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ORIGINAL RESEARCH

EPIDUROLYSIS IS A PROMISING TREATMENT FOR STAGE I-II LUMBAR DISC HERNIATION AT THE THREE-MONTH FOLLOW-UP

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Abstract

Introduction: About 90% of patients with lumbar disc herniation (LDH) improve with conservative treatment, while 10–19% require surgery. Epidural steroid injection (ESI) with local anesthetic provides pain relief for up to 6 months (30–40%) and up to 1 year (68.5%). Epidurolysis, using 1500 units of hyaluronidase before ESI, is often applied in patients who continue to experience pain after spinal surgery. This study compares pain intensity and activities of daily living (ADL) in Stage I–II LDH patients treated with either epidurolysis or ESI.

Methods: This experimental study used a pre- and post-test control group design. Patients with Stage I–II LDH at Dr. Kariadi Hospital, Semarang, were divided into two groups: epidurolysis and ESI. NRS, Pain DETECT, and ODI scores were evaluated before treatment, at Week 3, and at Month 3, then compared across observation times.

Results: From January to August 2022, 161 patients met the inclusion criteria: 84 received epidurolysis and 77 received ESI. Eighteen participants dropped out. Significant improvements in NRS, Pain DETECT, and ODI scores were observed up to Month 3 ($p < 0.05$). The epidurolysis group showed greater improvement, with lower NRS (1.21 ± 0.50 vs 1.51 ± 0.53), Pain DETECT (8.61 ± 2.66 vs 12.17 ± 2.78), and ODI (4.72 ± 3.34 vs 8.51 ± 3.67) scores. Demographic factors had no significant effect on ADL changes.

Conclusion Hyaluronidase reduces fibrosis and edema, enhances triamcinolone absorption, and may improve nerve recovery. Adding 1500 units of hyaluronidase before ESI results in better pain relief and functional outcomes in Stage I–II chronic LDH patients.

Keywords: Stage I-II LDH, triamcinolone, hyaluronidase, NRS, Pain DETECT, ODI

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Introduction

Some studies suggest that around 5% of adults experience low back pain (LBP), which can interfere with daily activities. LBP most commonly affects people aged 30–50, with an equal prevalence among men and women. Direct trauma (including repetitive microtrauma) and poor posture are risk factors for LBP. Over time, these factors can lead to non-physiological changes in the structures of the lower back, including a herniated nucleus pulposus (HNP).[1] The prevalence of stages I and II lumbar HNP is 25–30% in

the 20-year-old age group, reaching 84% in the 80-year-old age group. Common symptoms include pain resulting from compression of nerve structures.[2] Patients with lumbar HNP are managed in one of two ways: Conservative or surgical management. The aim is to repair the affected structures and address the inflammatory process. Available data indicates that approximately 90% of patients with lumbar HNP show good clinical improvement with conservative management, while the remaining 10–19% require surgical intervention.[1,2] Conservative management involves administering analgesic drugs and/or physical therapy, bearing in mind the potential side effects of long-term drug prescriptions. Surgical management involves decompression, i.e. reducing pressure on the nerves (e.g. laminectomy), whereas non-surgical invasive management involves procedures that do not require surgery (e.g. epidural steroid injections). The choice between operative and non-operative invasive management is generally made when conservative management fails to reduce pain by more than 50%, or when there is progressive neurological deterioration. Two years after the procedure, surgical management achieves greater clinical improvement than conservative management for patients with lumbar HNP. However, satisfactory pain relief is often not achieved in patients over the age of 60.[1,2]

An epidural steroid injection (ESI) combined with local anaesthesia is a treatment for lumbar disc herniation (LDH). Several studies have shown that this treatment alleviates pain by inhibiting pro-inflammatory agents such as neuropeptides, hydrolase acids, phospholipase A_2, histamine and kinins. Local anaesthesia also reduces nerve root sensitivity to irritants. Previous research has concluded that the ESI procedure is 30–40% effective in the short term (up to six months), with around two-thirds of patients experiencing positive results for up to one year after the injection. The ESI procedure has been shown to reduce pain caused by compression and inflammatory mechanisms. An increase in inflammatory mediators, including tumour necrosis factor (TNF)-α, interleukin (IL)-6, interferon (IFN)-γ and IL-4, has been observed in cases of intervertebral disc degeneration. Additionally, TNF-α and nitric oxide (NO) levels in the nucleus pulposus (NP) increase. Intraepidural steroid administration has been shown to reduce inflammatory mediator levels and decrease pain intensity in patients with LBP. Intraepidural hyaluronidase injections, administered prior to ESI and also known as epidurolysis, have been shown to prolong the therapeutic effects of steroids in patients with chronic LBP. Clinical pain improvement exceeding 50% has been demonstrated at 3, 6, and 12 months post-treatment. This hyaluronidase preparation has been shown to reduce tissue adhesions by breaking the glucosamine bonds that connect hyaluronic acid to the intracellular matrix and connective tissue. It also reduces fibrosis in these tissues. Additionally, hyaluronidase decreases tissue oedema and increases tissue permeability to injected drugs.[2-4]

Kim et al. concluded that, for patients with postoperative LBP,

administering 1,500 units of hyaluronidase intraepidurally alongside triamcinolone and a local anaesthetic resulted in better clinical improvement than triamcinolone and a local anaesthetic alone at week 12, as measured by VAS and ODI scores. This is based on the pain mechanism, which involves mechanical factors (such as compression) and root irritation, as well as inflammatory processes. During inflammation, peripheral vasodilation, oedema, fibrin deposition, leukocyte agglutination, phagocytosis, and other processes occur. Prolonged inflammation can cause the proliferation of peripheral blood vessels and fibroblasts, the deposition of collagen matrices and the formation of scar tissue, which can increase by up to 25% at any given time.[5-7]

This epidurolysis method has previously been used to treat chronic LBP (CLBP) and failed back surgery syndrome (FBSS) in patients who have undergone spinal surgery. The procedure involves breaking up tissue adhesions to alleviate pain.[5,8,9] However, it has never before been used to treat chronic lumbar HNP.[4,8,9] The aim of this study was to determine whether epidurolysis and ESI differ in their effectiveness in improving clinical pain, activities of daily living (ADLs), and inflammatory mediators.

Materials and Methods

This randomised controlled trial (RCT) is an experimental intervention study with a pre- and post-test control group design. All participants were examined at the Neurology Outpatient Clinic and enrolled via the Fast Track Service. They were admitted to Dr. Kariadi Hospital in Semarang the day before their procedure and discharged the day after. Inclusion criteria included magnetic resonance imaging (MRI) showing stage I–II lumbar disc herniation (LDH) with posterior compression, back pain for at least three months indicating chronicity, and no history of spinal surgery, hypersensitivity to contrast dye, systemic infectious disease, vertebral compression fracture or scoliosis. Participants also had to sign a personal agreement to take part. Participants were divided into two groups: the epidurolysis group and the steroid group. The following data were collected on each subject: age; gender; race; occupation; vital signs; weight and height (including BMI); symptom duration; and analgesic treatment history. These data were analysed for both groups after the intervention, including Numerical Rating Scale (NRS) scores, Pain DETECT scores, and Oswestry Disability Index (ODI) scores at pre-intervention, week 3, and month 3. The data were then statistically analysed using the SPSS programme. The study protocol was approved by the RSUP Dr. Kariadi Semarang Health Research Ethics Committee (1015-I/EC/KEPK-RSDK/2022).

An experienced pain and minimally invasive neurologist performed the epidural intervention under C-arm guidance and with the use of local anaesthesia. Prior to the procedure, the patient underwent a routine blood test, with particular attention paid to coagulation studies. Vital sign monitors were used correctly, and a 0.9% normal saline infusion was administered alongside

a pre-medication injection of 1 g of cefazolin. Aseptic and sterile surgical drapes were placed around the entry point through the caudal epidural space. Once the hiatus had been revealed by the C-arm approximately 1 cm below, 2% lidocaine local anaesthetic was injected. The epidural spinal Tuohy needle was then inserted via the hiatus. Under C-arm guidance, it was confirmed that the needle had not penetrated beyond the Sacral 3 (S3) level. This was a precaution against penetrating the dural sac underneath. Three millilitres of iopamiro contrast dye were then used to ensure precise penetration of the epidural space, as indicated by the 'Christmas tree' landmark on the C-arm (Figure 1). Next, 1,500 units of hyaluronidase in 10 ml were passed through the needle. This was left for ten minutes to allow it to spread and be absorbed into the epidural space. A further 1,500 units of hyaluronidase in 10 ml were then passed through the needle. This was left for a further ten minutes to allow it to spread and be absorbed into the epidural space. This was followed by the administration of 20 mg of triamcinolone in 4 ml. The space was then flushed with 5 ml of 0.9% normal saline to aid absorption. The steroid group received the same treatment: a 20 mg triamcinolone injection in 4 ml, followed by flushing with 10 ml of 0.9% normal saline. Following surgery, levofloxacina (500 mg every 24 hours for five days), vitamin B12 (50 µg every eight hours for five days) and paracetamol (500 mg every eight hours for five days) were prescribed. Vitamin B12 may be prescribed continuously during follow-up until the third month.

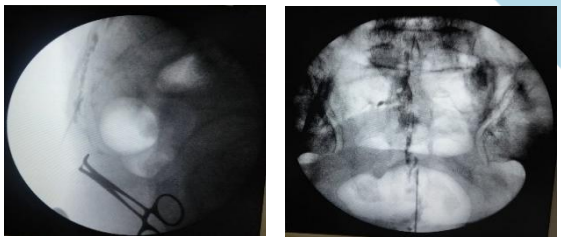

Figure 1. The main procedure performed on the groups was caudal epidural triamcinolone 20mg injection.

Results

A total of 161 participants, ranging in age from 18 to 79 years old (mean age: 50.28 years; standard deviation: 14.65 years), took part in this study. They were divided into two groups. The epidurolysis group comprised 84 participants (29 males and 43 females) aged between 18 and 78 years (mean age: 49.98 years; standard deviation: 13.09 years). The epidural steroid injection (ESI) group comprised 77 participants (28 males and 43 females) aged between 19 and 79 years (mean age: 50.58 years; standard deviation: 16.21 years). The mean BMI of all subjects was 24.54 (24.77 ± 2.36), compared to 24.69 (24.91 ± 2.50) for the epidurolysis group and 24.31 (range 20.83–30.86; mean ± SD 24.63 ± 2.21) for the ESI group. Eighteen subjects were excluded from the study because they failed to attend the three-month follow-up appointment. The Kolmogorov–Smirnov normality test is significant when the *p*-value exceeds 0.05. (Table 1)

Both procedures demonstrated clinical improvement. However, significant differences in changes to nociceptive and neuropathic pain intensity were observed between the pre-intervention period and week 3, and between week 3 and month 3, in both intervention groups ($p < 0.05$).

These changes were measured using the Numeric Rating Scale (NRS) for nociceptive pain (see Figure 2) and the PainDETECT questionnaire for neuropathic pain (see Figure 3). Additionally, changes in activities of daily living (ADLs), as evaluated by the Oswestry Disability Index (ODI) score, differed significantly between the epidurolysis and ISE groups. These differences were evident in the pre-intervention and week 3 assessments, as well as in the week 3 and month 3 assessments following the intervention (see Figure 4). The findings of this study suggest that both interventions led to significant reductions in nociceptive and neuropathic pain intensity over time, as reflected by improvements in NRS and PainDETECT scores. These results imply that epidurolysis and ISE are both effective in alleviating mixed pain components in patients with chronic low back pain.

Analysis of the relationship between changes in NRS (Numeric Rating Scale) and ODI (Oswestry Disability Index) scores revealed a significant positive correlation throughout the study period. In other words, as patients reported higher pain intensity on the NRS, their level of disability, as measured by the ODI, also increased. However, this pattern was not observed with the PainDETECT score, which showed no significant correlation with the NRS. Furthermore, the strength of the relationship between NRS and ODI scores varied over time. Before the intervention, the correlation was moderate, indicating a fair link between pain intensity and disability. By the third week after the intervention, the correlation had strengthened, suggesting that changes in pain levels were more closely associated with changes in disability at this stage. However, by the third month after the intervention, the correlation had weakened again, suggesting that the connection between pain and disability becomes less direct in the long term (see Table 2).

Table 1. Characteristics of subjects with grade I–II lumbar disc herniation

		Epidurolysis	ESI		*p* value
Sex	Male	29	28	X^2 = 0,11	p = 0,918
	Female	43	43		
BMI	Normoweight	5	3		
	Overweight	29	39		
	Obese	38	29		
Age	≤ 50 years old	28	23	X^2 = 53,989	p = 0,398
	> 50 years old	44	48		

Table 2. Shows the results of the Spearman's correlation test, which demonstrates the relationship between NRS, Pain DETECT and ODI scores.

	rho	*P* values
NRS-ODI		
Pre Intervention	0.344	0.003*
Week-3	0.574	<0.0001*
Month-3	0.258	0.029*
***Pain DETECT*-ODI**		
Pre Intervention	0.021	0.863
Week-3	0.068	0.571
Month-3	0.132	0.270

Note : *Spearman's correlation test showed significant when *p* values < 0.05

This study found that changes in ADL were not significantly affected by gender, age, educational attainment, occupation or BMI. However, subjects with a normal BMI tended to have lower ODI scores than overweight or obese subjects.

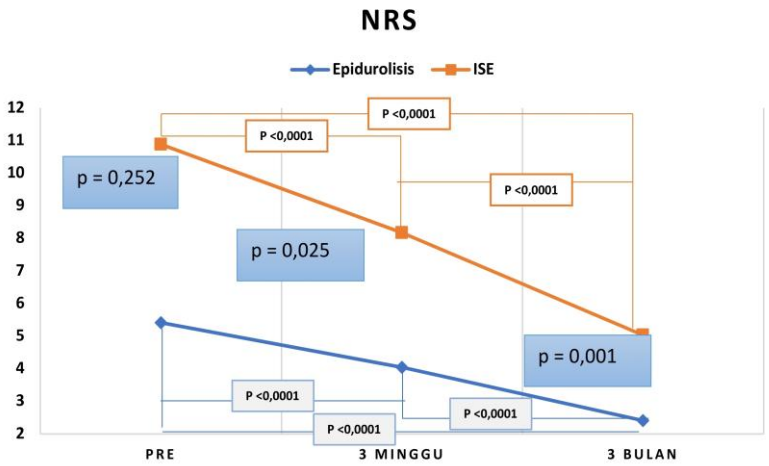

Figure 2. Shows the changes in reported nociceptive pain intensity (NRS) experienced by the epidurolysis and ESI groups over three months following the intervention.

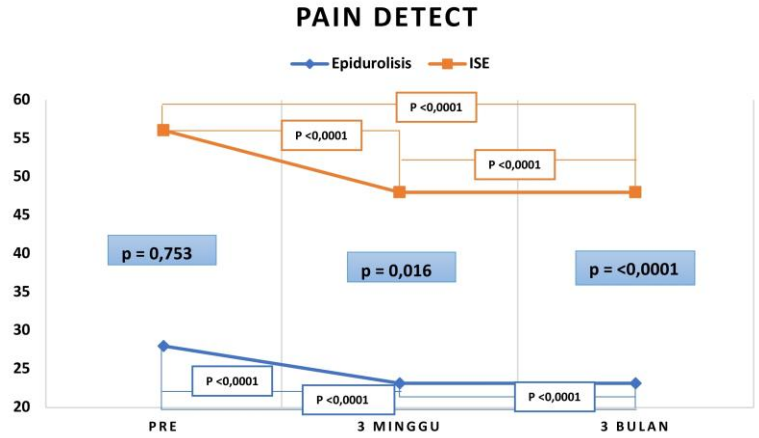

Figure 3. Shows changes in neuropathic pain intensity (Pain DETECT score) in the epidurolysis and ESI groups up to three months after the intervention.

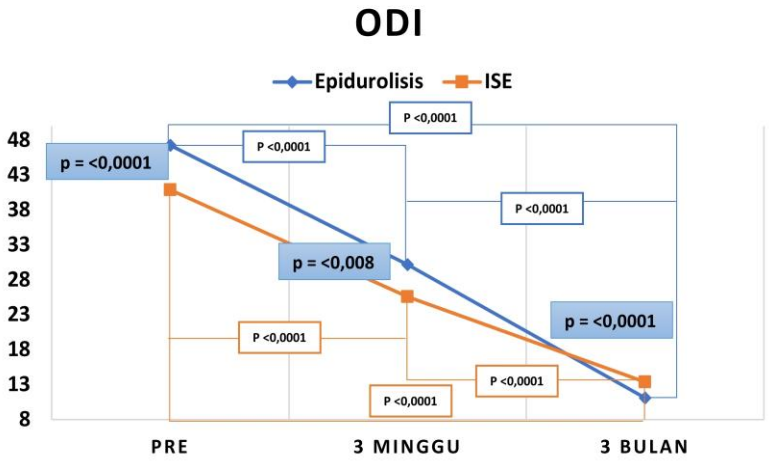

Figure 4. Shows the changes in daily activities (ODI score) experienced by the epidurolysis and ESI groups in the three months after the intervention.

Discussion

Triamcinolone is a slow-release steroid particle which has been shown to reduce inflammatory mediators effectively in the epidural space. Although the 20 mg intraepidural dose of triamcinolone used in this study is considered low, it still provides effective anti-inflammatory and analgesic effects.[10] This is because the effectiveness of the therapy depends on accurately identifying the location of the lesion causing the inflammation and pain rather than on the size of the drug dose.[11]Studies have also demonstrated that steroids can break down scar tissue, suppress electrical discharges from the lesion site and the dorsal root ganglion (DRG) and improve blood circulation in the periradicular area.[11] Previous studies have shown that the ISE procedure through the sacral hiatus effectively reduces pain intensity and improves quality of life with regard to activities of daily living (ADLs). In this study, no cases of hypersensitivity or allergy to 1,500 units of hyaluronidase (Epidurolysis Group) were observed, given that the incidence rate is low (one in 2,000 cases) and the half-life is short (two to three minutes in plasma).[12]

In this study, several subjects in both the epidurolysis and ESI groups with stage I–II lumbar HNP were classified as overweight or obese. Compared to normal-weight subjects, those who were overweight or obese exhibited a moderate correlation with disability and chronic LBP syndrome (47.2%). A higher BMI tends to cause chronic inflammation and exacerbate pain in patients.[13,14] However, this study found no significant difference in BMI between the epidurolysis and ESI groups.

Studies have shown that administering steroids can alleviate nociceptive and neuropathic pain within six to twelve weeks of injection into the spinal cord.[15,16] Local anaesthesia can block nociceptive impulses and reduce chronic pain sensitisation at the peripheral level. Therefore, combining steroids with local anaesthesia can prolong the effectiveness of analgesic therapy. In addition to their anti-inflammatory properties, steroids inhibit peptide synthesis and phospholipase A2 activation. They reduce nerve impulse bursts and peripheral sensitisation in the dorsal horn of the spinal cord. They also play a role in stabilising nerve cell membranes. The inflammatory process is often associated with the acute phase of radicular pain in patients with HNP. However, pro-inflammatory cytokines (IL-6, IL-8, TNF-α and IFN-γ) play a role in the chronic inflammatory process characterised by tissue fibrosis in patients with chronic HNP. These cytokines are found in cerebrospinal fluid (CSF). Herniated or degenerated disc lesions trigger the release of these pro-inflammatory cytokines, thereby prolonging the inflammatory cascade and hyperalgesia symptoms in patients with chronic HNP.[17] The Pain DETECT score for neuropathic pain syndrome (score >19) showed improvements of up to 30% within 12 months of dexamethasone and local anaesthetic administration.[18] Significant changes in nociceptive (NRS) and neuropathic (DETECT) pain scores were observed in the epidurolysis group compared to the ESI group three months after the intervention. It was concluded that hyaluronidase reduces local oedema and

dysregulation of nerve communication in the extracellular matrix, thereby inhibiting pain impulses.[19,20] Improvements in neuropathic pain intensity (Pain DETECT score) and ability to perform activities of daily living (ODI score) were observed in both groups. However, the epidurolysis group showed greater improvement in neuropathic pain than the ESI group.

Nevertheless, neuropathic pain syndrome persisted after hyaluronidase administration at three months, possibly due to the large size and viscosity of the preparation. This resulted in persistent hyperpolarisation due to particles remaining in the epidural space and stimulating action potentials.[21] Studies on animals observing lumbar intervertebral disc (IVD) degeneration have shown that administering hyaluronidase reduces hypersensitivity and pain transmission on the IVD surface.[22] Hyaluronidase has also been shown to reduce the release of pro-apoptotic mediators and insulin-like growth factor-binding protein 3 (IGFBP3) in the IVD lesion area.[23] By week three after the intervention, the epidurolysis group showed significantly greater changes to the ODI score than the ESI group. However, there was no difference between the two groups at three months post-intervention. Our results differ from those of previous studies, in which the administration of hyaluronidase had no significant effect on changes in the ODI score compared to triamcinolone administration alone.[20] However, as in previous studies, there was no significant difference in ODI scores in the follow-up results up to two weeks after an intralaminar epidural injection of triamcinolone, with or without hyaluronidase. Previous studies used bupivacaine for local anaesthesia (long duration of action), whereas this study used 2% lidocaine (short duration of action). Based on the results of other studies, it was concluded that adding hyaluronidase improved NRS scores by 40–71.43% and ODI scores by 23.5–68.18%.[10] The ODI score assesses activities of daily living (ADLs), with two assessment modalities relating to psychological/mental role and physical disability involving LBP complaints.[23] However, the ODI score only assesses psychological health, not physical disability (e.g. motor weakness).[24]

Three months after the intervention, a significant difference in TNF-α levels was observed between the epidurolysis and ESI groups. The epidurolysis group experienced a greater decrease in TNF-α levels than the ESI group. Hyaluronidase can stimulate fibroblast proliferation and break down extracellular matrix proteins. It can also regulate the immune system and control the duration of the inflammatory process. This increases drug absorption in tissues and reduces oedema in the surrounding area.[24,25] Administering hyaluronidase can accelerate tissue lesion repair or wound closure within 14 days. Meanwhile, TNF-α levels decrease on day 21 (three weeks) after hyaluronidase administration. Angiogenesis appears to increase during hyaluronidase administration, as indicated by elevated levels of vascular endothelial growth factor (VEGF) at the injury site.[24] VEGF levels increase 21–28 days after injury in response to resulting ischaemia. This is characterised by neovascularisation around the lesion, which improves ischaemia and tissue

metabolism. This has been observed in cases of lumbar herniated nucleus pulposus (HNP). It also inhibits further nerve damage and astrogliosis in the dorsal root ganglion (DRG) while releasing neurotrophic factors that promote nerve regeneration.[26,27] This may explain why the Pain DETECT score for neuropathic pain syndrome was higher in the epidurolysis group than in the ESI group three months after the intervention in this study.

Although stress and depression levels influence the intensity of chronic pain, this study does not analyse them. However, several studies have concluded that stress and/or depression play a role in chronic pain syndrome and persistent pain, including in patients with chronic non-specific back pain (cNSBP). The HPA axis influences stress and depression levels, and research has shown that it does not function physiologically in patients with chronic pain. Nevertheless, the effects of epidural injections on the HPA axis diminish after seven or 20 days.[28]

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