Retrospective Study

Efficacy of Adjuvant 10% Hypertonic Saline in Transforaminal Epidural Steroid Injection: A Retrospective Analysis

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Background: Chronic lower back pain with or without radiculopathy represents an important medical, social, and economic problem. Many treatment modalities and techniques, including surgery and epidural administration of steroids, have been used to manage this pain. Hypertonic saline, which has been used as an adjunct to percutaneous epidural adhesiolysis, can also be injected via a transforaminal approach in expectation of longer-lasting effects.

Objectives: This study aimed to determine the effect of adding hypertonic saline to conventional transforaminal epidural steroid injections (TFEI) to provide pain relief for chronic radiculopathy patients.

Study Design: A retrospective study.

Setting: Pain clinic of a university hospital.

Methods: Between January 2010 and December 2013, the medical records of 246 patients (94 in the hypertonic group, 153 in the control group) who received transforaminal epidural block were reviewed and analyzed. The hypertonic group received 10% sodium chloride solution added to lidocaine, triamcinolone, and hyaluronidase. Outcomes on pain reduction were measured using a numerical rating scale (NRS) and the responder rate at baseline, one, 3, and 6 months after procedure.

Results: The estimated difference in NRS scores from baseline throughout a 6-month follow-up period in the hypertonic group were significantly higher ($P = 0.0003$). The proportion of substantial responders (41.9% vs. 34.6% at one month, 40.9% vs. 26.8% at 3 months, and 33.3% vs. 14.4% at 6 months, respectively, $P = 0.0058$) and substantial/moderate responders (71.0% vs. 58.8% at one month, 65.6% vs. 40.4% at 3 months, and 48.4% vs. 20.3% at 6 months, respectively, $P < 0.0001$) were significantly higher in the hypertonic group. The Oswestry disability index (ODI) was not different between the groups ($P = 0.2697$).

Limitations: Retrospective design without a control group.

Conclusions: Hypertonic saline provides more superior and longer lasting pain relieving effects when added to TFEIs.

Key words: Back pain, epidural injections, epidural steroids, hypertonic saline, lumbar, radiculopathy, transforaminal

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Lower back pain (LBP) has been increasing and now represents as one of the largest contributors to the years that an individual lives with a disability (1-4). Approximately 70% of individuals experience LBP with varying degrees of symptoms at some point in time (5) and sciatica can often be recognized in many

cases in the clinic. Although 80% to 90% of individuals with chronic LBP improve by 12 weeks, 6% to 11% of individuals continue to report symptoms for more than 3 months. This often leads to an increased rate of patients with a persistent disability not returning to work, resulting in the consumption of more health resources and increased medical expenses (6).

Epidural steroid injection (ESI) is one of the treatment modalities for chronic LBP with or without lumbar radiculopathy. In most cases, the main cause of symptoms is thought to be inflammatory changes that result from irritation or compression of the affected nerve root by the surrounding tissues; ESI is thought to relieve pain by reducing this nerve root inflammation and ischemia (7). Among various approaches for ESI, transformainal epidural steroid injections (TFEI) have shown good-to-fair outcomes in the treatment of lumbar disc herniation (8-14) and spinal stenosis (8,10). However, most studies have reported short-term benefits with limited evidence of mid- or long-term efficacy. Epidural adhesion and fibrosis are thought to be some of the causes that lead to those limited results by interfering with the spread of drugs around the targeted nerve root, which can even occur in cases of lumbar disc herniation or spinal stenosis without a history of prior surgical interventions (15-17).

Percutaneous epidural adhesiolysis has been used to treat epidural adhesion and fibrosis in expectation of a long-term treatment effect. A randomized control study demonstrated significant treatment effect even for one year following percutaneous epidural adhesiolysis compared with placebo (18). Hypertonic saline (hyperosmolar sodium chloride) may be included during percutaneous epidural adhesiolysis as an adjuvant, but there is controversy about the effects of administering hypertonic saline (19,20). A previous randomized controlled study of the use of transforaminal hypertonic saline in patients with spinal stenosis showed superior short-term pain relieving efficacy compared with conventional lumbar TFEI, but the overall mid- and long-term results showed no advantage (21). In our current study, we retrospectively reviewed cases from our institution to further evaluate the mid-term and long-term effect of adding hypertonic saline to TFEI in the treatment of chronic LBP with radiculopathy.

Methods

This study was approved by the Institutional Review Board of Asan Medical Center and the necessity for obtaining informed consent was waived as we were only reviewing recorded data in this study.

This retrospective study was conducted by reviewing the electronic medical records of patients treated at our institution. All cases of transforaminal epidural block that were performed by a single physician using a fluoroscopy-guided technique between January 2010 and December 2013 were reviewed. The inclusion criteria were (1) age ≥ 20 years; (2) chronic LBP with unilateral leg pain with radiculopathy; and (3) a corresponding site of lesion based on magnetic resonance imaging (MRI) findings that were assessed by radiologists. Patients who met all 3 of these inclusion criteria were included. The exclusion criteria were (1) incomplete medical records or no follow-up visit within 3 months; (2) neuropathic pain without a definite MRI finding, such as complex regional pain syndrome; or (3) transforaminal epidural block level ≥ L2. The patients were classified into one of 2 groups as follows: a hypertonic group that was administered additional 10% sodium chloride solution and a conventional group.

The same physician performed all procedures with appropriate monitoring in an operating room. A single fluoroscopy C-arm system was used and all injections were performed in a standardized fashion. Each patient was placed in a prone position and a radiographic view was obtained to ensure a proper site of entry. Transforaminal entry was determined based on anatomic landmarks and the blunt needle was advanced and positioned in the upper quadrant of the target foramen under fluoroscopic guidance. After confirming needle entry into the foramen using anteroposterior and lateral views, aspiration for the presence of blood or cerebrospinal fluid (CSF) was performed to exclude location of needle tip in a blood vessel or CSF containing structures. Then contrast dye was injected under real-time fluoroscopic guidance to prevent intravascular or intrathecal injection and to confirm adequate flow to the epidural space. The patients in the hypertonic group received 2 mL 1% lidocaine with 1500 units of hyaluronidase initially. For 5 minutes after the administration of local anesthetics and hyaluronidase, the patients were asked whether they experienced any motor or sensory changes in the ipsilateral or contralateral lower extremities. No additional drugs were administered if the patient complained of severe paresthesia or pain during injection or presented possible signs of intrathecal or intravascular administration of local anesthetic. Then the patients received 2 mL 10% sodium chloride solution mixed with 20 mg triamcinolone acetonide. The patients in the conventional group received 3 mL 1%

lidocaine mixed with 1500 units of hyaluronidase and 20 mg of triamcinolone.

The objective of this study was to evaluate the effectiveness of the addition of hypertonic saline to conventional lumbar TFEIs for managing unilateral radiculopathy secondary to degenerative diseases of the lumbar spine. The medical records at baseline, and one, 3, and 6 months post-procedure were reviewed. The following data were collected and analyzed: age, gender, weight, height, body mass index, current analgesic medication, medical history, total duration of pain, and target level. Any recorded significant adverse effects after performing TFEB were also collected (e.g., severe pain, paresthesia, motor weakness, or arachnoiditis). To evaluate the degree of pain and functional disability, the values of the numerical rating scale (NRS) and Oswestry disability index (ODI) were collected. Patients often represented degrees of pain reduction by deciles and these data were collected as well. The primary outcome was the proportion of substantial responders measured based on the NRS pain score. The responder rate was defined in terms of the proportion of patients who reported a substantial response (≥ 50% or ≥ 4-point reduction in the pain score compared with baseline) or a moderate response (≥ 30 and < 50%, or ≥ 2 and < 4-point reduction in the pain score compared with baseline) (22).

Categorical data were compared using the chi-squared test (with Fisher's exact test when necessary) and *t*-tests were performed for comparisons of continuous data. NRS scores between 2 groups were analyzed using a linear mixed model, considering missing values. Responder analyses were performed using a logistic regression model with Generalized Estimating Equations. A *P*-value < 0.05 was considered to indicate a statistically significant difference.

Results

A total of 525 patients who received a transforaminal epidural block between January 2010 and December 2013 and fulfilled the inclusion criteria were assessed; 144 patients with incomplete medical records and 135 patients who did not visit the clinic during the first 3-month follow-up period were excluded. Thus, a total of 246 patients (93 in the hypertonic group; 153 in the control group) were analyzed.

Baseline demographic and clinical characteristics are shown in Table 1. We detected no statistically significant differences in baseline characteristics between the 2 groups.

The mean pain score after TFEI compared with the baseline decreased significantly throughout the 6-month follow-up period in both groups (Table 2). When the NRS pain score was compared between the 2 groups with a linear mixed model, using time as the random effect and the group as the fixed effect, we observed a statistically significant improvement in the hypertonic group compared with the control group (omnibus $P = 0.0003$). The proportion of substantial responders was higher in the hypertonic group than in the control group throughout the entire follow-up period (omnibus $P = 0.0058$; Table 3) and the proportion of substantial or moderate responders was also higher (omnibus $P < 0.0001$; Table 4; Fig. 1). Based on a logistic regression analysis of each group, the baseline characteristics had no significant influences on the proportion

Table 1. *Baseline characteristics of the study patients.*

	Hypertonic group (n = 93)	Conventional group (n = 153)	*P*-value
Age, yrs. [mean ± SD]	65.11 ± 10.95	65.53 ± 11.74	0.780
Gender: M/F	27(29.0%)/66(71.0%)	47(30.7%)/106(69.3%)	0.780
Weight, kg	62.6 ± 9.37	60.52 ± 11.31	0.617
Height, cm	158.34 ± 7.48	156.88 ± 8.45	0.667
Body mass index	24.93 ± 3.08	24.31 ± 4.23	0.311
Target level			0.246
L4	3	3	
L5	71	123	
S1	16	16	
Multiple level	3	11	
Treatment location (left/right)	51/42	75/78	0.529

Table 2. *Numerical rating scales of the hypertonic and conventional groups.*

Time	Mean pain score (95% CI)*		Estimated difference from baseline (95% CI)		*P*-value	
	Hypertonic (n = 93)	Conventional (n = 153)	Hypertonic (n = 93)	Conventional (n = 153)	Hypertonic (n = 93)	Conventional (n = 153)
Baseline	7.08 (6.77 – 7.38)	6.76 (6.48 – 7.03)	0	0		
1 month	4.54 (4.15 – 4.93)	4.84 (4.46 – 5.21)	-2.54 (-2.90 – -2.18)	-1.92 (-2.22 – -1.62)	< 0.001	< 0.001
3 month	4.43 (4.00 – 4.86)	5.39 (5.02 – 5.76)	-2.65 (-3.13 – -2.16)	-1.37 (-1.71 – -1.03)	< 0.001	< 0.001
6 month	4.92 (4.24 – 5.60)	5.00 (4.28 – 5.72)	-2.18 (-2.96 – -1.41)	-1.76 (-2.46 – -1.05)	< 0.001	< 0.001

CI: confidence intervals.
**Omnibus P = 0.0003 in comparison of the hypertonic and conventional groups*

Table 3. *The result of substantial responder analyses between the hypertonic and conventional groups throughout a 6-month follow-up period.*

	Substantial responder (%)		OR (95% CI)	*P*-value
	Hypertonic group (n = 93)	Conventional group (n = 153)		
1 month	39 (41.9%)	53 (34.6%)	1.83 (1.19 – 2.80)	0.0058
3 months	38 (40.9%)	41 (26.8%)		
6 months	31 (33.3%)	22 (14.4%)		

Table 4. *The results of substantial or moderate responder analysis between the hypertonic and conventional groups throughout the 6-month follow-up period.*

	Substantial or moderate responder (%)		OR (95% CI)	*P*-value
	Hypertonic group (n = 93)	Conventional group (n = 153)		
1 month	66 (71.0%)	90 (58.8%)	2.63 (1.77 – 3.92)	< 0.0001
3 months	61 (65.6%)	61 (40.4%)		
6 months	45 (48.4%)	31 (20.3%)		

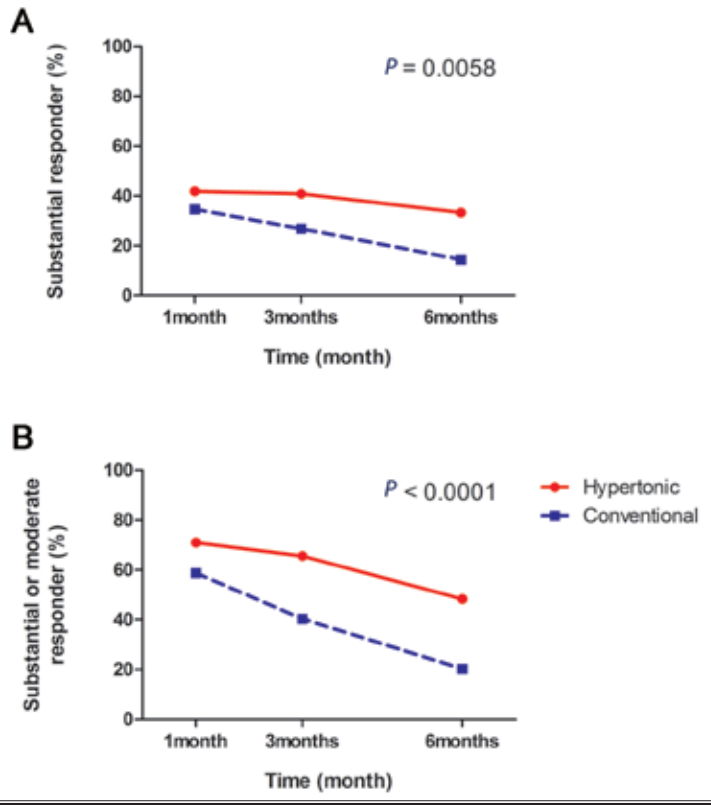

Fig. 1. The responder rate in the hypertonic and conventional groups The proportion of substantial responders was higher in the hypertonic group throughout the 6-month follow-up period (A) and the proportion of substantial or moderate responders was also higher (B). Data are presented as percentages (%); omnibus P = 0.0058 (A); omnibus P < 0.0001 (B).

Table 5. *Oswestry disability index of the hypertonic group and the conventional groups.*

Time	Mean ODI score (95% CI)*		Estimated difference from baseline (95% CI)		*P*-value	
	Hypertonic (n = 93)	Conventional (n = 153)	Hypertonic (n = 93)	Conventional (n = 153)	Hypertonic (n = 93)	Conventional (n = 153)
Baseline	61.2 (57.4 – 65.0)	58.4 (54.6 – 62.3)	0	0		
1 month	50.6 (47.1 – 54.2)	52.2 (47.6 – 56.9)	-10.5 (-14.5 – -6.5)	-6.2 (-11.3 – -1.2)	< 0.001	0.017
3 month	51.1 (46.8 – 55.4)	56.0 (51.3 – 60.6)	-10.1 (-14.9 – -5.2)	-2.5 (-8.2 – -3.2)	< 0.001	0.390
6 month	54.8 (51.3 – 58.4)	51.6 (45.9 – 57.3)	-6.3 (-10.1 – -2.6)	-6.8 (-13.5 – -0.1)	< 0.001	0.046

ODI: Oswestry disability index
CI: confidence intervals
** Omnibus P = 0.2697 comparing the hypertonic and conventional group*

of substantial responders in each group.

The ODI was also significantly reduced compared with the baseline values throughout the entire follow-up period in the hypertonic group (omnibus $P < 0.0001$). The ODI decreased significantly at both one and 6 months ($P = 0.017$ and $P = 0.046$, respectively), but not at 3 months ($P = 0.390$) in the conventional group. However, we detected no significant differences for the change in ODI between the 2 groups from baseline through 6 months (omnibus $P = 0.2697$; Table 5).

There was no recorded significant adverse effects after performing TFEI in either group of patients.

Discussion

In our present study, the addition of 10% hypertonic sodium chloride to TFEI resulted in a superior response to treatment compared with conventional TFEI. The NRS decreased significantly throughout the entire follow-up period in both groups, and the reduction was more considerable in the hypertonic group. The proportion of substantial responders and substantial or moderate responders was higher in the hypertonic group throughout the entire 6-month follow-up period. The ODI decreased in both groups and the reduction was greater in the hypertonic group, but the overall difference between the 2 groups was not significant.

Among several approaches for lumbar epidural injections, the transforaminal approach can deliver corticosteroids close to the site of pathology, presumably onto an inflamed nerve root (23). ESIs administered by this approach have been used to manage patients with disc herniation and radiculitis, resulting in short- and long-term pain relief, as has been reported in various randomized studies (8-14). To manage patients with spinal stenosis, several randomized studies have also shown positive results in pain relief for a 3-month follow-up period (10,14). However, conflicting long-term effects have been observed, with only one randomized controlled study reporting positive results beyond a 6-month follow-up examination (8). Additionally, only one randomized trial in patients with post-spinal surgery syndrome has been reported, in which pain relief was most prominent after one month, but then decreased at 3 and 6 months (24). These limitations of ESI could be attributed to failure of the injectate to spread out towards the desired target site because of epidural adhesions. Notably, epidural adhesions can be observed not only in post-surgery patients, but also in patients with spinal stenosis and disc herniation (15-17).

The effects of percutaneous epidural adhesiolysis have been described in numerous studies, and favorable short- and long-term results have been reported (18-20,25-27). The addition of 10% hypertonic saline during percutaneous epidural adhesiolysis is thought to contribute to the adhesiolysis of potential adhesions and fibrous tissues in the epidural and perineural space. Indeed a higher rate of responders was observed in the hypertonic group compared with the conventional group at 3 and 6 months in this study. Although mechanical adhesiolysis has been reported to be a critical factor in adhesiolysis, the role of hypertonic saline in breaking fibrous adhesions is controversial (19). Chemical adhesiolysis, such as diminution in edema and inflammation, may also be an important factor. Furthermore, hypertonic saline was found to have an inhibitory effect on human fibroblast cell proliferation (28). Another possible explanation for our results is the neuromodulatory effects of hypertonic saline. A few experimental animal studies have previously described the neuromodulatory effects of chloride solutions and

the effects of hyperosmolar solutions on nerve conduction (29,30). King et al (29) reported that chloride ions play a major role in establishing a persistent C fiber blockade, which can be observed when dorsal rootlets are exposed to hypertonic saline. Additionally, hyperosmolar solutions effect signal propagation and the compound action potential amplitude of A-fibers in the rat dorsal root ganglion (30), so it is assumed that the hyperosmolarity of the sodium chloride solution that was administered could have contributed to changes in pain conductivity.

The patients who were treated with adjuvant hypertonic saline relatively represent a subset of patients who are difficult to treat with conventional TFEI. The guideline of our clinic considers the use of adjuvant hypertonic saline to extend the treatment respond of TFEI only when the patient presents a limited or unsatisfactory response to conventional TFEI.

This study is limited because of its retrospective design. First, we could not control and evaluate medication use and its change during the follow-up period. Although we ask patients about pain relief after TFEI itself in our clinic, the pain relief effect was not adjusted for the changes in medications, which can also influence the patient's responses. The specifics of additional interventions, including surgery, also could not be evaluated because there was a considerable number of patients lost to follow-up, and they were counted as having no effect. This could have caused our results to show worse outcomes than presented because the cases that did not show up during follow-up actually might have had good pain-relief effects. Second, the injectate volumes administered to the 2 groups were not equivalent, as the hypertonic and conventional groups received 4 mL and 3 mL, respectively. Only a few studies have suggested that epidural injections are more effective when administered in larger volumes (31), and no controlled clinical trials have described the effect of epidural volume on pain as an independent outcome for a transforaminal epidural block. Park et al (32) reported that 3 mL injected media by a transforaminal approach reached the inferior pedicle and medial superior pedicle in 95.3% of cases. Also, Teske et al (33) reported that a mean volume of anterolateral epidural space at L5/S1 was 1.1 mL by anatomical determination and 0.9 mL by surgical determination. In our present study, injected volumes were equal to or greater than 3 mL in both groups, so the injected volume in both groups is thought to be sufficient to cover the lesions. Another concern is an actual concentration of hypertonic saline. We administered 2 mL 10% sodium chloride solution mixed with 20 mg triamcinolone acetonide after the injection of a test dose. Then the concentration of hypertonic saline can be diluted with previously injected local anesthetics and it may be less than 10%.

There are known complications of hypertonic saline administration, such as severe pain during injection, paresthesia, and chemical arachnoiditis (34). Furthermore, the spread of liquid in the epidural space depends on the state of epidural space and in the diseased epidural space, due to scarring, stenosis, and adhesions; the spread of injected hypertonic saline may be difficult to predict (35). Although no severe adverse events or complications were reported in our current study, special care must be taken to avoid the possible complications described above. We have previously recommended safety guidelines for transforaminal hypertonic saline injections to increase the margin of safety which includes real-time fluoroscopic guidance of both anteroposterior and lateral view, frequent aspiration during injection, use of non-particulate steroids, and use of blunt needle and catheter technique with a sufficient interval between the test dose and hypertonic saline injection (21). At least 20 minutes delay before the use of hypertonic saline is necessary to rule out loculation or subdural injection and the catheter technique rather than the single needle technique would be more preferable. The subsequent hypertonic saline injection should be abandoned if there is any pain, numbness, weakness, or paralysis. In our institution, we consider these safety precautions when there is any requirements for the use of hypertonic saline; no severe adverse effects or complications were reported during this study period.

Conclusion

In conclusion, our current findings suggest that the addition of hypertonic saline results in a superior response over a 6-month period compared with conventional TFEI. Larger cohort studies will be necessary to address the safety and complications of using hypertonic saline in a transforaminal epidural block to obtain further safety profiles and more valid information. A large scale prospective randomized study is also required to validate efficacy and long-term benefits of adding hypertonic saline during TFEI.

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