Retrospective Review

Can Repeat Injection Provide Clinical Benefit in Patients with Lumbosacral Diseases When First Epidural Injection Results Only in Partial Response?

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Background: Epidural steroid injection (ESI) is known to be an effective treatment for lower back or radicular pain due to herniated intervertebral disc (HIVD) and spinal stenosis (SS). Although repeat ESI has generally been indicated to provide more pain relief in partial responders after a single ESI, there has been little evidence supporting the usefulness of repeat injections in cumulative clinical pain reduction.

Objectives: The purpose of this study was to determine whether repeat ESI at a prescribed interval of 2 to 3 weeks after the first injection would provide greater clinical benefit in patients with partial pain reduction than that provided by intermittent injection performed only when pain was aggravated.

Study Design: An Institutional Review Board (IRB)-approved retrospective chart review.

Setting: Spine hospital.

Methods: Two hundred and four patients who had underwent transforaminal ESI (TFESI) for treatment of lower back and radicular pain due to HIVD or SS and could be followed-up for one year were enrolled. We divided the patients into 2 groups. Group A (N = 108) comprised partial responders (NRS ≥ 3 after first injection) who underwent repeat injection at a prescribed interval of 2 to 3 weeks after the first injection. Group B (N = 96) comprised partial responders who did not receive a repeat injection at the prescribed interval, but received repeat injections only for aggravation of pain. Various clinical data including total number of injections during one year, duration of NRS < 3 during one year (NRS < 3 duration), and time interval until aggravation of pain required additional injections after repeat injection in group A, or after first injection in group B (time to reinjection), were assessed. These data were compared between groups A and B in terms of total population, HIVD, and SS.

Results: In the whole population, the mean time to reinjection was 6.09 ± 3.02 months in group A and 3.69 ± 2.07 months in group B. The NRS < 3 duration was 9.72 ± 2.86 months and 6.2 ± 2.61 months in groups A and B, respectively. In HIVD patients, the mean time to reinjection was 5.82 ± 3.23 months in group A and 3.84 ± 2.34 months in group B, and NRS < 3 duration was 9.40 ± 3.34 months and 7.15 ± 2.40 months in groups A and B, respectively. In SS patients, the mean time to reinjection was 6.40 ± 2.85 months in group A and 3.59 ± 1.88 months in group B, and NRS < 3 duration was 9.98 ± 2.41 months and 5.52 ± 2.55 months in groups A and B, respectively. Group A had a significantly longer time to reinjection and longer NRS < 3 duration than group B in the whole population, HIVD, and SS.

Limitation: Retrospective design.

Conclusions: Repeat TFESI conducted at 2- to 3-week intervals after the first injection in partial responders contributed to greater clinical benefit compared to intermittent TFESI performed only upon pain aggravation. These benefits were observed in patients with HIVD and in those with SS, irrespective of severity or location of disease.

Key words: Epidural steroid injection, transforaminal approach, repeat injection, numeric rating scale, lumbar spine, herniated intervertebral disc, spinal stenosis, partial pain reduction

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Epidural steroid injection (ESI) is known to be effective for the treatment of lower back and radicular pain due to herniated intervertebral disc (HIVD) and spinal stenosis (SS). In patients who achieve only partial pain relief after the first injection, repeat ESI has been recommended to provide better pain relief after re-evaluation at one- to 3-week intervals, while it was not usually indicated when there is no relief or complete relief (1,2).

However, many physicians have been concerned about the side effects related to repeated steroid administration and have wondered if repeat ESI improved clinical outcomes at long-term follow-up. Arden et al (3) have shown that a second or third injection was not helpful in improving clinical outcomes when the first injection failed, and such findings explained the reluctance of the physicians to perform repeat ESI even in cases of partial success. Thus, decisions about repeat ESI have frequently been made based on individual experience and preference rather than on evidence supported by reports on standardized guidance (1,4). There is little literature and no consensus whether repeat injections were, in fact, clinically useful. Thus, it was assumed that it might be useful to provide information on whether or not repeat ESI at regular intervals would result in better clinical progression than intermittent injections performed only when pain became severe after partial clinical improvement with the first injection.

There are 3 main approaches to ESI: transforaminal (TF), interlaminar (IL), and caudal. TFESI has advantages in that it allows for direct distribution of medication to the ventral epidural space as well as around the dorsal root ganglion, where back and radicular pain originate (5,6). For this reason, we chose TFESI as the method to evaluate the clinical efficacy of repeat ESI.

The purpose of this study was to assess whether repeat TFESI conducted at 2 to 3 weeks after the first injection in cases of partial pain reduction would lead to better clinical outcomes than intermittent TFESI performed only when pain was aggravated.

Methods

Patient Selection

This retrospective study was approved by the institutional review board of our hospital. Patients aged over 18 years who had undergone a first TFESI for treatment of lower back pain with radicular pain due to HIVD or SS from January 2014 to May 2014 and could be followed for one year were enrolled. These diagnosis were determined on the basis of clinical manifestation and radiological evaluation including magnetic resonance image (MRI). Patients with sacroiliac joint or facet joint disease were also diagnosed by radiological and clinical evaluation including diagnostic or therapeutic injections and were not included in this study. Those with neurological deficits, vertebral fractures, or previous lumbar surgery within the past 2 years were also excluded. Three-hundred and seventy-five patients satisfied the enrollment criteria. Among them, those who had achieved satisfactory pain relief to a score of < 3 on the numeric rating scale (NRS) and those with no response (NRS reduction by < 2 points) with the first injection were excluded. The patients (N = 204) who showed a partial response were included in this study. Partial response was defined as 3 or more on NRS after the first injection.

We divided the patients into 2 groups. Group A (N = 108) consisted of the patients who had a partial response to the first injection and underwent repeat ESI at 2 to 3 weeks for further treatment. Group B (N = 96) consisted of patients who had partial relief with the first injection but did not receive repeat injections at 2 to 3 weeks and instead underwent repeat injections only when pain was aggravated.

Data Collection

Information regarding age, gender, diagnosis (HIVD or SS), duration of pain, and predominant pain location (axial back pain/lower limb pain) was collected by review of medical records. As well, NRS at pretreatment, number of injections during one year, duration of NRS < 3 during one year (NRS < 3 duration), and time interval until pain was aggravated to require reinjection after repeat injection in group A or after first injection in group B (time to reinjection) were assessed. These data were compared between groups A and B in terms of total population as well in terms of each diagnosis (HIVD, SS).

Transforaminal Epidural Steroid Injection

All TFESIs were performed under fluoroscopy by one physician (first author) who is an expert in this procedure with over 10 years' experience. Injections were performed ipsilaterally at a single level identified on MRI which was compatible to clinical manifestation. The patient was placed in the prone position, and the fluoroscopic tube was rotated obliquely to an ipsilateral oblique angle with respect to the nerve root suspected of being the source of pain. The goal of this position-

ing was to allow a perpendicular needle track toward the classic injection site underneath the pedicle in the safe triangle, which is defined by the pedicle superiorly, the lateral border of the vertebral body laterally, and the outer margin of the spinal nerve medially. A 12-cm, 21-gauge spinal needle was advanced with fluoroscopic guidance into the safe triangle. The needle position was intermittently checked on the anterior-posterior and lateral fluoroscopic views. Approximately 0.5 mL of contrast medium was then injected. Anterior-posterior and lateral views were obtained to confirm the distribution of the contrast medium into the ventral epidural space under real time fluoroscopy, after which a combination of 2 mL lidocaine (0.5%) and 5 mg (1 mL) dexamethasone was slowly injected ipsilaterally. Dexamethasone was used exclusively for injections due to concerns of the potential for serious complications such as spinal cord infarctions related to particulate corticosteroids.

Statistical Analysis

The SPSS Version 14.0 statistical package (SPSS Inc., Chicago, IL) was used for statistical analysis. Chi-square test with Fisher's exact test was used to compare gender proportion, predominant pain location, injection numbers, and location and severity of HIVD and SS between the 2 groups. Student T test was performed to determine the difference in age, duration of pain, NRS at pretreatment, mean number of injections, NRS < 3 duration, and time to reinjection. Results were considered statistically significant if the *P* value was < 0.05.

Results

Total Population

Group A (N = 108) consisted of 51 men and 57 women, group B (N = 96) consisted of 46 men and 50 women. There were 48 patients with HIVD and 60 with SS in group A and 40 patients with HIVD and 56 patients with SS in group B. No significant difference was found in terms of age, gender ratio, duration of pain, predominant pain location, NRS at pretreatment, and proportion of HIVD and SS between the 2 groups.

The mean number of injections for group A and B, respectively, during one-year follow-up was 2.63 ± 0.64 and 2.67 ± 0.78; the difference was not statistically significant. In group A, 73 patients underwent 2 injections and 35 patients underwent 3 injections at 2 to 3 week intervals in order to attain an NRS score < 3. The mean number of repeat injections was 2.32 ± 0.47 in group A. Among the 73 patients who received 2 injections, 22 required one reinjection and 2 required 2 reinjections for pain aggravation during the one year following the prescribed course of repeat injections. Among 35 patients who received 3 prescribed repeat injections, 7 required one reinjection during one year. The mean time to reinjection was 6.09 ± 3.02 months in group A and 3.69 ± 2.07 months in group B. Group A showed a significantly longer time to reinjection than group B. The mean NRS < 3 duration was 9.72 ± 2.86 months and 6.2 ± 2.61 months in groups A and B, respectively. Group A had a significantly longer duration of satisfactory pain remission than group B (Table 1).

Herniated Intervertebral Disc

Eighty-eight patients were diagnosed with HIVD, of whom 48 were included in group A and 40 in group B. No significant difference was found in terms of age, gender, NRS at pretreatment, pain duration, or pain location between the 2 groups. There was no significant difference between the 2 groups in terms of HIVD location and severity. In group A, 36 patients received 2 injections and 11 received 3 injections at 2 to 3 week intervals in order to attain an NRS < 3. The mean time to reinjection was 5.82 ± 3.23 months in group A and 3.84 ± 2.34 months in group B. Group A showed a significantly longer time to reinjection than group B. The mean NRS < 3 duration was 9.4 ± 3.34 months and 7.15 ± 2.4 months in groups A and B, respectively. Group A had a significantly longer duration of satisfactory pain remission than group B (Table 2).

Spinal Stenosis

One-hundred and sixteen patients were diagnosed with SS, of whom 60 were included in group A and 56 were in group B. No significant difference was found in age, gender, NRS at pretreatment, pain duration, and pain location between the 2 groups. There was no significant difference in terms of SS location and severity. In group A, 36 patients received 2 injections, and 24 patients received 3 injections at 2 to 3 week intervals in order to reach NRS < 3. The mean time to reinjection was 6.4 ± 2.85 months in group A and 3.59 ± 1.88 months in group B. Group A had a significantly longer time to reinjection than group B. The mean NRS < 3 duration was 9.98 ± 2.41 months and 5.52 ± 2.55 months in groups A and B, respectively. Group A had a significantly longer duration of satisfactory pain remission than group B (Table 3).

Table 1. *Comparison of clinical variables between groups A and B.*

		A (N = 108)	B (N = 96)	*P*
Age		56.5 ± 14.3	57.2 ± 15.2	0.743
Gender ratio	Male	51	46	1
	Female	57	50	
NRS at pretreatment		7.02 ± 1.00	7.16 ± 1.04	0.137
Duration of pain		7.72 ± 4.85	8.33 ± 4.68	0.363
Predominant pain location	Back	41	35	0.226
	Radicular	67	61	
Diagnosis	HIVD	48	40	0.777
	SS	60	56	
Number of injections per year		2.63 ± 0.64	2.67 ± 0.78	0.709
	2	49	48	0.182
	3	50	34	
	4	9	12	
	5	0	2	
Time to reinjection (months)		6.09 ± 3.02	3.69 ± 2.07	< 0.001
NRS < 3 duration (months)		9.72 ± 2.86	6.2 ± 2.61	< 0.001

NRS: numeric rating scale, HIVD: herniated intervertebral disc, SS: spinal stenosis
Time to reinjection: time interval until pain was increased to require another injection after repeat injection of group A and after first injection of group B, NRS < 3 duration: duration of less than 3 on NRS during one year.

Group A consisted the patients who had partial response to the first injection and underwent repeat injections at 2 to 3 weeks for further treatment. Partial response was defined as 3 or more on NRS after first injection. Group B consisted of patients who had partial relief on the first injection but did not receive repeat injections at 2 to 3 weeks and instead underwent repeat injections only when pain was aggravated.

Discussion

Although repeat ESI has generally been indicated to provide pain relief in partial responders after a single ESI (1,2,7), there has been little evidence as to whether repeat injections actually provide greater and more prolonged pain relief. And even the literature regarding repeat injections has not clarified when repeat injections were required or whether repeat injections at established intervals had better clinical effects than injections performed at random intervals (3,6,8-10). On the other hand, it has also been reported that repeat injections at 3 to 6 weeks did not have prolonged or cumulative effects. However, this study evaluated IL injections using a blind method; hence, the exact needle placement was not confirmed (3).

In the present study, the mean number of injections during one year was not significantly different between the repeat injection group (group A) and the intermittent injection group (group B). NRS < 3 duration and time to reinjection for aggravation of pain was significantly longer in group A than that in group B. This indicated that the protocol of repeat injections at 2 to 3 weeks after the initial treatment contributed to a longer period of pain remission and had a more useful clinical effect than intermittent injections without an increase in treatment sessions. These results suggested that if first injection provided even partial pain relief, repeat injections at 2 to 3 weeks should be recommended for better clinical progression over a longer time period. This benefit of repeat injections was also revealed in each disease category such as HIVD as well as SS. Considering that there was no significant difference between groups in terms of severity and location of HIVD and SS, it appeared that repeat injections at a prescribed interval could lead to better clinical outcomes irrespective of severity and location of HIVD and SS. This longer effect might be the result of a cumulative clinical benefit and restoration of benefit that could subsequently be diminished after the first injection (9).

A maximum of 3 sessions of repeat injections has been recommended for partial responders (1,2). In our study, 35 (32.4%) of 108 patients who underwent at

Table 2. *Comparison of clinical variables between groups A and B diagnosed as HIVD.*

		A (N = 48)	B (N = 40)	*P*
Age		47 ± 11.6	47.1 ± 14.4	0.984
Gender ratio	Male	28	20	0.52
	Female	20	20	
NRS at pretreatment		6.9 ± 0.83	7.10 ± 1.12	0.14
Duration of pain		7.58 ± 4.66	7.3 ± 3.4	0.75
Predominant pain location	Back	25	17	0.653
	Radicular	23	23	
Number of injections per year		2.58 ± 0.68	2.65 ± 0.86	0.686
	2	25	22	0.508
	3	18	12	
	4	5	4	
	5	0	2	
Time to reinjection (months)		5.82 ± 3.23	3.84 ± 2.34	0.013
NRS < 3 duration (months)		9.4 ± 3.34	7.15 ± 2.4	0.001
HIVD location	Central	21	21	0.75
	Subarticular	18	13	
	Foraminal	9	6	
HIVD severity	Bulging	18	19	0.112
	Protrusion	18	18	
	Extrusion	12	3	

HIVD: herniated intervertebral disc, NRS: numeric rating scale
Time to reinjection: time interval until pain was increased to require another injection after repeat injection of group A and after first injection of group B, NRS < 3 duration: duration of less than 3 on NRS during one year

Group A consisted the patients who had partial response to the first injection and underwent repeat injections at 2 to 3 weeks for further treatment. Partial response was defined as 3 or more on NRS after first injection. Group B consisted of patients who had partial relief on the first injection but did not receive repeat injections at 2 to 3 weeks and instead underwent repeat injections only when pain was aggravated.

least 2 injections required a third injection 2 to 3 weeks later to attain an NRS < 3. According to another study in which repeat TFESI was conducted at approximately 2 weeks in patients with partial response, 21 of 51 patients (40%) required only one injection, 20 of 51 (40%) required 2 injections, 9 of 51 (18%) required 3 injections, and only one of 51 (2%) required 4 injections. Thus, among 30 patients who underwent at least 2 injections, 10 (33.3%) required 3 or 4 injections to reach satisfactory outcomes (11). These results were in agreement with our results. Among the patients in the group A, approximately 70% required only 2 sessions of TFESI to achieve optimum pain relief. In addition, there was no difference in total number of injections per year in group A compared with group B, demonstrating that repeat injections at a prescribed interval could be performed without any concerns about increased number of steroid injections. Therefore, physicians did not need to be reluctant to perform repeat injections at 2 – 3 weeks, with concerns about side effects related to excessive steroid administration.

We needed to choose the same technique (C-arm fluoroscopy-guided TFESI) for all patients to avoid the influence that might come from a different approach method or inaccurate drug administration by a blind method. We tried to remove other factors that could affect clinical results except repeat injection at regular intervals as much as possible, because increased clinical efficacy could be interpreted as a cumulative effect obtained by repeat injection rather than an inappropriate or different treatment method.

Conflicting opinions or results existed regarding the clinical usefulness of TF injections in comparison with IL or caudal injections (12-15). As well, the evidence level of TFESI was relatively lower in spinal stenosis. The evidence was reported to be good for low back

Table 3. *Comparison of clinical variables between groups A and B diagnosed as SS.*

		A (N = 60)	B (N = 56)	*P*
Age		64.1 ± 11.5	64.4 ± 11.3	0.883
Gender ratio	Male	23	26	0.453
	Female	37	30	
NRS at pretreatment		7.12 ± 1.11	7.14 ± 0.98	0.47
Duration of pain		7.83 ± 5.04	9.07 ± 5.33	0.201
Predominant pain location	Back	16	18	0.126
	Radicular	44	38	
Number of injections per year		2.67 ± 0.6	2.68 ± 0.72	0.923
	2	24	26	0.228
	3	32	22	
	4	4	8	
	5	0	0	
Time to reinjection (months)		6.4 ± 2.85	3.59 ± 1.88	< 0.001
NRS < 3 duration (months)		9.98 ± 2.41	5.52 ± 2.55	< 0.001
SS location	Central	30	29	0.967
	Subarticular	21	18	
	Foraminal	9	9	
SS severity	Bulging	25	28	0.347
	Protrusion	27	18	
	Extrusion	8	10	

SS: spinal stenosis, NRS: numeric rating scale
Time to reinjection: time interval until pain was increased to require another injection after repeat injection of group A and after first injection of group B, NRS < 3 duration: duration of less than 3 on NRS during one year

Group A consisted the patients who had partial response to the first injection and underwent repeat injections at 2 to 3 weeks for further treatment. Partial response was defined as 3 or more on NRS after first injection. Group B consisted of patients who had partial relief on the first injection but did not receive repeat injections at 2 to 3 weeks and instead underwent repeat injections only when pain was aggravated.

and radicular pain due to disc herniation and fair for spinal stenosis (13,16). Also, there was concern about serious side effects related to TFESI such as lower limb paraplegia resulting from intravascular penetration or embolic infarct. The incidence of nerve root damage and intradiscal penetration by needle were higher in TFESI than ILESI (2,17,18).

In spite of these concerns, we chose the TF approach because we assumed that it had the advantage of delivering the medication more directly into the ventral epidural space and around the nerve root sheath which were responsible for back and radicular pain. Whereas, an IL or caudal approach was an indirect method, and spread of injectate into the ventral epidural space might be prevented by mechanical barriers such as hypertrophied ligaments, bony structures, or epidural adhesions (5,6,19,20). In such cases, greater pain reduction after repeat injection might be the result of accurate injection at the second or third session rather than the cumulative effect of repeated sessions (21). According to a survey by Cluff et al (22), the mean maximal number of ESI at each year was 4.74 ± 2.6 in academic institutions and 6.9 ± 6.98 in private practice. These numbers were larger in comparison to our results of 2.63 ± 0.64 sessions during one year in group A and 2.67 ± 0.78 sessions in group B. A large proportion of institutions in this study used the IL approach or no radiological guidance during ESI. Another study examining repeat ILESI showed that 21% of 120 total participants received only one injection, 32% received 2 injections, and 47% received 3 injections (3). Among 95 patients who underwent a second injection, 56 (59%) required a third injection, which demonstrated that a larger proportion of patients required a third injection than our study (32.4% of patients who underwent 2 injections required a third injection to accomplish NRS

< 3). This might be because the IL approach was less efficient in providing pain relief than the TF approach and required an increased number of injections (12,23).

However, recent literature indicated that the parasagittal IL approach had the ability to spread the medication in the ventral epidural space and therefore overcame the limitation of a midline IL approach. Consequently, the parasagittal IL provided comparable clinical outcomes to TFESI (18,24,25). These reports suggested that parasagittal ILESI could substitute for TFESI with more safety. We assume that especially when TF injections at 2 or more levels were needed, the parasagittal IL approach will be suitable alternative, considering its ability to spread medication into ventral epidural spaces and to avoid serious neurologic complications.

Neurologic deficits of the lower limb related to TFESI were caused by spinal cord infarct due to embolism or thrombosis of the radicular artery. This might be associated with intravascular particulate steroid injection or needle penetration into the radicular artery, which was more closely related to the TF approach (26). But no paraplegia of the lower limbs occurred when non-particular steroid was used for TFESI (17,27,28). Also our study could prevent this devastating complication by injecting non-particulate steroid such as dexamethasone and by avoiding intravascular needle penetration as much as possible using real time fluoroscopy.

In terms of clinical efficacy, non-particulate steroid such as dexamethasone showed no significantly worse clinical outcomes and shorter duration than particulate steroid in lumbar epidural steroid injections conducted in patients with radicular pain (29,30). Interestingly, one study demonstrated that even though dexamethasone showed similar effectiveness to triamcinolone, the dexamethasone group required slightly more injections than the triamcinolone group (31). This was because dexamethasone is a non-particulate and its duration of effect was shorter than particulate steroids. This property of dexamethasone enabled it to be more appropriate to this study evaluating cumulative or restorative effects of repeat injections.

The present study had limitations related to its retrospective design. First, only patients who could be followed up for one year were selected, and those with a partial response at first injection who were lost to follow-up before one year were not included or analyzed in this study. Second, some patients were not included because they underwent surgery before completion of the one-year follow-up due to aggravated pain. Third, we used only pain score, NRS, as the clinical evaluation method and did not measure functional score or patients' satisfaction score. This was overly simplistic and did not take into account various aspects of clinical outcomes. We suppose that a prospective cohort study with using more clinical assessment tools would provide more informative and supportive evidence for repeat ESI at regular intervals.

Conclusion

Repeat TFESI conducted at 2 to 3 weeks after the first injection in patients with partial pain reduction contributed to enhanced and prolonged clinical benefits compared to those in patients administered intermittent TFESI when pain became severe. These clinical benefits were observed in patients with HIVD and those with SS, irrespective of severity or location of disease.

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