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Original Article

Pain Improvement Among Chronic Lumbar Disc Herniation Patients Underwent Epidural Triamcinolone with or without Hyaluronidase Injection within 3 Months of Follow-Up: A Prospective Study

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Abstract

Background : Chronic lumbar disc herniation (CLDH) will accompany by chronic inflammation, so the fibrosis tissues formed in the epidural space and adjacent nerve roots, and lead to mixed pain syndrome. The objectives of this study was to compare between triamcinolone only and hyaluronidase 1500 international unit (IU) administration epidural injection for treating bulged or protrusion CLDH.
Methods : This prospective study involved CLDH patients visiting the outpatient department of Neurology at Dr. Kariadi Hospital Semarang Indonesia from November 2021 until August 2022. They divided: triamcinolone (Group 1) and hyaluronidase 1500 IU and triamcinolone epidural injection (Group 2) with 3 days of hospitalization. Neurotrophic was prescribed during 3 months of follow-up and ordered for personal physical treatment. They analyzed pain improvements (NRS and Pain DETECT), and the Oswestry Disability Index (ODI) scores.
Results : The 37 subjects were recruited but 1 female dropped out cause of re-injection, so 13 males and 23 females aged between 24 to 72 years old (mean 48+2) were followed. They significantly improved (Wilcoxon test p=.000), as the NRS score was 47.9% (Group 1) and 55.4% (Group 2). ODI scores without significance (Mann-Whitney p> .005), such at 2 weeks (group 1= 20.4%, group 2= 23.6%) and 3 months (group 1= 58.1%, group 2= 53.7%). They observed nociceptive and neuropathic improvement even though needed more time for the healing process.
Conclusion : This study proved hyaluronidase administration before triamcinolone epidural injection with better improvements for treating bulged or protrusion CLDH patients.

Keywords : CLDH, nerve compression, fibrosis, pain, triamcinolone, hyaluronidase, epidural injection

INTRODUCTION

Hyaluronidase has been used for chronic inflammation diseases as its ability to inflammation mediators and inflammatory cell interaction. It can prevent many inflammatory processes such are: leukocyte attraction, vascular permeability, and edema formation. So the pro-inflammatory mediators (TNF-α, IL-1b, IL-6), IL-8, and anti-inflammatory cytokines (e.g. IL-10, TGF-b) might interfere after hyaluronidase admission. They are managed in well-regulation so able to protect injured tissues, then promote remodeling processes and re-established the healed tissues.[1] For chronic lumbar disc herniation (CLDH) patients who underwent surgeries, it could be remains of concern, as the post-surgical pain incidence on 40% to 68% even though without radicular pain syndromes find. As post-surgical epidural fibrosis formation can be reached in 20% to 36% of cases. Transforaminal or caudal epidural steroid injections might lead to pain reduction for short or moderate termed. Wherein the addition of hyaluronidase before epidural steroid and local anesthetic then followed by 25 mL normal saline presented better clinical pain improvement.[2] This fact is supported by fibrous or adhesion tissue formation inside the epidural space, so with the chance for adhering of the dura mater and nerve roots. So the tethered dura mater or nerve roots lead to chronic lower back pain.[3] Nowadays, the hypertonic saline 10% is barely applied in accordance caused by potent side effects such are: autonomic nerve system, metabolic formation, cardiac dysrhythmias, paraplegia, or the worst is dead. It can substitute with hyaluronidase 1500 unit initially, then followed by epidural steroid dan normal saline 0.9% for mechanically flushed inflammation mediators with good results.[4] Commonly the transforaminal epidural and serial caudal epidural steroid injections observed of strong for short-term and moderate for long-term reliefs among failed back surgery syndromes (FBSS) patients. The rationale used of hyaluronidase relies upon its ability to disrupt epidural adhesions might be effective for long-term pain relief, either the improvement of the lumbar spine range of motion.[5,6]

The LDH can attribute to tissue's mechanical compression at the lesion sites and accompany the sciatic pain syndrome. And approximately 76% of herniated disc patients are definite by magnetic resonance imaging (MRI) without any symptomatic complaints. Whereas the symptomatic found no correlation between the herniated volume and either severity of symptoms, neurological signs, or degree of disability. This might be explained that the chemical radiculopathy origin from inflammatory substances released due to annular tears in the disc fibrous ring playing a role in the pain present.[7] The intervertebral disc (IVD) is contained in the nucleus pulposus (NP), which is involved in immunoreactivity action when penetrating epidural space. Surrounded vascular might change its endothelial cell then lead to a permeability increase, so vasodilatation happened and the tissue's adhesion processes have been started. However the inflammatory cells may be collected and found at the herniated disc sites, such are cyclooxygenase-2 (COX-2), follistatin-like protein-1 (FSTL-1), and tumor necrosis factor-alpha (TNF-α). Administrated steroids into epidural space might give benefits for 80% to 90% to avoid surgeries for 1year of follow-up.[8]

Hyaluronidase is a water-soluble enzyme that is made of tissues rendered more permeable to fluids traveled through within. It can improve traumatic swelling, lesion site(s) edema formation, or absorption improvement.[9] This hyaluronidase is commonly administrated for treating failed back surgery syndromes (FBSS) with valuable outcomes. And by using intra epidural diluted with normal saline 0.9% then followed by steroid injections, could be separate the adhesion tissue as well as hypertonic saline. Whereas the hypertonic saline intraepidural injection can cause hypertension, dysrhythmias, or tachycardia, the opportunity of pulmonary edema, nerve disorders, increasing intracranial pressure, or event of death even though with small numbers.[10] CLDH is accompanied by common adjacent fibrosis tissues at the lesion site(s). This study is to investigate the comparison between caudal epidural steroid (triamcinolone) injection only and by adding hyaluronidase initially with a single treatment among bulged and protrusion of chronic LDH. They will be evaluated for pain improvement for a 3-month follow-up or intermediate term. Whereas commonly a 1-year follow-up underwent of epidural steroid injection might improve approximately 36% to 43% of patients.[11]

METHODS

This study is accepted for Ethical Approval by Health Research Ethics Committee RSUP Dr. Kariadi Semarang No. 1015/EC/KEPK-RSDK/2022 on 17 January 2022. The study involved CLDH with bulged and protrusion stages subjects, who were selected and collected by consecutive sampling in the outpatient Neurology department in Dr. Kariadi Hospital Semarang in Indonesia. The procedures have proceeded in the operation theater facilities under fluoroscopy guidance, and assisted by radiograph and operation room crew Subjects were prone lying on the operation table initially, then prepared for vital signs monitor with a pulse oxymeter and automatic tensimeter kit. The aseptic dropping was performed on the lower back to the sacrum area and covered by sterile clothes. The posteroanterior view will be presented of ilium and sacrum bones, also the sacral hiatus above of coccygeus or according to sacral level four in lateral view. A 3mL of lidocaine 2% was

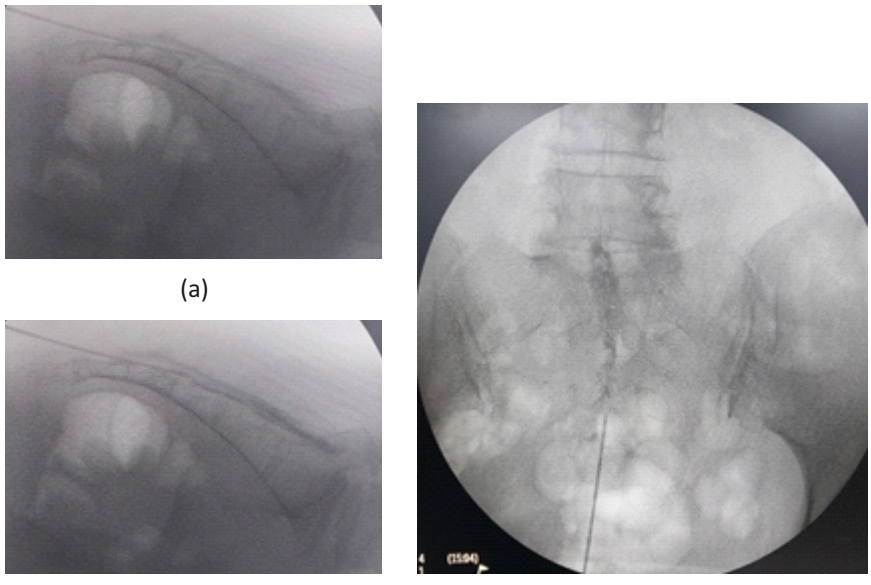

Figure 1. The caudal epidural steroid injection was performed under fluoroscopy guidance: lateral view **(a)** epidural Tuohy needle reach below of S2 vertebra level, **(b)** dye contrast injection flew within sacral epidural space, and posteroanterior view **(c)** dye contrast spreads and filling the non-compressed site (Filling Defect) likely "Christmas Tree" appearance.

injected as a local anesthetic near the entry point o the sacral hiatus, then followed by epidural Tuohy with the tip should be placed below S2 or just above S3 level. A 1 or 2 mL of Iopamiro dying contrast was injected for sure that reached into sacral and lower back epidural space. They divided into 2 groups: Group 1 as control and Group 2 with hyaluronidase interventions. Group 1 is performed of triamcinolone 40 mg/ mL in dilution with lidocaine 2% 2 mL and normal saline 0.9% 2 mL (total 5 mL), then let in 10 minutes before flushing by normal saline 0.9% 10 mL. Group 2 performed of epidural caudal injection of 1500 international unit (IU) hyaluronidase diluted in 10 mL of normal saline 0.9%, then let for 10 minutes and continued with triamcinolone 40 mg/ mL in dilution with lidocaine 2% 2 mL and normal saline 0.9% 2 mL (total 5 mL) under fluoroscopy guidance (Figure 1). The total volume of epidural injection, include with the dye contrast, is not more than 20 mL for preventing potential intracranial pressure increase. The medications were prepared by the operation nurse assistant nurse, so the agents of drugs were administrated without being recognized by the patient or the injection-performing physician. Subjects will stay for at least 30 minutes in the recovery room later for post injections observational purposes, then send back to their inpatient room department for 24 hours hospitalized. Post injections medication prescribed of levofloxacin 500 mg/ day for 4 days, and paracetamol 500 mg/ 8 hours for 5 days. While thiamine 50 mg/ 12 hours, B12/ 12 hours, and folic acid 1 mg/ 12 hours are given for 3 months as neurotrophic medications. The study is running from periods November 2021 until August 2022. This is a prospective study that analyzed pain improvement after having had analgesics prescription and conservative treatments without satisfaction.

They were followed up to determine the degree of pain relief by NRS (1-3 = mild pain, 4-6 = moderate pain, 7-10 = severe pain) and Pain DETECT (0-12 = nociceptive pain, 13-18 = mixed pain, 19-38 = neuropathic pain) scores parameter. Subjects are ordered for personal physical therapy by performing external rotation movements to the right and left in a relaxed manner in a lying position on the bed and knees flexed. This movement is performed for 30 counts and 4 cycles a day, to relax the paravertebral muscle spasm and floss the adhesion tissues inside the epidural space. This personal treatment should perform for 3 months of follow-up, so they might be in the same physical treatment applied. Failure in treatment was defined as continuous pain requiring intervention or to the extent the patient had to request additional injections or surgery.

RESULTS

Initially, this study is followed by 37 subjects CLDH, but 1 subject refused cause of her need for more analgesics prescription during 3-month followed-up. So, 36 subjects who agreed to participate are planned for intervention by 3 days hospitalized at Dr. Kariadi Hospital Semarang in Indonesia (Figure 2). They consisted of 13 males and 23 females, ages between 24 to 72 years old (mean 48±2). The pain observed reduced in both groups at 3 months

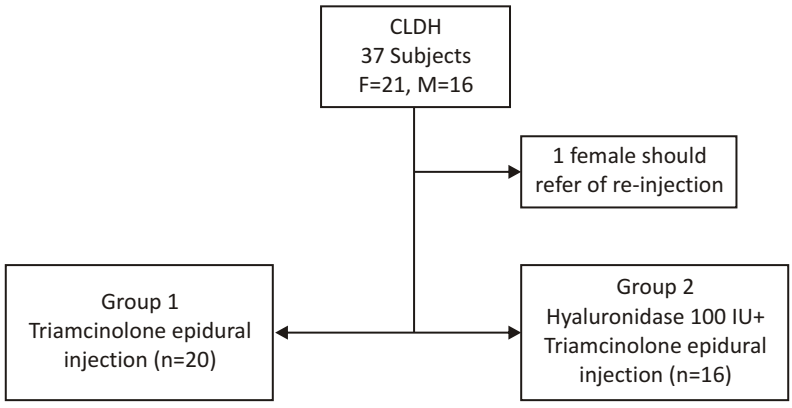

Figure 2. Subjects are recruited the study

TABLE 1
Descriptive monitoring of pain improvement in each group

Variable		Group 1		Group 2	
		(Mean±SD)	Median (Min–Max)	(Mean±SD)	Median (Min–Max)
NRS Scores	Before interventions	4.9±0.788	5 (4–6)	4.75±0.85	5 (3–6)
	at 2 weeks	3.35±0.74	3 (2–5)	3.31±0.47	3 (1–4)
	at 3 months	2.55±0.68	3 (1–4)	2.12±0.61	2 (1–3)
Pain DETECT	Before interventions	25.3±4.99	26 (14–38)	26.56±5.93	27 (18–37)
	at 2 weeks	19.25±2.91	20 (12–24)	21.81±4.26	20 (16–30)
	at 3 months	19.8±4.2	19 (12–28)	20.31±3.34	20 (14–28)
ODI	Before interventions	47.25±7.01	46 (38–68)	43.87±5.08	44 (34–54)
	at 2 weeks	38.0±6.15	38 (26–50)	33.5±4.81	24 (24–44)
	at 3 months	19.8±4.2	19 (12–28)	20.3±3.34	20 (14–28)

follow-up, as the NRS score improved by 47.9% in Group 1 and 55.4% in Group 2 (Table 1). And statistically observed with significance for both groups (Wilcoxon test, p= .000) in comparison of before and 2 weeks or 3 months of follow-up (Table 2). The pain improvement without statistical significance between Groups 1 and 2 at 2 weeks and 3 months of follow-up (p> .005) (Table 2). There was no significant differentiation of age and pain intensity improvement among both groups at 2 weeks and 3 months of follow-up (p> .005) (Table 2). Pain DETECT score is commonly used to evaluate the neuropathic pain modalities, which founds significant improvement among both groups at 2 weeks of follow-up (p< .005), and at 3 months of follow-up observed without significant (p>.005)(Table 2). Oswestry Disability Index (ODI) with improvement in both groups, as of week 2 showed a reduction of approximately 20.4% (Group 1) and 23.6% (Group 2) while at 3 months 58.1% (Group 1) and 53.7% (Group 2). But statistically without significance on both (Mann-Whitney p> .005). This study showed that subjects suffering from CLDH might observe nociceptive and neuropathic component improvement after epidural triamcinolone or epidurolysis injection.

DISCUSSIONS

Pain syndrome measurements might need detail and personalized, as pain is quite involved subjective responses. The nociceptive pain rises from inflammatory processes and might represent by NRS scores, whereas the Pain DETECT scores for evaluating the neuropathic pain involvement represent nerves injured. It seemingly represents comprehensive neuropathic pain syndromes with a sensitivity of 85% and specificity of 80%.[12,13] Both groups have shown NRS and Pain DETECT

TABLE 2
Statistical analysis

		Group 1	Group 2	All groups
NRS scores (Wilcoxon Signed Rank test)	Pre vs 2 weeks	.000*	.000*	.000*
	Pre vs 3 months	.000*	.000*	.000*
(Mann-Whitney test)	Pain improvement at 2 weeks	–	–	.694
	Pain improvement at 3 months	–	–	.422
Ages ≤50 dan >50 years	2 weeks	–	–	.888
	3 months	–	–	.355
Pain DETECT scores (Wilcoxon Signed Rank test)	Pre vs 2 weeks	.000*	.001*	.000*
	Pre vs 3 months	.005	.006	.000*
(T-test)	Pain improvement at 2 weeks	–	–	.290
	Pain improvement at 3 months	–	–	.898
Ages ≤50 dan >50 years	2 weeks	–	–	.255
	3 months	–	–	.628

*: significant results (p< .005)

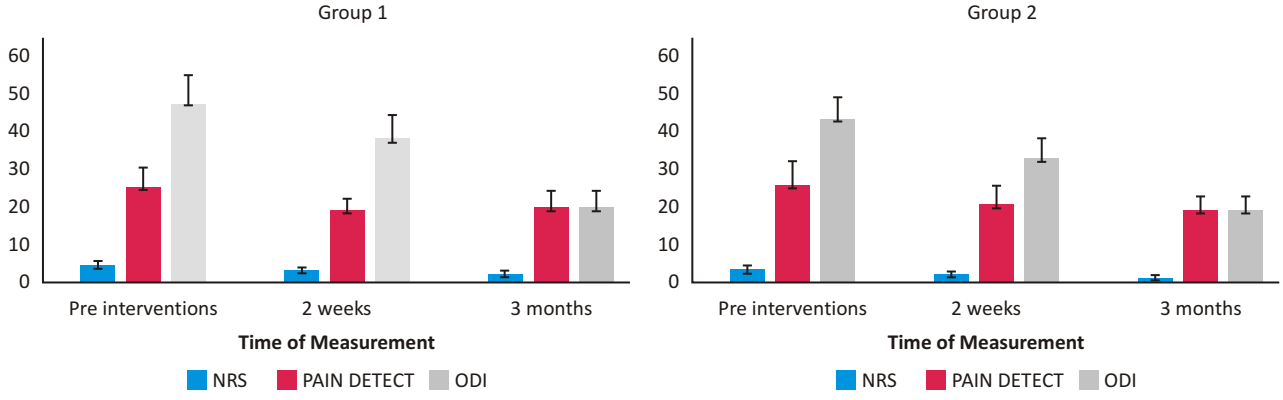

Figure 3. Pain improvement graphic of Groups 1 and 2

improvement at 2 weeks and 3 months after procedures treatment. It means the epidural steroid injection might treat both nociceptive and neuropathic pain too. A sprouted nerve founds inserted into the annular layer that leads to neuropathic pain symptoms, as the nerve ending will transmit the pain impulses to the central nerve system (CNS). It might so a common find in CLDH or degenerative disc diseases, so in this study even though leads to improvement but neuropathic pain remains. Meanwhile, a chronic state of LDH will initiate vascularisation interfered, so local ischemic tissues appeared, then anaerobic metabolism occurs. Otherwise, this hypoxic state on adjacent tissues might lead to hyperacidity environments, so the action potentials immediately appear and pain impulses are transmitted. The advanced step might present demyelination nerves that play role in neuropathic pain or radiculopathy syndromes.[7,14] An animal study of the CLBP model showed an alteration of nerve conduction velocity (NCV) which was detected by electrophysiological examination or disrupted of blood and also the cerebrospinal liquid circulation due to epidural fibrosis formation.[15,16] Intraepidural space adhesion or fibrosis formation was found in chronic LBP (CLBP) due to LDH, as in association with repetition trauma, tears on annulus fibrosis ring surface, hence leading to tethered compression at the nerve roots or adjacent structures. Herniated disc materials could be irritating on the dural sac and lesion sites around the nerve roots.[8] The herniated disc materials lead to glutamate release which induced the inflammatory response and root compression without traumatic spine experience. These alterations

might lead to gradual adhesion or fibrosis inside the epidural space, and it can be clinically examined with a dural tug maneuver. This maneuver is performed by sitting position on the bed and both legs lying down accompanied with anteriorly flexed, so can reach of toes. When the adhesion or fibrosis tissues inside the epidural space are presented, patients might feel paravertebral muscle spasms.[3,8,17] By performing the right and left external rotation movements on the bed and knees flexed, could be optimizing of the nerve roots sleeved movement. Thus the sticky tissues due to fibrosis formation can be released more, and the pain will reduce. The aging process seemed not related to the severity of the pain symptoms among CLDH patients. It is based on the degeneration process accompanied by aging accompanied by the reduction of inflammation and volume or atrophy of the disc tissues. It can cause herniated disc compression might be reduced.[18] The physical treatments addressed after epidural steroid injections or surgical might improve clinical outcomes, such are leg or radicular pain or daily activities.[19] Paravertebral structures might an essential for improving back pain, such are deep abdominal muscles, superficial muscles, transversus abdominis, and multifidus. This can improve vertebral stability in either of the pain origins. Hip muscle strengthening accompanied by lumbar stabilization could be helped with pain improvement for at least 3 weeks. The hip is frequently compensation affected while the lower back pain syndromes remain.[20]

Pain impulses might transmit going to the central nerve system (CNS) through the terminals pathway, the dorsal root ganglion (DRG) first receives pain afferent fiber of nociception. Lidocaine is a local anesthetic drug that blocked pain transmission by interfering with voltage-gated ion (Na+, K+, and Ca2+) channels. It was blocked on voltages-gate Na+or sodium channels (VGSC) then nerve excitability and potential actions reduce. Postsynaptic neurons in DRGs were influenced by K+ ion channels and the excitability might reduce when blocked by lidocaine. It also play the role in Ca2+intracellular and extracellular regulation, so the sensory and nociceptive transmission remains controlled by blocked depolarization states. Lidocaine properties can reduce spinal hyperexcitability and pain behaviors involved in chronic pain development. Meanwhile, epidural space administration could interfere with the firing of pain sensation and potential actions presented, and the DRG membrane hyperpolarized during inflammation states can be reduced.[21,22] Glutamate is the main excitatory neurotransmitter that the production of the presynaptic terminal might inhibit by lidocaine. The expression of the proinflammatory, cytokines interleukin-1b, interleukin-6, and tumor necrosis factor-α (TNF- α); might reduce after lidocaine is administrated so improving the inflammation and pain sensation. Similarly, the lidocaine administration through the epidural space might have these beneficial effects as its lipophilic agent.[21,23] Epidural steroid injection has often been applied as a therapy for LDH, either through transforaminal, interlaminar, or caudal epidural approaches even though they might relapse within 2 weeks later (35%). But others might be effective in pain improvement moderately until 2 or 9 months. The transforaminal approach could have better results than others, as approximately 25% to 57% for the long-term and 50% to 75% for a temporary duration. Around 45% to 50% of patients might feel pain recurred at 3 months later. This could be caused by a limitation of steroid action duration of around 2 to 3 weeks and can be interfered with by chronic inflammation. The fibrocyte proliferation collected collagen around the lesion site(s), or even a cicatrization around the nerve roots could be obstructed the flow of drugs.[24] All subjects with moderate disabilities regard Oswestry Disability Index (ODI) scores initially compared to post-injection. Epidural steroid injection among LDH or nerve roots compression patients commonly with post-surgical improvement following ODI scores improvement within the short or long term of 1-year follow-up.[11,25]

This study with similarities mentioned the effectiveness of pain improvement underwent epidural steroid injections at 3 and 6 months follow-up.[26] The nociceptive pain rises from inflammatory processes and might represent by NRS scores, whereas the Pain DETECT scores for evaluating the neuropathic pain states. Both groups have shown NRS and Pain DETECT improvement at 2 weeks and 3 months after procedures treatment. It means the epidural steroid injection might promote both nociceptive and neuropathic pain too. A sprouted nerve founds inserted into the annular layer that leads to neuropathic pain symptoms, as, the nerve ending will transmit the pain impulses to the central nerve system (CNS).[27] After inflammation happened will be followed by peripheral vasodilation, edema, fibrin deposition, white blood cell agglutination, and phagocytosis. Thus in a long-termed period might lead to peripheral vascular and fibroblast proliferation, the collagen collected and adhesion or fibrosis tissue formation occur at the lesion site(s). Sodium channels at the nerve roots affected might express, which facilitate pain impulses transmitted and mechanically more sensitive. The cytokine mediators accumulated around the lesion site(s) and adjacent nerve roots, then the nerve function could be easily excited by even a very weak stimulus.[9] Meanwhile, a chronic state of LDH will initiate vascularization interfered, local ischemic tissues happened, then anaerobic metabolism occurs. Otherwise, this hypoxic state on adjacent tissues might lead to hyperacidity environments, so the action potentials immediately appear and pain impulses are transmitted.[7] Fibrosis or adhesion tissue might exist at the lesion site(s) during the chronic inflammation process, so provoked

pain triggered by sticky tissue due to fibrosis inside epidural space, and will obstruct antiinflammation drugs. This study showed of the NRS score's gradual improvement was better with hyaluronidase administration or epidurolysis group at 2 weeks and 3 months post surgeries (Table 1). Even though the statistical analysis observes not significant, descriptively the improvement might be better (Figure 3). This fact might be supported the hypothesis that hyaluronidase administration with better outcomes as compared to epidural steroids alone for treating bulged and protrusion LDH. Thus with better triamcinolone flow inside the epidural space, the pain and neurofunctional improvement too. Triamcinolone with the mechanism of action antiinflammation in the long term when administration intra epidural space for managing LDH, which sprouted nerve on the annular surface so neuropathic pain present.[28] Adding 1500 IU of hyaluronidase is referred to hydrolysis mechanism on glucosamine bonds and connective tissues mucopolysaccharides. It can reduce and prevent fibrosis or scar tissue formation around. Then particularly improve the compressed os lesion site(s), nerve root sleeves moved easily within the neuroforamen, and local circulation more smoothly. Other than that steroid drugs can be spread and flow more in the epidural space.[9] It means that hyaluronidase might help optimize antiinflammation or analgesic drugs spread reach to the target site(s) better.

CONCLUSION

We realize that more numbers of the subject involved, or duration of follow-up might give good comprehensive results. This study is originally following stages 1 (bulged) or 2 (protrusion) of chronic LDH with better outcomes with hyaluronidase administration before triamcinolone epidural injection. And by the performing through of caudal epidural space also develop pain improvement. For treating chronic disc herniation, thus hyaluronidase might give a better outcome for bulged or protrusion disc herniation.

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