Randomized Trial

Effect of High-Volume Injectate in Lumbar Transforaminal Epidural Steroid Injections: A Randomized, Active Control Trial

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Disclaimer: There was no external funding in the preparation of this manuscript. Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received:07-24-2014
Revised manuscript received: 08-16-2014
Accepted for publication: 06-02-2015

Free full manuscript: www.painphysicianjournal.com

Background: There have been many studies proving the effectiveness of lumbar transforaminal epidural steroid injections (TFESIs) for the treatment of radicular pain. Dexamethasone has been suggested as an alternative to particulate steroids. However, no controlled trials have investigated the effect of different injected volumes for a same dose of dexamethasone.

Objective: To compare the effects of a high-volume injectate with those of a low-volume injectate using the same dose of dexamethasone for 2 groups in lumbar TFESI.

Study Design: A prospective, randomized, active control trial.

Setting: The outpatient clinic of a single academic medical center.

Methods: A total of 66 patients were randomized to receive lumbar transforaminal epidural dexamethasone injections with either a low-volume injectate (3mL, N = 30) or a high-volume injectate (8mL, N = 32). The primary outcome measures for this study were the incidence of the patients achieving meaningful pain relief and a reduction on the Visual Analogue Scale (VAS, range 0 – 100) at 4 weeks after the procedure. The definition of "meaningful pain relief" was ≥ 50% from baseline. The secondary outcomes included the Roland-Morris Disability Questionnaire (RMDQ, range 0 – 24) score and adverse effects. The outcomes were assessed 4 weeks after the procedure.

Results: Four weeks after the procedure, in the DL8 group, the incidence of achieving meaningful pain relief was higher compared with DL3 group (19, 59.4% vs. 9, 30%, $P = 0.024$). Both groups demonstrated a significant improvement in their VAS and RMDQ scores ($P < 0.05$). The VAS of the high-volume injectate group (DL8) was significantly lower than that of the low-volume injectate group (DL3) (33.3 ± 25 vs. 46.3 ± 25, $P = 0.036$). There was no significant difference in the RMDQ score between the 2 groups.

Limitations: We enrolled a small number of patients and did not assess the long-term outcomes.

Conclusions: Injectate at a volume of 8 mL was more effective than injectate at a volume of 3 mL for radicular pain in a lumbar transforaminal steroid injection, although both of the injectates contained the same dose of dexamethasone.

Key words: Dexamethasone, disc herniation, epidural injection, lumbar, radiculopathy

Pain Physician 2015; 18:519-525

A systematic review shows that there is strong evidence for transforaminal epidural steroid injections (TFESIs) in the treatment of lumbosacral radicular pain for both short-term and long-term relief (1,2). Several mechanisms have been suggested to explain the anti-inflammatory action of epidural corticosteroid on lumbosacral radiculopathy. It may inhibit the production of arachidonic acid and

the occurrence of ectopic discharge from unmyelinated C-fiber. It may also relieve central sensitization (3,4).

Several types of corticosteroids have been used for TFESIs, including triamcinolone, methylprednisolone, betamethasone, and dexamethasone. Dexamethasone is a non-particulate steroid and no serious adverse events (such as death or persistent neurologic deficit) have been reported in relation to transforaminal dexamethasone injections (5). Moreover, existing research has found no evidence for dexamethasone being less effective than particulate steroids in lumbar TFESIs performed for radicular pain with or without radiculopathy (6). However, evidence for the efficacy of dexamethasone for TFESIs remains limited to date.

The effect in TFESIs may be influenced not only by the dose and type of steroid, but also by the volume of the injected material. There was a positive correlation between the injection of larger volumes of fluid into the epidural space and greater relief of radicular leg pain and low back pain. In addition to the anti-inflammatory effect, the injected material produces a displacement of the dura forward and inward, and a stretch of the nerve roots. The effects lead to lysis of the neural adhesions (7). Nevertheless, there have been no controlled trials to evaluate the effect of the injected volume itself.

We conducted a randomized controlled trial to compare the effects of a high-volume injectate with those of a low-volume injectate using the same dose of dexamethasone for 2 groups undergoing lumbar TFESIs.

Methods

This study was conducted with the full approval of the Institutional Review Board (2014-04-002-001), and written informed consent was obtained from all participants. The inclusion criteria encompassed patients experiencing lumbar radicular pain with a pain intensity of ≥ 40/100 who had been diagnosed with a herniated nucleus pulposus or spinal stenosis after a series of physical, neurologic, and radiologic examinations. Their durations of pain were more than 6 weeks. All patients received conservative treatment including medication (such as pregabalin, nonopioid) and physical therapy prior to the procedure when they had not shown any significant improvement in radicular pain.

The exclusion criteria included patients with a history of spinal intervention or similar procedures in the prior month, patients who require long-term oral steroid treatment, and those who fell into one of the following categories: pregnancy, cognitive impairment, or use of any anti-coagulant.

Sixty-six patients were offered enrollment and were randomly assigned to one of 2 groups. The random numbers were kept sealed and were opened by an anesthesiologist uninvolved in this study. Those in the DL3 group received 3 mL of injectate composed of 0.33% lidocaine and 4 mg dexamethasone. Those in the DL8 group received 8 mL of injectate made of 0.33% lidocaine and 4 mg of dexamethasone. Lumbar TFESIs were performed by the one investigator (HSP). The patients were followed by the other investigator (EHC). The patients and the investigator (EHC) were unaware of which group they had been assigned to.

The primary outcome measures for this study were the incidence of the patients achieving meaningful pain relief and a reduction on the Visual Analogue Scale (VAS, range 0 – 100) at 4 weeks after the procedure. The definition of "meaningful pain relief" was ≥ 50% from baseline. The secondary outcomes included the Roland-Morris Disability Questionnaire (RMDQ, range 0 – 24) score and adverse effects. Patients were asked to fill out a questionnaire in the clinic – or were interviewed by phone when not available to meet the physician – 4 weeks after the procedure.

Procedure

The patients were placed in the prone position and the procedure was performed using an aseptic technique. One percent lidocaine was diffused at the needle insertion site. A 22-gauge Quincke tip spinal needle (TaeChang, Korea) was inserted using a preganglionic transforaminal approach under fluoroscopic guidance. A syringe with a filter needle (filter needle, Donghwa C&M, Korea) was used to prepare the solution as the dexamethasone was stored in glass ampoules. About 1 mL of contrast media (Pamiray, Dongkook, Korea) was used to confirm the epidural spread. In the DL3 group, 3 mL of 0.33% lidocaine (Lidocaine HCl, Huons, Korea) with 4 mg dexamethasone disodium phosphate (Dexamethasone, Yuhan, Korea) were injected. In the DL8 group, 8 mL of 0.33% lidocaine (Lidocaine HCl, Huons, Korea) with 4 mg dexamethasone disodium phosphate (Dexamethasone, Yuhan, Korea) were injected.

Statistical Analysis

All statistical analyses were performed using statistical software (SPSS 18, Chicago,IL, USA). Data were presented as the mean ± standard deviation unless otherwise noted. A Mann-Whitney U-test was performed

to compare the continuous variables between groups. Fisher's exact test was used to compare the incidence of meaningful pain relief. The proportions of each group achieving such were compared using 95% confidence intervals (CIs). The discrete variables were analyzed through chi-square testing. The results were considered statistically significant at P value < 0.05.

Results

The 66 patients who visited the outpatient clinic were randomized into equal groups of 33. In the DL3 group, one patient discontinued the study and 2 patients were lost in the follow-up. Two patients were lost in the follow-up in the DL8 group. Consequently, 30 patients remained in the DL3 group, and 32 in the DL8 group (Fig. 1).

Before treatment, there were no significant differences in the diagnostic characteristics for radicular pain between the 2 groups (Table 1). There were no significant differences in the baseline VAS (62 ± 17 vs. 64.9 ± 15, $P > 0.05$) and RMDQ (14.8 ± 3 vs. 14.8 ± 2, $P > 0.05$) for radicular pain between the 2 groups.

Table 2 compares the characteristics of the procedures including the injected level and outcomes at 4

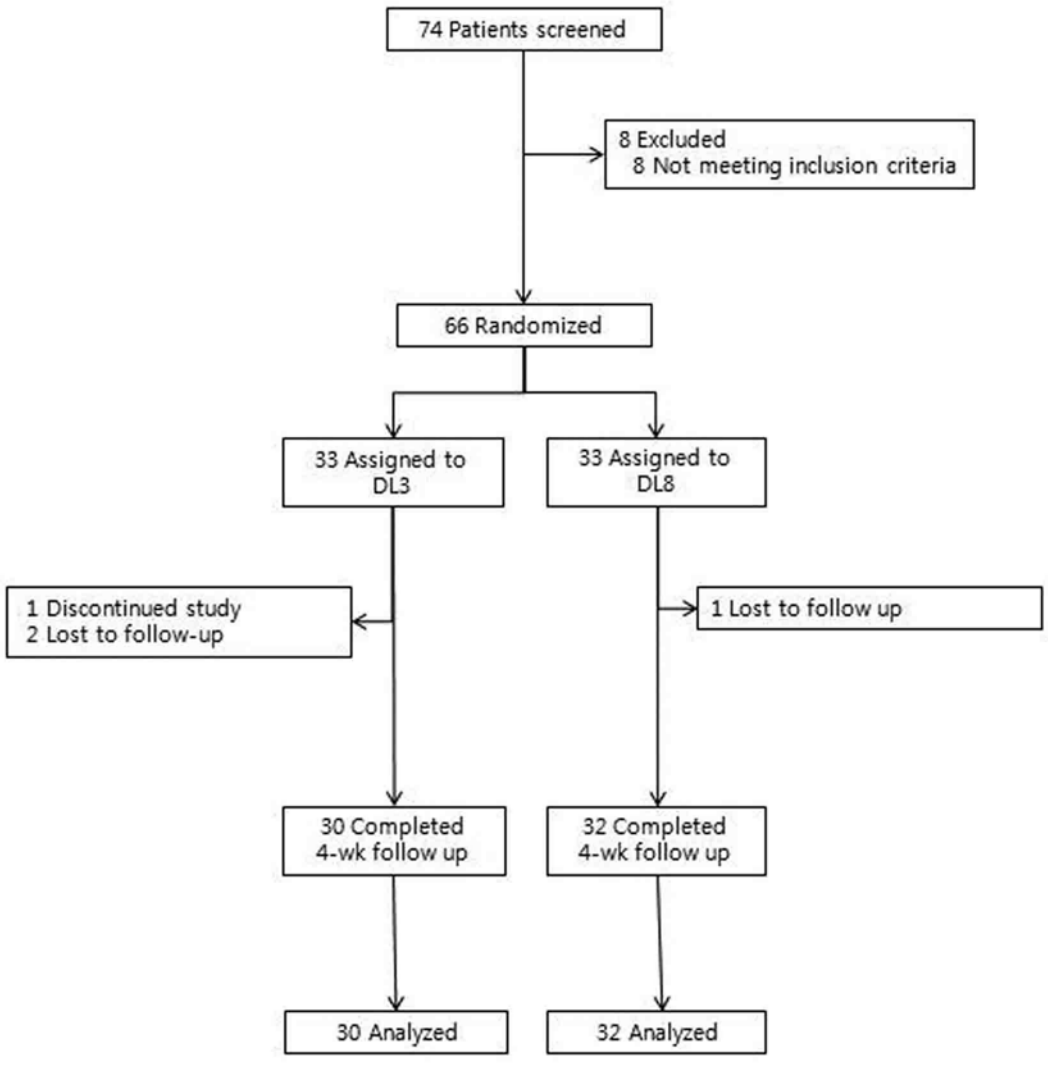

Fig. 1. *Flow chart of patient enrollment.*

Table 1. *Demographic and clinical features of patients.*

	DL8 (n = 32)	DL3 (n = 30)	*P* value
Age (years)	64 ± 11	68 ± 11	> 0.05
Male/female	14/18	12/18	> 0.05
Duration of pain			> 0.05
< 3months	3	9	
3 to 12 months	6	6	
1 to 5 years	16	10	
> 5 years	5	7	
Radiologic findings			
Spondylolisthesis	7	4	> 0.05
Central stenosis	11	12	> 0.05
Foraminal stenosis	12	14	> 0.05
L3/4 HNP	0	0	> 0.05
L4/5 HNP	9	9	> 0.05
L5/S1 HNP	6	5	> 0.05
Postlaminectomy	1	4	> 0.05
Spondylolysis	1	1	> 0.05
Instability	1	1	> 0.05

Values are the mean ± SD or numbers.
DL8: 8 mL group, DL3: 3 mL group

Table 2. *Procedure characteristics and outcomes.*

	DL8 (n = 32)	DL3 (n = 30)	*P* value
Injected level			
L4/5	10	9	> 0.05
L5/S1	21	21	> 0.05
S1	1	0	> 0.05
Meaningful pain relief (%)	19 (59.4%)	9 (30%)	0.024
95% CI	40.6 – 76.3%	14.7 – 49.4%	
VAS for radicular pain			
Baseline	62 ± 17	64.9 ± 15	> 0.05
4 weeks after	33.3 ± 25*	46.3 ± 25*	0.036
RMDQ score			
Baseline	14.8 ± 3	14.8 ± 2	> 0.05
4 weeks after	10.4 ± 4*	11.5 ± 4*	> 0.05
Adverse events			
Pain on injection	1	0	NS

Values are numbers.
DL8: 8 mL group, DL3: 3 mL group, Meaningful pain relief: more than 50% pain relief from baseline, CI: confidence interval, VAS: visual analogue scale, RMDQ: Rolland-Morris Disability Questionnaire, *: $P < 0.05$ relative to baseline, NS: not significant

weeks after the TFESI. In the DL8 group, the incidence of achieving meaningful pain relief was higher compared with DL3 group (19, 59.4% [95% CI = 40.6 – 76.3] vs. 9, 30% [95% CI = 14.7 – 49.4], $P = 0.024$). The incidence of achieving meaningful pain relief did not reach a statistically significant difference with the overlapped confidence intervals.

Both groups demonstrated clinically and statistically significant improvement in radicular pain according to the VAS, and it was revealed that the DL8 group demonstrated significant pain relief according to the VAS as compared to the DL3 group (33.3 ± 25 vs. 46.3 ± 25, $P < 0.05$) (Fig. 2-A). Both groups demonstrated clinically and statistically significant improvement in the functional status according to the RMDQ ($P < 0.05$). There was no significant difference in functional status according to the RMDQ between the 2 groups (10.4 ± 4 vs. 11.5 ± 4, $P > 0.05$) (Fig. 2-B).

No severe adverse events were reported in this study. In the DL8 group, one patient complained of moderate pain on injection which was resolved immediately after the injection. In the DL3 group, one patient was referred to the neurosurgery department one week after the procedure and he was discontinued the study. He showed increasing pain intensity despite the injection. For the same reason, one patient in each of the 2 groups underwent epidural adhesiolysis and neuroplasty after the study ended.

Discussion

As far as we know, this study is the first randomized controlled trial describing the effect of the epidural volume on pain relief with dexamethasone. Although we used the same dose of dexamethasone for the 2 groups, the high-volume injectate was more effective than the low-volume injectate in lumbar TFESI.

The optimal volume for lumbar TFESIs is debatable. It is suggested that there is a positive correlation between the injection of larger volumes of fluid into the epidural space and greater relief of radicular pain (7). Much smaller volumes are probably appropriate when performing transforaminal injections (8). Only 0.5 mL of contrast can be extended either to a superior or inferior spinal segment or crossing the midline spine to the contralateral side (9). A volume of 4.0 mL of injectate reaches both the superior aspect of the superior intervertebral disc and the inferior aspect of the inferior intervertebral disc (10). However, the degree of epidural fibrosis and adhesion is variable in each patient. Previous studies had limitations in that the volume was

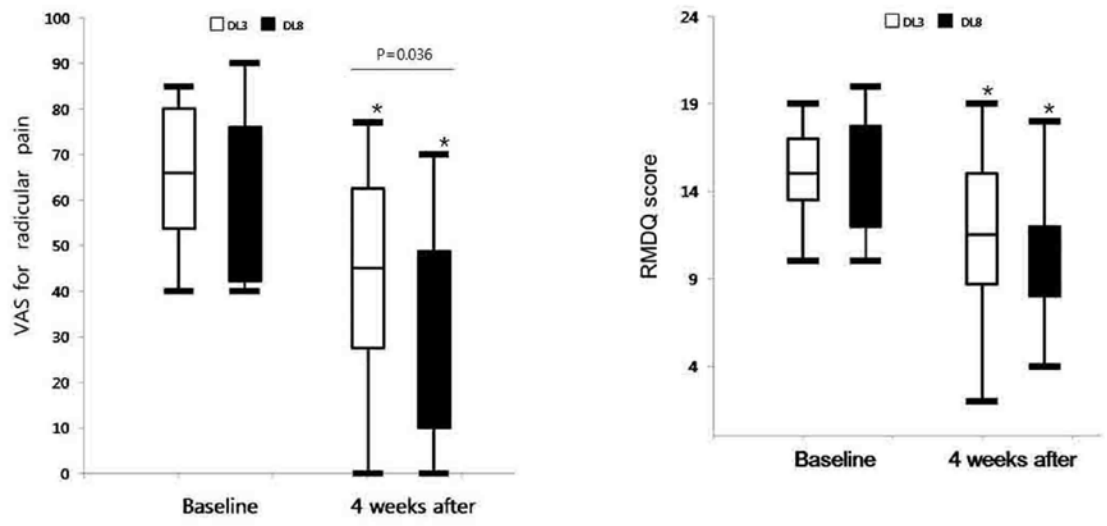

Fig. 2. *Outcome in radicular pain (A) and functional status (B). VAS: visual analogue scale, RMDQ: Rolland-Morris Disability Questionnaire, *:P < 0.05 relative to baseline. There was a significant difference in the postprocedure VAS between the 2 groups. There was no significant difference in the postprocedure RMDQ score between the 2 groups.*

not always suitable for various pathologic conditions. It is suggested that the mechanism of epidural adhesiolysis is the washing out of inflammatory cytokines from the affected area. Furthermore, the added volume enables the lavage of the epidural space, the suppression of ectopic discharge from the injured nerve, and enhancement of the blood flow to the ischemic nerve roots (11). In 1999, a 3-day adhesiolysis protocol study was conducted. The patients were allocated to one of 4 groups using 1) hypertonic saline, 2) hypertonic saline with hyaluronidase, 3) isotonic saline, and 4) isotonic saline with hyaluronidase. There was no statistical difference between the groups in terms of pain relief (12). In this respect, the volume of the injectate may be more important to the efficacy of TFESI than the contents of the injectate. We therefore hypothesized that a high-volume injectate was more effective than a low-volume injectate in lumbar TFESIs, and we decided that 8 mL of injectate would be optimal for the epidural lysis of adhesion.

Epidural steroid injection can be performed through 2 approaches including interlaminar and transforaminal. Previous studies have demonstrated that with the midline interlaminar epidural injections, the injectate spreads into the anterior epidural space only 36% of the time (13). TFESIs are an attractive form of therapy because they enable the physician to deliver the steroid closer to the site of pathology than the interlaminar and caudal approaches (14). In present study, we delivered 8 mL of injectate to the site of pathology. Unlike the interlaminar approach, the volume could reach the specific target site effectively.

Kennedy et al (15) published the study comparing dexamethasone to triamcinolone in lumbar TFESIs. They injected 2 mL of 1% lidocaine and 1.5 mL of dexamethasone phosphate 10 mg/mL. They concluded that the dexamethasone group received slightly more injections than the triamcinolone group to achieve the same outcome. Their injectate volume was 3.5 mL, similar to our low volume injectate group, DL3 (3 mL). However their dexamethasone dose was higher than those of the present study (15 mg vs. 4 mg). Futhermore 46% of patients received repeated injections within 6 months. We suggested that in respect of hypothalamus-pituitary-adrenal axis regulations, high volume injectate with a low dose of steroid is beneficial.

Dexamethasone itself provides substantial anti-inflammatory effects for TFESIs (6). Thus there was a significant improvement of the VAS in both groups 4 weeks after the procedure. Dexamethasone does not create a dose-dependent relationship with respect to efficacy. Previous studies indicate that doses greater than 4 mg of dexamethasone do not provide additional benefits in terms of magnitude or duration of the re-

sponse. The optimal dose of epidural dexamethasone may be less than 4 mg (5). Epidural steroids can affect the hypothalamus-pituitary-adrenal axis regulations after only one injection (16,17). So far, there has been no consensus as to what constitutes appropriate steroid use for TFESIs. There are no guidelines for practice with dexamethasone considering hypothalamus-pituitary-adrenal axis regulations. Further studies to investigate the optimal dose and volume of dexamethasone are needed.

In the DL3 group, the injectate consisted of 1% lidocaine 10 mg, dexamethasone 4 mg, and isotonic saline 1.2 mL. In the DL8 group, the injectate consisted of 1% lidocaine 26 mg, dexamethasone 4 mg, and isotonic saline 4.6 mL. The role of the local anesthetics in TFESI was to dilute the inflammatory cytokines, lyse the scar tissue, enhance the blood flow to the ischemic nerve roots, suppress ectopic discharges from the injured nerves, and to "unwind" central sensitization (18). In the present study, the high-volume injectate contained a greater dose of lidocaine than the low-volume injectate. It is possible that the difference in the local anesthetics dose caused the difference in the improvement of radicular pain. However, the difference in the lidocaine dose was so minimal that it is unlikely to be the main factor determining the efficacy for TFESIs.

Significant improvement was reported in the RMDQ scores of both groups, but there was no statistical difference between the 2 groups. In our opinion, 82% of the patients in the present study had suffered from chronic radicular pain and they tended to preserve their customary activity patterns in order to avoid the pain. Therefore, it seems that the variability of the RMDQ scores may not reflect the functional improvement in each patient.

This study had several limitations. First, we enrolled small number of patients and it was not powered to find some difference in incidence of meaningful pain relief between groups. Second, we did not check the long-term outcomes, and we focused on the VAS and RMDQ only. We assumed that high volume injectate contributes to epidural adhesiolysis but we did not check the postprocedure epidurogram. Third, the proportion of postlaminectomy patients were different between the 2 groups (DL8, 1 vs DL3, 4). The difference was not statistically signifiant but it may contribute to the result. Postlumbar surgery syndrome responds poorly to conservative treatment and epidural steroid injections (19). The 8 patients with postlaminectomy syndrome failed to achieve the meaningful pain relief after the procedure. We assumed that high volume injectate contributed to epidural adhesiolysis but we did not check the postprocedure epidurogram.

Conclusions

The injectate volume may be one of the most important factors to determine the efficacy of lumbar TFESIs. We suggested that injectate at a volume of 8 mL was more effective than injectate at a volume of 3 mL for radicular pain in a lumbar transforaminal steroid injection. Further studies to determine the optimal dose and volume of the dexamethasone are needed.

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