doses greater than 4 mg do not provide additional benefit in magnitude or duration of response. The optimal dose of epidural DXM may be less than 4 mg. We administered DXM undiluted based on the notion that efficacy is a dose-related phenomenon rather than a volume-related one. The injection volumes consisted of 1, 2, or 3 mL for DXM 4-, 8-, or 12-mg groups, respectively. Further investigation to determine the optimal dose and volume of DXM for TFESI is indicated.

Our results confirm that, for most patients with persistent radicular pain on maintenance therapy with TFESI, a 10- to 14-week interval between treatments is optimal. This corresponds directly to our clinical observations with epidural betamethasone 6 to 12 mg. This, in combination with lower doses of DXM, will minimize risk of long-term adverse events related to corticosteroids.

No SAEs were observed in this study, and all other adverse events were self-limited. Our results are reassuring with regard to safety and tolerability of DXM. However, the incidence of neurovascular complications from TFESI is of low-enough magnitude that only long-term epidemiologic studies and clinical surveillance will provide ultimate proof of safety. We observed a 5% incidence of intravascular cannulation. Needle aspiration was positive for blood in 2 subjects. However, an additional 3 subjects experienced negative aspiration despite radiographic evidence for intravascular spread. This underscores the necessity of live image guidance when performing this procedure.

An important limitation of this study is the lack of placebo control, which was not feasible because of fiscal limitations. A commonly used alternative is an active control, such as a particulate steroid in current clinical use. Dreyfuss et al[18] used this approach in comparing cervical epidural DXM versus triamcinolone but noted that the sample size required to distinguish the efficacy of the 2 drugs would be prohibitive (n = 769). Our power analysis confirmed this fact. All available evidence on epidural DXM currently suffers the same limitation, making definitive conclusions impossible.[16,17] Furthermore, although the reported SAEs related to particulate steroids are rare, they are of such magnitude that they may not be acceptable even in small numbers, making particulate steroids a poor choice of an active control. The dose-response design chosen here was felt to be an ideal alternative providing clinically relevant data addressing the key questions at hand.

A second limitation in this study was that significantly fewer females were randomized to the DXM 4-mg dose condition than to the DXM 8-mg and DXM 12-mg groups. This was an unanticipated but isolated finding. There was no statistical difference between groups with regard to any other baseline measures. Therefore, sex was specifically entered as a factor into the ANOVAs conducted on VAS for pain and ODI and found to be of no consequence.

Finally, the interventionalist performing the study injection was not blinded to the dose of DXM. This introduces the possibility of an intervention bias. Such a bias would have skewed the results in favor of larger doses of DXM—with the expectation that larger doses would yield greater effect—a notion that was refuted by our results. Therefore, any such bias was either absent or inconsequential.

CONCLUSIONS

In subjects with persistent moderate to severe radicular pain, epidural DXM provides statistically significant and clinically meaningful relief of pain with a corresponding improvement in functional status. Peak improvement is reached by 4 weeks after injection. These values gradually approach baseline during a 12-week period, although they still remain statistically significant at 12 weeks compared with baseline. Regardless of magnitude or duration of relief, a high proportion of subjects report satisfaction from this therapy. Dexamethasone 4 mg seems to be as effective as higher doses, and the optimal dose may indeed be lower than 4 mg, leading to further long-term safety and tolerability of this treatment.

No SAEs were observed in this study. Other adverse events were self-limited. Our results are reassuring regarding safety of DXM for lumbar TFESI. However, because of the low incidence of SAEs, long-term surveillance will be necessary to confirm safety. Future investigations are warranted regarding the efficacy and safety of cervical TFESI with DXM and to determine the lowest effective dose of DXM and optimal volume of injection.

ACKNOWLEDGMENT

The authors are grateful to Paul Clopton, MS, for advice and commentary on statistical analysis.

REFERENCES

1. Vad VB, Bhat AL, Lutz GE, Cammisa F. Transforaminal epidural steroid injections in lumbosacral radiculopathy: a prospective randomized study. *Spine (Phila Pa 1976)*. 2002;27:11–16.
2. Houten JK, Errico TJ. Paraplegia after lumbosacral nerve root block: report of three cases. *Spine J*. 2002;2:70–75.
3. Rozin L, Rozin R, Koehler SA, et al. Death during transforaminal epidural steroid nerve root block (C7) due to perforation of the left vertebral artery. *Am J Forensic Med Pathol*. 2003;24:351–355.
4. Huntoon MA, Martin DP. Paralysis after transforaminal epidural injection and previous spinal surgery. *Reg Anesth Pain Med*. 2004;29:494–495.
5. Karasek M, Bogduk N. Temporary neurologic deficit after cervical transforaminal injection of local anesthetic. *Pain Med*. 2004;5:202–205.
6. Glaser SE, Falco F. Paraplegia following a thoracolumbar transforaminal epidural steroid injection. *Pain Physician*. 2005;8:309–314.
7. Ludwig MA, Burns SP. Spinal cord infarction following cervical transforaminal epidural injection: a case report. *Spine (Phila Pa 1976)*. 2005;30:E266–E268.
8. Beckman WA, Mendez RJ, Paine GF, Mazzilli MA. Cerebellar herniation after cervical transforaminal epidural injection. *Reg Anesth Pain Med*. 2006;31:282–285.

9. Muro K, O'Shaughnessy B, Ganju A. Infarction of the cervical spinal cord following multilevel transforaminal epidural steroid injection: case report and review of the literature. *J Spinal Cord Med*. 2007;30:385–388.
10. Ruppen W, Hugli R, Reuss S, Aeschbach A, Urwyler A. Neurological symptoms after cervical transforaminal injection with steroids in a patient with hypoplasia of the vertebral artery. *Acta Anaesthesiol Scand*. 2008;52:165–166.
11. Kennedy DJ, Dreyfuss P, Aprill CN, Bogduk N. Paraplegia following image-guided transforaminal lumbar spine epidural steroid injection: two case reports. *Pain Med*. 2009;10:1389–1394.
12. Lyders EM, Morris PP. A case of spinal cord infarction following lumbar transforaminal epidural steroid injection: MR imaging and angiographic findings. *AJNR Am J Neuroradiol*. 2009;30:1691–1693.
13. Wybier M, Gaudart S, Petrover D, Houdart E, Laredo JD. Paraplegia complicating selective steroid injections of the lumbar spine. Report of five cases and review of the literature. *Eur Radiol*. 2010;20:181–189.
14. Scanlon GC, Moeller-Bertram T, Romanowsky SM, Wallace MS. Cervical transforaminal epidural steroid injections: more dangerous than we think? *Spine (Phila Pa 1976)*. 2007;32:1249–1256.
15. Dawley JD, Moeller-Bertram T, Wallace MS, Patel PM. Intra-arterial injection in the rat brain: evaluation of steroids used for transforaminal epidurals. *Spine (Phila Pa 1976)*. 2009;34:1638–1643.
16. Park CH, Lee SH, Kim BI. Comparison of the effectiveness of lumbar transforaminal epidural injection with particulate and nonparticulate corticosteroids in lumbar radiating pain. *Pain Med*. 2010;11:1654–1658.
17. Lee JW, Park KW, Chung SK, et al. Cervical transforaminal epidural steroid injection for the management of cervical radiculopathy: a comparative study of particulate versus non-particulate steroids. *Skeletal Radiol*. 2009;38:1077–1082.
18. Dreyfuss P, Baker R, Bogduk N. Comparative effectiveness of cervical transforaminal injections with particulate and nonparticulate corticosteroid preparations for cervical radicular pain. *Pain Med*. 2006;7:237–242.
19. Dworkin RH, Turk DC, Farrar JT, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2005;113:9–19.
20. Dworkin RH, Turk DC, Peirce-Sandner S, et al. Research design considerations for confirmatory chronic pain clinical trials: IMMPACT recommendations. *Pain*. 2010;149:177–193.
21. Benzon HT, Chew TL, McCarthy RJ, Benzon HA, Walega DR. Comparison of the particle sizes of different steroids and the effect of dilution: a review of the relative neurotoxicities of the steroids. *Anesthesiology*. 2007;106:331–338.
22. Farrar JT, Young JP Jr, LaMoreaux L, Werth JL, Poole RM. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical pain rating scale. *Pain*. 2001;94:149–158.
23. Farrar JT, Polomano RC, Berlin JA, Strom BL. A comparison of change in the 0-10 numeric rating scale to a pain relief scale and global medication performance scale in a short-term clinical trial of breakthrough pain intensity. *Anesthesiology*. 2010;112: 1464–1472.