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Clinical Study

Prolonged pain reducing effect of sodium hyaluronate-carboxymethyl cellulose solution in the selective nerve root block (SNRB) of lumbar radiculopathy: a prospective, double-blind, randomized controlled clinical trial

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ABSTRACT

BACKGROUND: The pattern of linear graph schematized by visual analogue scale (VAS) score displaying pain worsening between 2 days and 2 weeks after selective nerve root block (SNRB) is called rebound pain.

PURPOSE: The purpose of this study was to determine if sodium hyaluronate and carboxymethyl cellulose solution (HA-CMC sol) injection could reduce the occurrence of rebound pain at 3 days to 2 weeks after SNRB in patients with radiculopathy compared with injection with corticosteroids and local anesthetics alone.

STUDY DESIGN/SETTING: Double blinded randomized controlled clinical trial.

PATIENT SAMPLE: A total of 44 patients (23 of 24 patients in the Guardix group and 21 of 24 patients in the control group) who finished the follow-up session were subjects of this study.

OUTCOME MEASUREMENT: Patients were asked to write down their average VAS pain scores daily for 12 weeks. Functional outcomes were assessed by Oswestry Disability Index, Roland Morris Disability Questionnaire , and Short Form-36.

METHOD: A cocktail of corticosteroids, 1% lidocaine, 0.5% Bupivacaine, and 1 mL of normal saline was used for the control group whereas a cocktail of corticosteroids, 1% lidocaine, 0.5% Bupivacaine, and 1 mL of HA-CMC solution was used for the G group. Study participants were randomized into one of two treatment regimens. They were followed up for 3 months.

RESULTS: VAS score at 2 weeks after the procedure was 4.19±1.32 in the control group, which was significantly ($p<.05$) higher than that (2.43±1.24) in the G group. VAS score at 6 weeks after the procedure was 4.00±1.23 in the control group and 3.22±1.45 in the G group, showing no significant ($p=.077$) difference between the two groups. There were no significant differences in functional outcomes at 6 or 12 weeks after the procedure.

CONCLUSIONS: Compared with conventional cocktail used for SNRB, addition of HA-CMC sol showed effective control of rebound pain at 3 days to 2 weeks after the procedure.

Keywords: Hyaluronic acid; Lumbar radiculopathy; Lumbar spine; Radiating pain; Rebound pain; Selective nerve root block.

Introduction

Selective nerve root block (SNRB) as a treatment of radiculopathy was introduced in 1971 by Macnab [1]. Since then, several authors have descripted the usefulness of SNRB for diagnosis and treatment of lumbar radiculopathy [2,3]. This minimally invasive procedure is now commonly

FDA Device/Drug Status: sodium hyaluronate and carboxymethyl cellulose solution (HA-CMC sol) injection.

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performed. SNRB is a procedure that can relieve symptoms by selectively injecting corticosteroids and local anesthetics around the dural sheath and the culprit nerve root that is compressed which triggers radiculopathy. Although SNRB is doubted to have curative effects, some authors insist that this minimally invasive procedure can effectively manage lumbar radiculopathy by reducing the need for surgery [4,5].

Medications used in SNRB include corticosteroids, which can inhibit the production and release of proinflammatory materials and local anesthetics that can inhibit the transmission of nociceptive receptors. Numerous studies have reported the mechanism of actions, effects, and side effects of these medications. However, the mechanism of how SNRB relieves symptoms remains unclear [6]. According to Pfirrmann et al. [7], although SNRB shows effectiveness initially, symptomatic relief does not occur until 2 weeks. There are also different views in terms of the duration of symptomatic relief [7–14]. Yeom et al. [15] have claimed that SNRB could be a diagnostic tool for confirming the nerve involved in radiculopathy. Other authors [11,12] have reported that, besides its usefulness for diagnosis, SNRB can lead to symptomatic relief for over 3, 6, or 12 months. However, long-term effects of SNRB differ among authors and its effects are doubtful in some articles.

Most articles about SNRBs or epidural steroid injections have measured visual analogue scale (VAS) scores before and after the injection (at 2 weeks, 4 weeks, or 3 months after the injection). Measured values are displayed as linear graphs in which lines are used to connect each VAS score measured by time. We have measured daily VAS scores until the follow-up session after a week. It has been reported that pain worsening between 2 days and 2 weeks after injection, also known as rebound pain, can be effectively controlled by the addition of hyaluronate during SNRB [16]. Based on this knowledge, we hypothesized that injection of sodium hyaluronate (HA) carboxymethyl cellulose (CMC) solution (HA-CMC sol) after SNRB might increase the effect of nerve root block by reducing the severity of rebound pain with hyaluronate whereas also lengthening duration of the effect by CMC.

Thus, the purpose of this study was to determine if HA-CMC sol injection could reduce the occurrence of rebound pain at 3 days to 2 weeks after SNRB and examine whether injection of HA-CMC sol, a mixture of HA and CMC, could improve the quality of life by offering long-term pain relief in patients with lower extremity radiculopathy compared with injection of corticosteroids and local anesthetics alone.

Materials and methods

Study design and patients selection

After obtaining approval from our Institutional Review Board (IRB) (approval Number: MDCR-16-005), informed consent was obtained from all participants. A prospective double-blind, randomized controlled trial was carried out for 3 months. Study participants were randomized into one of two treatment regimens. They were followed for 3 months. A total of 80 patients who underwent SNRB at our outpatient clinic from January 1, 2016 to March 31, 2016 were included in this study. Thirty patients who did not meet the inclusion criteria and two patients who refused to participate were excluded from this study. Thus, a total of 48 patients were enrolled for this study (Fig. 1). The sample size showing power of 0.9, effect size of 1.06, and α error of 0.05 with VAS score difference of 15% was 20 for each group. Thus, 40 subjects were needed for this study. Finally, 24 patients were enrolled for each group considering possible losses during follow-up sessions (See Appendix 1). Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) score was used to assess radiculopathy in all patients. Patients were eligible for participation if LANSS score was 7 or more and their radiculopathy could not be controlled by oral medications with VAS score of 5 or more. All patients showed foraminal stenosis in magnetic resonance imaging. Exclusion criteria were pregnancy, patients with secondary gains such as insurance issues, significant comorbidities, patients contraindicated to medications used in SNRB, or patients participated in other studies during or right before this study. Patients with cancer pain either due to primary or metastatic cancer, acute radiculopathy to the lower extremities due to herniated disc, patients who could not understand questions of the questionnaire were also excluded (Table 1). This study was also conducted for patients with bony foraminal stenosis or hypertrophic ligamentum flavum. These diseases do not have self-limiting course. They have rather poor natural course. This study analyzed a total of 44 patients, including 23 of 24 patients in the G group and 21 of 24 patients in the control group who finished the follow-up session.

Blinding and randomization

Two physicians coordinated the clinical assessment, diagnosis, and treatment. All study investigators, hospital staff, and patients were blinded to information on which patient was given HA and CMC mixture (Guardix-sol◯R, Hanmi Medicare, Seoul, Korea) cocktail or control cocktail. The control group patients were injected with cocktail of corticosteroids (1 mL, dexamethasone), 1% lidocaine (1 mL, Lidocaine hydrochloride), 0.5% Bupivacaine (1 mL, Bupivacaine hydrochloride), and 1mL of normal saline prepared by nurses who were not involved in this study. G group patients were injected with cocktail of corticosteroids (1 mL, dexamethasone), 1% lidocaine (1mL, Lidocaine hydrochloride), 0.5% Bupivacaine (1 mL, Bupivacaine hydrochloride), and 1 mL of HA-CMC solution. Random allocation of treatment regimens using permuted block randomization method was performed by another doctor who was not involved in treatment or evaluation. The final analysis

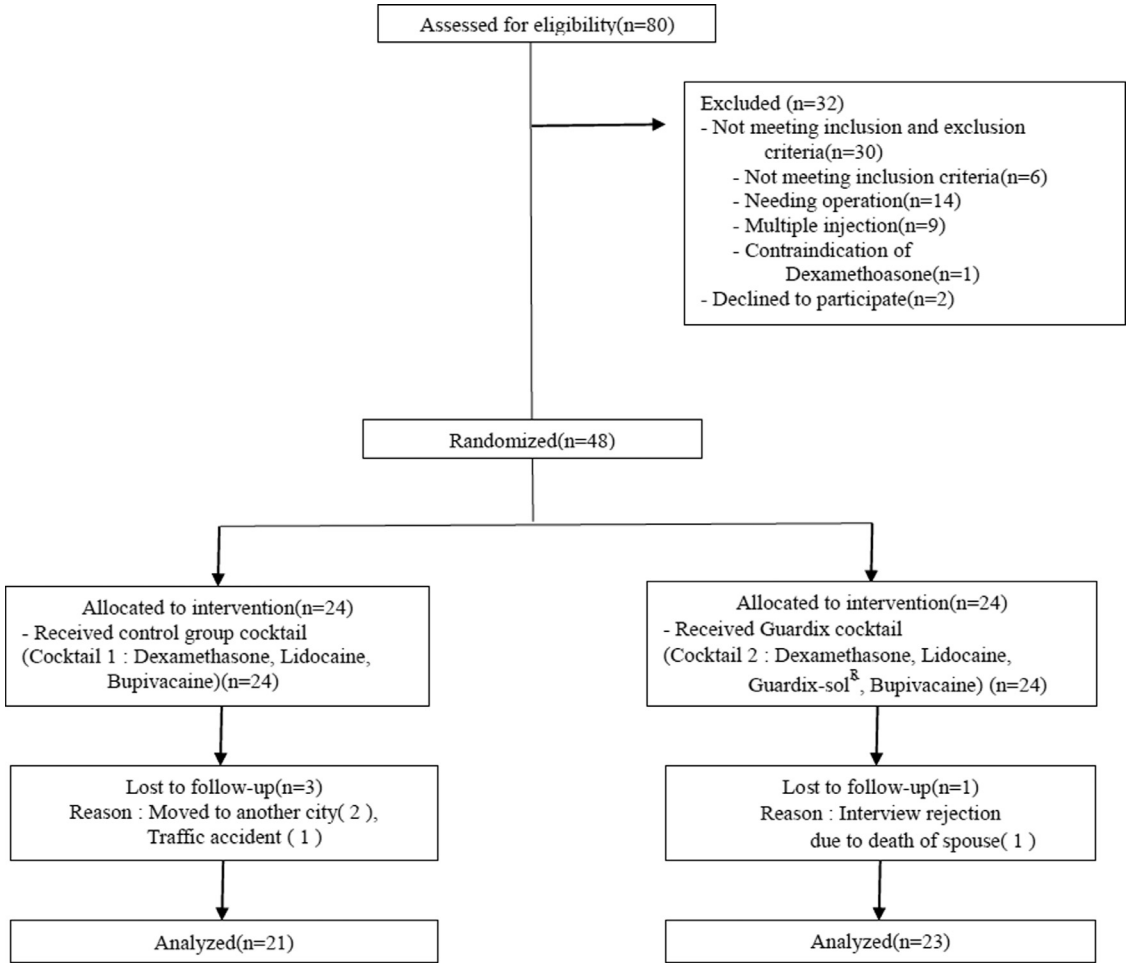

Fig. 1. Flow diagram showing the procedure used in this study.

included only those patients who completed the treatment regimen. They were clinically evaluated and followed up at weeks 2, 6, 12 after the treatment.

Methods

All patients underwent assessment, including full history-taking, neurological examination, and physical examination by the lead researcher (SBK). They were asked to express their pain in VAS score. The level of the culprit nerve root and the date of procedure were decided considering magnetic resonance imaging findings and assessment results. The procedure of SNRB was performed by skilled doctors who were not involved in this study. They did not participate in the randomization process either. All procedures of SNRBs were performed to patients under prone position after confirming the injection site with assistance of a C-arm image intensifier. The skin was cleaned thoroughly with antiseptic solution before injection was performed. The C-arm image intensifier was tilted parallel to the injection angle to obtain an oblique view of the spine (Scotty dog appearance). After an injection of local anesthesia to the skin (2% lidocaine was applied to the injection site), a 23-gauge spinal needle was inserted to the inferolateral side of the pedicle (called "safety triangle") of

Table 1
Inclusion and exclusion criteria

Inclusion criteria
1 LANSS Score >7
2 Radiating pain VAS ≥5
3 Agreement for participating
4 Foraminal stenosis in MRI
Exclusion Criteria
1 Pregnant woman
2 Patients with secondary gains
3 Significant comorbidities
4 Patients contraindicated to medications used in SNRB
5 Patients participated in other studies during or right before the study
6 Patients with cancer pain either due to primary or metastatic cancer
7 Acute radiculopathy to the lower extremities due to herniated disc
8 Patients who cannot understand the questions of the questionnaire

LANSS Score, the Leeds Assessment of Neuropathic Symptoms and Signs; SNRB, Selective Nerve Root Block.

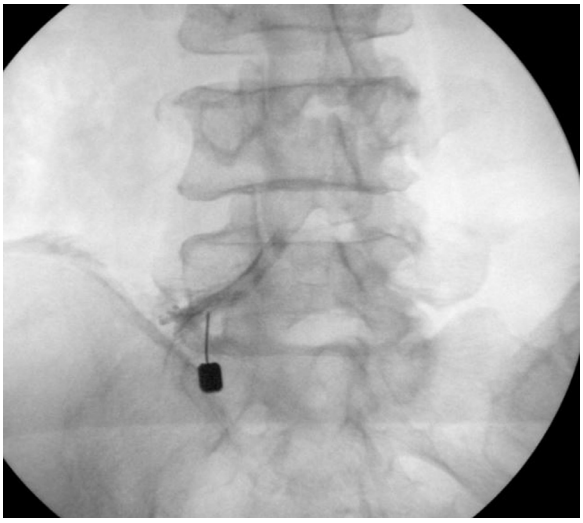

Fig. 2. Contrast media (1 mL) was injected to reconfirm the culprit nerve root.

nerve roots. After confirming arousal of the same symptoms as the patient's chief complaints, 1 mL of contrast media (Iohexol: Omnipaque GE Healthcare Ireland, IDA Business Park, Carrigtohill, Co. Cork Ireland, 300 mg/mL) was injected to reconfirm the culprit nerve root (Fig. 2). The physician who was blind to patient assignment injected the allocated cocktail into the nerve root. Considering both patient selectivity and therapeutic effect, the doctor tried to inject the cocktail into only to a single nerve root in this trial. Medications were injected at their minimal therapeutic doses in less than 2 cc to avoid false positive results. The first author (SBK) received funding from Hanmi Medicare (Seoul, Korea).

Outcome measurement

All patients filled in LANSS sheets prepared by the other researcher (YML) at the out-patient department. Patients were asked to write down their severity of radiculopathy and their average pain scores until their next follow-up session. The primary efficacy outcome was VAS score of their radiculopathy at the follow-up session which was a week after the procedure. VAS scores were assessed as numbers from 1 to 10. Other efficacy outcomes were radiculopathy at 6 weeks and 12 weeks after the procedure. Functional outcomes were assessed by Oswestry Disability Index (ODI) and Roland Morris Disability Questionnaire (RMDQ) at 6 and 12 weeks after the procedure. An additional Short Form-36 (SF-36) was used for functional outcome assessment at 12 weeks after the procedure.

Statistical analysis

All analyses were performed with SPSS version 19.0 software. Summary for epidemiological results were performed using descriptive analysis, mean ± standard deviation for quantitative variables and the values of frequency (percent) for qualitative variables. The differences of

Table 2
Epidemiological results of all populations

Variables		Control group	G group
Gender	Male	9 (43%)	9 (39%)
	Female	12 (57%)	14 (61%)
Age (Year-old)		67.19±11.78	66.52±7.42
Weight (Kg)		52.86±11.42	51.87±10.42
BMI (Kg/m^2)		22.15±2.98	22.39±3.37
LANSS score		18.19±2.84	17.87±2.91
VAS (Initial)		7.24±1.37	7.70±1.25
Smoker/nonsmoker		5/16 (24%)	5/18 (22%)

BMI, Body Mass Index; LANSS Score, the Leeds Assessment of Neuropathic Symptoms and Signs; VAS, Visual Analogue Scale.

NOTE. Data are presented as mean ± standard deviation or frequency (percent).

epidemiological results (age, weight) between the two groups (Control group and G group) were analyzed by independent *t* test. Differences in VAS scores and functional outcomes (ODI, RMDQ, and SF-36) after injection between the two groups (Control group and G group) were analyzed by Mann-Whitney method and results were presented by mean (lower 95% confidence interval, upper 95% confidence interval). The power of result in VAS score difference at 2 weeks after the procedure was determined with G power 3.1. p Values of .05 or below were considered to indicate statistical significance.

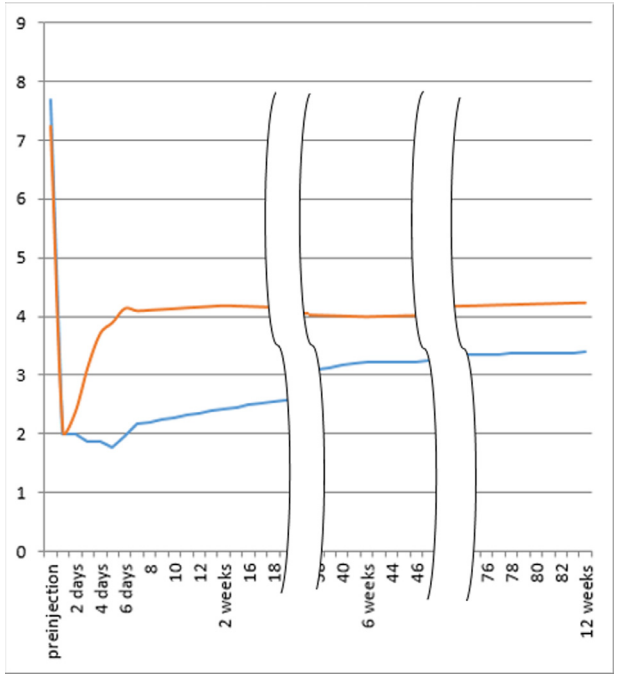

Fig. 3. Compared to conventional cocktail of corticosteroids and local anesthetics used for SNRB, addition of HA and CMC mixture showed effective control of rebound pain occurring at 3 days to 2 weeks after the procedure with statistical significance.

Results

Epidemiological results

A total of 48 patients who met the inclusion criteria were eligible for participation. Of 24 patients assigned to the control group, follow-up loss occurred in 3 patients (2 patients moved out during the study and one patient had car accident), resulting in 21 patients (9 males, 12 females) at the final follow-up session. Of 24 patients who were assigned to the G group, follow-up loss occurred in 1 patient due to loss of the patient's spouse, resulting in 23 patients (9 males, 14 females) at the final follow-up. There was no significant difference in age between the two groups (p=.82). There was no significant difference in mean body weight either between the two groups (p=.15) (Table 2).

Postinjection pain results

Initial VAS scores of radiculopathy in the control group and the G group were 7.24±1.38 and 7.70±1.26, respectively, showing no significant difference (p=.302). VAS score

Table 3
Postinjection pain results of all populations

			VAS										
G(+)/G(-)	Sex	Age	Initial VAS	1st D	2nd D	3rd D	4th D	5th D	6th D	7th D	2 W	6 W	12 W
G(+) 1	F	72	6	2	2	2	2	2	2	2	1	4	5
G(+) 2	M	55	8	4	4	3	3	2	2	2	2	3	0
G(+) 3	F	62	7	1	3	3	3	3	3	3	4	3	3
G(+) 4	M	52	10	1	1	1	1	1	1	2	2	4	4
G(+) 5	F	69	9	1	1	1	1	1	1	1	2	3	3
G(+) 6	M	77	8	1	1	1	1	1	1	1	3	3	2
G(+) 7	F	74	10	1	1	1	1	1	1	2	2	4	3
G(+) 8	M	56	8	2	2	2	2	1	1	1	0	0	0
G(+) 9	F	65	7	3	2	2	2	2	2	2	2	0	3
G(+) 10	F	74	7	5	4	3	3	3	4	4	2	4	5
G(+) 11	F	61	8	3	3	2	2	1	1	1	3	5	7
G(+) 12	M	66	8	4	4	4	4	4	4	4	2	3	0
G(+) 13	M	71	7	0	0	0	0	0	1	1	2	4	2
G(+) 14	M	76	8	2	2	2	2	3	3	4	0	2	5
G(+) 15	F	60	7	1	1	1	1	1	1	1	2	3	6
G(+) 16	M	61	8	2	2	2	2	2	3	3	4	4	4
G(+) 17	F	73	7	1	1	1	1	1	1	1	3	4	4
G(+) 18	F	68	6	4	4	4	4	4	4	4	4	5	3
G(+) 19	F	68	7	2	2	2	1	1	1	2	2	3	3
G(+) 20	M	79	10	0	0	0	0	0	1	2	5	6	6
G(+) 21	F	59	6	2	2	2	2	2	2	2	3	3	6
G(+) 22	F	67	9	1	1	1	2	2	2	3	4	3	3
G(+) 23	F	65	6	3	3	3	3	3	3	2	2	1	1
G(-) 1	F	72	6	4	4	4	4	4	4	3	3	4	6
G(-) 2	M	75	7	1	2	2	2	2	2	2	5	5	3
G(-) 3	F	80	6	2	2	2	4	5	5	5	4	4	5
G(-) 4	F	80	5	4	5	5	5	5	5	5	4	5	6
G(-) 5	F	69	6	2	4	4	5	5	5	5	6	5	4
G(-) 6	F	72	6	3	3	3	3	3	3	3	5	5	4
G(-) 7	F	60	5	1	1	2	2	2	2	2	1	5	5
G(-) 8	M	55	8	4	4	6	6	6	6	4	2	2	0
G(-) 9	M	55	8	3	3	3	1	1	1	1	4	3	5
G(-) 10	F	77	8	1	2	2	3	3	4	5	5	2	4
G(-) 11	M	62	6	1	1	3	3	3	3	3	3	3	3
G(-) 12	M	56	7	2	3	3	3	4	4	4	4	6	7
G(-) 13	M	45	8	2	2	5	5	5	5	5	5	2	2
G(-) 14	M	67	8	2	2	2	3	3	4	4	5	4	4
G(-) 15	F	81	7	3	3	3	4	4	5	6	6	4	6
G(-) 16	F	40	7	1	1	4	5	5	5	5	4	3	3
G(-) 17	M	79	10	0	1	2	4	4	6	6	3	3	3
G(-) 18	F	77	10	2	3	4	4	5	5	5	6	5	5
G(-) 19	F	76	8	0	0	1	3	4	4	4	3	4	2
G(-) 20	F	66	8	2	2	2	4	4	4	4	5	4	4
G(-) 21	M	67	8	3	2	4	5	5	5	5	5	6	8

VAS, Visual Analogue Scale; D, Days; W, Weeks; G(+), HA-CMC solution group; G(-), Control group.

Table 4
Serial VAS change for radiating pain and between-group difference

		Control group	G group	G group- Control group	p value
Initial (Preinjection)		7.24 (6.61, 7.86)	7.70 (7.15, 8.24)	0.45 (−0.34, 1.25)	0.30
Postinjection	1st day	2.05 (1.50, 2.60)	2.00 (1.42, 2.58)	−0.04 (−0.82, 0.73)	0.75
	2nd day	2.38 (1.81, 2.95)	2.00 (1.46, 2.54)	−0.38 (−1.13, 0.37)	0.30
	3rd day	3.14 (2.56, 3.72)	1.87 (1.39, 2.35)	−1.27 (−1.99, −0.55)	<0.05*
	4th day	3.71 (3.15, 4.27)	1.87 (1.39, 2.35)	−1.84 (−2.55, −1.13)	<0.05*
	5th day	3.90 (3.33, 4.48)	1.78 (1.30, 2.27)	−2.12 (−2.84, −1.39)	<0.05*
	6th day	4.14 (3.54, 4.74)	1.96 (1.48, 2.44)	−2.18 (−2.92, −1.44)	<0.05*
	7th day	4.10 (3.49, 4.70)	2.17 (1.71, 2.64)	−1.92 (−2.65, −1.18)	<0.05*
	2 weeks	4.19 (3.59, 4.79)	2.43 (1.90, 2.97)	−1.75 (−2.53, −0.97)	<0.05*
	6 weeks	4.00 (3.44, 4.56)	3.22 (2.59, 3.84)	−0.78 (−1.60, 0.03)	0.07
	12 weeks	4.24 (3.40, 5.08)	3.39 (2.53, 4.25)	−0.84 (−2.01, 0.32)	0.17
VAS (Preinjection−1st day)		5.19 (4.25, 6.13)	5.70 (4.75, 6.64)	0.50 (−0.79, 1.80)	0.43
VAS (2nd day−3rd day)		−0.76 (−1.24, -0.29)	0.13 (−0.02, 0.28)	0.89 (0.42, 1.35)	<0.05*
VAS (4th day−3rd day)		0.57 (0.13, 1.02)	0.00 (−0.13, 0.13)	−0.57 (−1.00, −0.13)	<0.05*
VAS (4th day−2nd day)		1.33 (0.68, 1.98)	−0.13 (−0.33, 0.07)	−1.46 (−2.09, −0.83)	<0.05*

VAS, Visual Analogue Scale.
NOTE: Data are presented as mean (lower 95% confidence interval, upper 95% confidence interval)
* Mann-Whitney method was performed, statistically Significant with p<0.05.

at the day after the procedure was 2.05±1.20 in the control group and 2.00±1.35 in the G group, showing no significant difference (p=.753). However, both groups showed significant improvement in pain (p<.05). VAS scores at 2 days after the procedure in the control group and the G group were 2.38±1.24 and 2.00±1.24, respectively, showing no significant difference (p=.304). VAS scores at 3 days after the procedure in the control group and the G group were 3.14±1.27 and 1.87±1.10, respectively, with the control group showing significantly higher pain score (p<.05). However, compared with the day before, pain was not significantly improved in either group (p=.057 in the control group and p=.071 in the G group). VAS scores at 4 days after the procedure in the control group and the G group were 3.71±1.23 and 1.87±1.10, respectively, showing significantly lower pain scores in the G group (p<.05). Although the pain at 4 days after the procedure in either group showed no significant difference compared with that at the day before (p=.148 in the control group and p=1.0 in the G group), the pain at 4 days after the procedure was significantly higher than that at 2 days after procedure in the control group (p=.001). However, this was not the case in the G group (p=.708). VAS score at 5 days after the procedure was 3.90±1.26 in the control group and 1.78±1.12 in the G group. VAS score at 6 days after the procedure was 4.14±1.31 in the control group and 1.96±1.10 in the G group. VAS score at 7 days after the procedure was 4.10±1.33 in the control group and 2.17±1.07 in the G group. VAS scores at 5−7 days after the procedure were significantly lower in the G group (all p<.05). Although VAS score at 2 weeks the after procedure was 4.19±1.32 in the control group and 2.43±1.24 in the G group, showing significantly lower pain score in the G group (p<.05), VAS score at 6 weeks after the procedure was 4.00±1.23 in the control group and 3.22±1.45 in the G group, showing no significant difference between the two groups (p=.077) (Fig. 3). Power analysis performed on VAS score difference at 2 weeks after the procedure showed a power above 90% (Appendix 2). VAS score at 12 weeks after the procedure was 4.24±1.84 in the control group and 3.39±1.99 in the G group, showing no significant difference between the two groups (p=.170). Table 4 also report between-group difference in means with 95% confidence intervals (Tables 3 and 4).

Result of functional outcome

ODI, RMDQ, and SF-36 were assessed to determine functional outcomes (Table 5). At 6 weeks after the procedure, ODI score was 17.57±8.50 in the control group and 16.91±8.83 in the G group whereas RMDQ score was 8.33±5.05 in the control group and 6.17±5.82 in the G group. There were no significant differences in functional outcomes at 6 weeks after the procedure (p=.916 for ODI score and p=.137 for RMDQ score). At 12 weeks after the procedure, ODI score was 17.10±8.19 in the control group and 17.09±7.33 in the G group whereas RMDQ score was 7.38±6.41 in the control group and 5.35±4.22 in the G group. There were no significant differences in functional outcomes at 12 weeks after the procedure either (p=.222 for ODI score and p=.312 for RMDQ score). Table 6 also report between-group differences by means (lower 95% confidence interval, upper 95% confidence interval).

Discussion

In clinical practice, medications are injected in larger amounts to achieve therapeutic effects compared with that needed for diagnostic effects. To lower the false positive rate, using the minimal amount of medication is important for diagnostic values [15,17−19]. Bogduk et al. [20] have insisted that pain relief after injection may last for over 6 months with possible therapeutic effects, thus avoiding or

delaying surgery in such cases. However, they also mentioned such therapeutic effects as an enigma. Although outcomes are different in several articles, after a dramatic short-term pain relief, effects will gradually subside by time, showing no significant difference with control groups in long-term follow-ups [19,21–23]. Although most patients showed favorable outcomes within 3 months after the procedure, pain aggravation by time is thought to be due to the duration of action of corticosteroids.

The mechanism of pain control is as follows. Local anesthetics injected to painful nerves can inhibit the generation of action potentials, thus possessing temporary effects by inhibiting the transmission of pain stimuli to the brain. They also have anti-inflammatory effects. Anti-inflammatory effects of corticosteroids may be intensified when nerve roots are swollen due to foraminal stenosis or inflammation [12,24–27]. Some authors have insisted that corticosteroid injection to the nerve root may relief pain by

Table 5
Result of functional outcome of all populations

G(+)/G(-)	Sex	Age	6 weeks		12 weeks		SF-36	
			ODI	RMDQ	ODI	RMDQ	PCS	MCS
G(+) 1	F	72	12	7	18	6	20.625	24.625
G(+) 2	M	55	16	5	0	0	86.25	83
G(+) 3	F	62	15	7	18	10	23.75	45.875
G(+) 4	M	52	9	2	12	3	56.25	83.75
G(+) 5	F	69	3	0	20	11	26.875	29
G(+) 6	M	77	17	0	21	10	26.875	45.75
G(+) 7	F	74	24	13	19	11	21.25	25
G(+) 8	M	56	21	15	14	0	73.125	59
G(+) 9	F	65	20	9	26	8	39.375	45
G(+) 10	F	74	25	13	25	7	36.875	25
G(+) 11	F	61	25	8	17	4	64.375	71.5
G(+) 12	M	66	9	2	12	4	73.125	73.25
G(+) 13	M	71	8	0	5	0	78.125	78.416
G(+) 14	M	76	14	0	25	0	11.875	26.25
G(+) 15	F	60	11	5	25	11	31.25	43.75
G(+) 16	M	61	17	5	17	5	43.125	43
G(+) 17	F	73	23	16	16	7	66.25	77
G(+) 18	F	68	18	0	17	0	70.625	76.5
G(+) 19	F	68	18	0	17	0	70.625	76.5
G(+) 20	M	79	37	16	22	12	16.875	31.375
G(+) 21	F	59	34	14	31	7	5	27
G(+) 22	F	67	13	5	7	5	79.375	83
G(+) 23	F	65	0	0	9	2	80	84
G(-) 1	F	72	12	7	18	6	20.625	24.625
G(-) 2	M	75	6	10	9	5	82.5	72.75
G(-) 3	F	80	30	10	21	19	14.375	27.75
G(-) 4	F	80	11	3	39	21	5	3
G(-) 5	F	69	14	7	13	7	61.25	73.75
G(-) 6	F	72	26	19	22	11	20	42
G(-) 7	F	60	15	8	20	11	35	40.25
G(-) 8	M	55	16	5	0	0	86.25	83
G(-) 9	M	55	32	20	13	7	26.875	36.75
G(-) 10	F	77	17	3	16	11	15	13.5
G(-) 11	M	62	18	10	16	9	35	40.5
G(-) 12	M	56	17	10	20	0	26.725	34.25
G(-) 13	M	45	25	11	7	0	16.825	29.25
G(-) 14	M	67	13	6	11	1	63.125	75.875
G(-) 15	F	81	13	0	13	6	32.5	40.125
G(-) 16	F	40	17	6	16	2	71.25	76.25
G(-) 17	M	79	37	16	22	12	16.875	31.375
G(-) 18	F	77	12	8	30	18	16.875	31
G(-) 19	F	76	22	7	24	1	61.875	77.25
G(-) 20	F	66	14	5	14	7	65	71
G(-) 21	M	67	2	4	15	1	71	84

G(+), HA-CMC solution group; G(-), Control group; ODI, Oswestry Disability Index; RMDQ, Roland-Morris Disability Questionnaire; SF-36, Short-Form 36; PCS, Physical Component Score; MCS, Mental Component Score.

Table 6
Results of functional outcome and between-group difference analyzed

Functional outcome			Control group	Guardix group	Guardix-Control	p value*
Postinjection 6 weeks	ODI		17.57 (13.70, 21.44)	16.91 (13.10, 20.73)	−0.65 (−5.94, 4.62)	0.91
	RMDQ		8.33 (6.03, 10.63)	6.17 (3.66, 8.69)	−2.15 (−5.49, 1.17)	0.13
Postinjection 12 weeks	ODI		17.10 (13.36, 20.82)	17.09 (13.91, 20.25)	−0.00 (−4.72, 4.71)	0.66
	RMDQ		7.38 (4.46, 10.29)	5.35 (3.52, 7.19)	−2.03 (−5.30, 1.23)	0.32
	SF-36	PCS	40.18 (28.44, 51.93)	47.90 (36.65, 59.16)	7.72 (−8.06, 23.50)	0.22
		MCS	48.01 (36.68, 59.33)	54.67 (44.61, 64.74)	6.66 (−7.98, 21.31)	0.31

ODI, Oswestry Disability Index; RMDQ, Roland-Morris Disability Questionnaire; SF-36, Short-Form 36; PCS, Physical Component Score; MCS, Mental Component Score.

NOTE: Data are presented as mean (lower 95% confidence interval, upper 95% confidence interval).

* Mann-Whitney method was performed, statistically Significant with $p<0.05$.

inhibiting the activity of phospholipase A2 (PLA_2) [10,12,27]. Other authors [27,28] have insisted that pain relief is achieved due to direct analgesic effects of the unmyelinated nociceptive C-fiber. Bogduk et al. [20] have explained two possible mechanisms of the long-term effect of corticosteroid injection. First, it could be related to the effect of local anesthetics such as prolonged dampening of C-fiber activity [17]. Second, it could be a physical effect such as clearing adhesions or inflammatory exudates from around the nerve root sleeve. However, they also concluded that data for distinguishing or validating such explanations are needed.

Pain reduction and paresthesia occur at 3–8 hours after injection. After the short pain-relieving period, pain may come back or worsen after 1, 2, or 3 days. This is thought to be due to nerve irritation by needles, contrast media, or corticosteroids injected. As the injected corticosteroid slowly starts to act, the pain is alleviated. The pain occurring at days to weeks after the injection is called "rebound pain". Ko et al. [16] have reported that rebound pain can be successfully controlled by additional HA injection after injection of corticosteroids and local anesthetics.

When medications are injected and spread into the epidural space, they might bathe the painful nerve fibers, thus relieving pain and reducing inflammatory reactions. Moreover, injection of lidocaine might provide immediate pain relief whereas bupivacaine could provide pain relief at 3–6 hours after injection. However, the duration of action remains controversial regarding corticosteroids. Jacob et al. [29] have reported temporary dysfunction of the adrenal cortex for 2–3 weeks after epidural injection of corticosteroids and that the duration of the action of corticosteroids might be approximate to such duration, although such effects are systemic. Therefore, corticosteroids might act from 3 to 5 days after injection and until 2–3 weeks after injection. There is a drug-free period between the time when lidocaine and bupivacaine show action (immediately and 3–6 hours after injection) and the time when corticosteroids show action (3–5 days after injection). Pain occurring at this period is defined as rebound pain. As shown in our study, rebound pain could be effectively controlled by injection of HA. If corticosteroids affect our body for only 2–3 weeks, pain might occur after that. Therefore, the encapsulating property or adhesiveness of CMC might expand the duration of action of local anesthetics and corticosteroids. Pain might also intensify at hours to days after injection due to wash-out of corticosteroids. Since HA and CMC of Guardix-sol◯R can inhibit such wash-out and possess some viscosity, rebound pain occurring at 3 days to 2 weeks after the injection can be effectively controlled. Limitations of this study include its small sample size. Second, normal anatomical variations of patients or differences in the severity of their symptoms were not taken into account. In addition, lack of baseline ODI, RMDQ, and SF-36 preclude assessment of between group differences in baseline to follow-up changes in functional status.

Conclusions

Compared with conventional cocktail of corticosteroids and local anesthetics used for SNRB, addition of HA-CMC solution showed effective control of rebound pain occurring 3 days to 2 weeks after the procedure. Compared with conventional cocktail, results with HA-CMC solution were superior until 2 weeks after the injection. However, such pain relief did not occur until 6 or 12 weeks after injection, showing no significant difference in functional outcomes at 6 or 12 weeks after the injection. Based on such short-term effect, further study is needed to determine the duration of pain reducing effect according to the dose of HA-CMC solution. To date, there is no definite standard for the rate of injection used for SNRB procedure. Thus, new formulation ratio for HA-CMC solution needs to be determined in the future.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.spinee.2018.10.011.

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