REVIEW ARTICLE
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An Evidence Based Review of Epidurolysis for the Management of Epidural Adhesions

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ABSTRACT ~ Purpose of Review: *This review presents epidurolysis as a procedure to alleviate pain and disability from epidural adhesions. It reviews novel and groundbreaking evidence, describing the background, indications, benefits and adverse events from this procedure in an effort to provide healthcare experts with the data required to decide on an intervention for their patients.* ***Recent Findings:*** *Epidural adhesions (EA) or epidural fibrosis (EF) is defined as non-physiologic scar formation secondary to a local inflammatory reaction provoked by tissue trauma in the epidural space. Often, it is a sequelae of surgical spine intervention or instrumentation. The cost associated with chronic post-operative back pain has been reported to be up to nearly $12,500 dollars per year; this, coupled with the increasing prevalence of chronic lower back pain and the subsequent increase in surgical management of back pain, renders EF a significant cost and morbidity in the U.S. Though risk factors leading to the development of EA are not well established, epidural fibrosis has been reported to be the culprit in up to 46% of cases of Failed Back Surgery Syndrome (FBSS), a chronic pain condition found in up to 20–54% of patients who receive back surgery. Moreover, EF has also been associated with lumbar radiculopathy after lumbar disc surgery. Epidurolysis is defined as the mechanical dissolution of epidural fibrotic scar tissue for persistent axial spine or radicular pain due to epidural fibrosis that is refractory to conservative therapy Endoscopic lysis of adhesions is a procedural technique which has been shown to improve chronic back pain in one-third to one-half of patients with clinically symptomatic fibrous adhesions. Here we review some of the novel*

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evidence that supports this procedure in EA and FBSS. ***Summary:*** *The literature concerning epidurolysis in the management of epidural adhesions is insufficient. Prospective studies, including randomized controlled trials and observational studies, have suggested epidurolysis to be effective in terms of pain reduction, functional improvement, and patient satisfaction scores. Observational studies report epidurolysis as a well-tolerated, safe procedure. Current evidence suggests that epidurolysis may be used as an effective treatment modality for epidural adhesions. Nonetheless, further high quality randomized controlled studies assessing the safety and efficacy of epidurolysis in the management of epidural adhesions is needed.* Psychopharmacology Bulletin. *2020;50(4, suppl. 1):74–90.*

Introduction

Epidural adhesions (EA), also referred to as epidural fibrosis (EF), is defined as non-physiologic scar formation secondary to a local inflammatory reaction provoked by tissue trauma in the epidural space.[1] EA is well known as one of the more frequent complications of lumbar surgery, with studies reporting an incidence as high as 91%.[2,3] Endoscopic lysis of adhesions is a procedural technique which has been shown to improve chronic back pain in one-third to one-half of patients with clinically symptomatic fibrous adhesions.[4] Epidurolysis is defined as the mechanical dissolution of epidural fibrotic scar tissue for persistent axial spine or radicular pain due to EF that is refractory to conservative therapy.[5,6] It was initially described in 1989[7] and thought to be beneficial due to local lavage of proinflammatory mediators through the targeted delivery of corticosteroids, anesthetics, hypertonic saline, and hyaluronidase to the site of inflammation.[1,6,7] The procedure involves use of a flexible spinal endoscope to deliver medications and mechanically lyse adhesions under direct visualization of target sites.[6] Candidates for therapy include patients with chronic refractory low back pain not responsive to less invasive remedies including physical therapies, oral and topical medications, and epidural injections. Compared to percutaneous lysis of adhesions, epiduroscopy offers clinicians direct visualization of the epidural space and pathologic adhesions. Endoscopic lysis of adhesions is a newer technique than the percutaneous approach, and as such, there is less evidence supporting its use.[8] The purpose of this review is to provide a comprehensive update on existing literature addressing the efficacy, safety, and therapeutic benefit of epidurolysis in the management of EA.

Epidemiology of Epidural Adhesions

The existing literature regarding the incidence and prevalence of EF following back surgery is limited. The diagnosis of EF following

back surgery is most often made through imaging modalities such as computed tomography or magnetic resonance imaging.[9,10] The prevalence has been reported to be between 24% and 100% of patients who receive back surgery, varying according to imaging test of choice and definition of EF.[9,11] However, Bosscher et al. found epiduroscopy to be most sensitive in diagnosis, and subsequently concluded that EF is an underdiagnosed condition due to the underuse of epiduroscopy.[3] The relationship between persistent back pain and EF was originally reported by Ross et al. in 1996 where he showed a clear association between the presence of EF and radicular pain, stating that patients with extensive fibrosis were 3.2 times more likely to experience radicular pain compared to those with less extensive scarring.[12] This was confirmed three years after in 1999 by Maroon et al. showing a direct relationship between pain and presence of epidural scarring.[13] Lastly, Bosscher reported that 83.3% to 91% of patients with persistent pain after back surgery had severe EF.[3] The cost associated with chronic post-operative back pain has been reported to be up to nearly $12,500 dollars per year; this, coupled with the increasing prevalence of chronic lower back pain and the subsequent increase in surgical management of back pain, renders EF a significant cost and morbidity in the U.S.[14–17]

Risk Factors for the Development of Epidural Adhesions

There are few studies evaluating specific risk factors that might contribute to the development EA, the majority of them focusing on surgical risk factors. Masopust et al. identified insufficiently treated perioperative bleeding in the operative site involving the nervous structures as a surgical risk factor for the development of EF.[16] Adequate hemostasis and subsequent absent or minimal development of hematoma is critically important in the prevention of EF.[1,18] Reoperation of the lumbar spine is also associated with increased incidence of EF, with rates as high as 60%.[19,20] Jayson also found that patients with significant defects in the fibrinolytic system had more severe symptoms in the context of EF.[21] Extent of surgery has also been shown to be associated with severity of fibrosis.[12,22]

Additionally, many surgical and pharmacological methods have been developed to prevent the development of EA following back surgery. Proposed techniques revolve around minimizing the incidence and size of post-operative hematomas at the site of operation, creating a physical barrier between the dura and the tissues being operated on, and lastly, local injection of various drugs to decrease the formation of scar tissue.[18] Techniques vary widely, including, but not limited to, placement

of surgical drains at the operation site, use of fibrin glue or carboxymethylcellulose and polyethylene oxide barriers, injections of hyaluronic acid at the operation site, corticosteroid injections, recombinant tissue plasminogen activator injections, intra-operative topical Rifamycin use, targeted pre and intra-operative low-dose radiation, and even topical application of honey.[23–29] Despite all of the different approaches, there still remains no widely accepted standard treatment for prevention of post-operative EF.

Though risk factors leading to EF are not well established, EF has been reported to be the culprit in up to 46% of cases of Failed Back Surgery Syndrome (FBSS), a chronic pain condition found in up to 20%–54% of patients who receive back surgery.[17,19] EF has also been associated with lumbar radiculopathy after lumbar disc surgery, with the earliest report in 1988 by Cervellini et al.[30] Lastly, the development of EF has been shown to aid in the acceleration of osteophyte formation, contributing to the development of lumbar stenosis.[31] Prevention of EF is limited to appropriate presurgical patient assessment, reducing operating time, and achieving excellent hemostasis.

Pathophysiology of Epidural Adhesions

The pathophysiology of EF has proven to be complex. The earliest proposed explanation, by Key and Ford in 1948, revolved around damage to the annulus fibrosis.[31] This was refuted by LaRocca and Macnab in 1974, who posited that, in fact, trauma to the erector spinae muscle mass overlying the dura is the principal source of scarring.[32] They explained that just as in muscle trauma elsewhere in the body, fibroblast infiltration ensues, which then replaces any residual epidural hematoma with granulation tissue.[32] The granulation tissue then evolves into dense fibrous tissue due to the polymerization of fibrinogen into fibrin, compressing surrounding structures.[21,25] Long et al. in a study done in 1991, supports the proposed mechanism by concluding as well that EF is a consequence of normal wound healing.[33] Additionally, residual microscopic cotton debris from surgery is described to possibly contribute to EF, acting as a local fibrogenic stimulus.[21]

The morbidity associated with EF, however, is due to nerve root damage. The relationship between EF and nerve root damage has been well described in the literature. Rydevik first showed in 1981 that direct compression to the nerve leads to impaired intraneural circulation and consequential ischemic damage.[34] This damage to endoneurial vessels may result in increased permeability of the vessels with formation of endoneurial edema, further jeopardizing the microcirculation in the nerve fascicles due to increased pressure.[34] Jayson proposed that EF

along with subsequent osteophytic proliferation leads to compression of epidural veins, resulting in hypoxic neuronal atrophy.[21] Mechanical compression and inadequate perfusion both contribute to the local discomfort as well as radiating pain often felt by patients with EF.

Clinical Presentation and Diagnosis of Epidural Adhesions

The diagnosis of EF in the post-operative setting is difficult and elusive. Patients with EF may present with a variety of symptoms, of which many may fit well under the diagnosis of FBSS. As a result, discovery and subsequent independent diagnosis of EF is rare, and it is often instead found as an incidental imaging finding in the work-up of FBSS.[3] The definition of FBSS being poorly defined, coupled with historically inefficient and cost ineffective evaluation of post-operative chronic lumbar pain, results in a significant delay in establishing the causative root problem.[35] Additionally, formation of adhesions in the epidural cavity is a normal response to back surgery, which further complicates the diagnosis.[3,36]

The importance of the history and physical exam in the diagnosis of EF cannot be overstated. A complete evaluation allows the provider to rule out secondary etiologies for post-operative pain, such as infection or malignancy. Due to the varying degrees of symptom severity seen in EF, the history and clinical examination of persistent back pain in the post-operative setting needs to be comprehensive. This includes but is not limited to presence of saddle anesthesia, loss of bladder or bowel control, loss of sensation and/or strength in the lower extremities, presence of fever, unexplained weight loss, etc. Review of surgical reports, pre-operative radiographs, and medical records must also be done. Duration and onset of symptoms may not be helpful in the diagnosis of EF, with previous studies reporting presence of symptoms as early as 6 weeks post-operatively and as late as 6 months post-operatively.[30,37]

Generally, the minimal laboratory work-up should include a complete blood count with white blood cell differential to evaluate for post-operative infection. Imaging studies are undeniably the most valuable in diagnosing EF. Historically, MRI evaluation with gadolinium is the test of choice due to the benefit of being able to differentiate EF from other pathologies, such as first-time or recurrent disc herniation.[38] Jinkins described in 1993 that neural enhancement seen on MRI may serve as a helpful marker in the diagnosis of FBSS, and subsequently, EF.[39] BenDebba et al. added by reporting a relationship between the presence of epidural scar on MRI and activity-related pain, stating that the odds of extensive scar seen on MRI decreased by 30% for every 31% decrease

in activity-related pain score.[12] For patients who have contraindications for MRI, CT myelography may be used.[40] Lastly, Bosscher reports Epiduroscopy as an underused but valuable tool in determining EF as the primary diagnosis behind FBSS.[3] A diagnosis of EF may only be made with supporting imaging findings.

Epidural Adhesiolysis

Epidural adhesiolysis is an intervention used to treat chronic back or radicular pain that is refractory to conservative treatments. Scar tissue in the epidural space is thought to not only directly causes pain, but also inhibit the distribution of medications to the area. Accordingly, the efficacy of epidural adhesiolysis is a result of removing this fibrotic tissue from the epidural space. The intervention as it is most commonly performed today was originally described by Racz et al. in 1989.[41] In brief, a large bore needle and catheter is inserted through the sacral hiatus and into the epidural space. The catheter is used to access the fibrotic regions, where saline or medications are then utilized to lyse the adhesions.

The procedure's efficacy is thought to be primarily from directly removing the adhesions adjacent to nerves and nerve roots. The mechanism of scar tissue resulting in pain continues to be worked out, but it has been established that select spinal structures most sensitive to pain are those with nerves constrained by fibrosis.[42] A study that further investigated this finding demonstrated that the probability of recurrent pain shares a positive correlation with scarring and that patients with significant scar tissue were 3.2 times more likely to experience radicular pain.[12] Considering these findings, decreasing the scar tissue burden on the nerves is thought to be the primary mechanism by which epidural adhesiolysis achieves pain relief.

Epidural adhesiolysis is also thought to produce beneficial effects resulting from the local effects of fluid administration. Various studies have demonstrated that pro-inflammatory cytokines can initiate or exacerbate existing radiculopathy and lumbar back pain.[43–45] Accordingly, it is hypothesized that washing out these cytokines with epidural injections prompts pain resolution.[46] In support of this, a review of 15 studies found a statistically significant correlation between the amount of fluid used in epidural injections and pain relief.[47] Authors propose that this finding is due to enhancing vascularity to ischemic nerves and limiting excess discharge from affected nerves in addition to effectively washout out the epidural space of inflammatory cytokines.[46,47]

The two most common indications for epidural ahesiolysis include failed back syndrome and spinal stenosis.[46] Failed back surgery

syndrome is pain of various causative etiologies that persists despite surgical intervention. Epidural fibrosis is purported as a common cause of this condition that boasts an incidence as high as 40%.[48,49] Spinal stenosis is less common in the general population but increases dramatically with age with an incidence as high as 47% in the elderly.[50] Although mechanistic details remain under investigation, spinal stenosis is associated with increased collagen fibers and fibrocartilaginous cells within the ligament flavum that in turn cause hypertrophy.[51,52] As a result, the patient experiences symptoms of spinal cord and nerve root compression without any herniation of the nucleus pulposus.[53]

Percutaneous Lysis of Adhesions

Achieving adhesiolysis percutaneously was introduced in 1981 as a means to achieve anesthesia or analgesia.[54] The efficacy of a percutaneous epidural adhesiolysis has been studied repeatedly. In a study of 92 patients, percutaneous lysis of adhesions showed a significant improvement in visual analog scale scores (VAS) at six month follow up when compared to the control group treated by injected dexamethasone.[55] In a study that followed failed back surgery patients over 2 years post-percutaneous adhesiolysis, 82% of the 120 showed significant improvement as defined by at least 50% relief.[56] This trend also applies to PLOA in lumbosacral intervertebral disc herniation. In a study of 228 such patients, a significant improvement in pain was found at the 3 month follow up.[57] However, promising results are not unanimous. A 2014 case series of four patients reported no long-lasting effects or functional improvement of PLOA with the Racz or NaviCath catheter.[58] Although reported success varies, authors have concluded that PLOA has sufficient evidence for short term efficacy and moderate evidence for long-term efficacy, as defined by less than or greater than 3 month follow up.[59]

Select factors have been shown to prognosticate outcomes of PLOA. A review of 407 cases of lumbar disc herniation demonstrated that the presence of high intensity zones on MRI is an independent variable associated with favorable long-term outcomes. Conversely, a herniated disc involving the vertebral foramen predicts poor results.[60] Initial investigation into the effects of anatomical variables on the success of PLOA have shown improvement regardless of sacral morphology type.[57] Further research into these areas will provide enhanced understanding of procedural success rates and insight into optimal patient selection.

PLOA can be executed in a variety of ways as determined by surgeon preference. Notably, the procedure can be achieved by caudal,

interlaminar, L5 foraminal, or L5-S1 transforaminal approaches. Each of these have demonstrated comparable and significant improvement over baseline without differences in complication rates.[61,62] Intraoperatively, the catheter that dispenses the medication can be placed ventrally or dorsally in the spinal canal. Anatomically, the ventral approach offers the potential for improved drug administration. In the first study comparing these two approaches, the ventral approach demonstrated improved VAS scores at postoperative months three and six.[63] Increased focus on these areas of associated risks and success of procedural options may allow for technique specific to the patient and their pathology.

The role of administering steroids during or shortly after percutaneous adhesiolysis remains under investigation. Although epidural steroids have been applied for lumbar discectomy cases for more than 20 years, the literature is lacking on steroid use for adhesiolysis patients.[64] Further, there is debate whether steroids are best administered intravenously or epidurally as it is reported that many surgeons opt not to administer epidural steroids for fear of infection susceptibility.[65,66] In an analysis of 16 trials investigating this risk in lumbar discectomy cases, there was a trend of epidural steroids toward increased infection although this difference was not significant.[67] In a study considering only percutaneous adhesiolysis cases, epidural application was demonstrated to have significantly superior pain-control in the post-operative and short-term periods.[68] However, this difference was not significant at 1, 6, and 12-month follow up. In this series, epidural application showed no increased infection rate over the intravenous or control groups. Other relevant factors that should be considered with this decision include the longer anti-inflammatory effects of epidural injections, but also the delated wound healing and potential to predispose to disc herniation.[69]

The procedure is not without several risks. Commonly observed complications include dural puncture, medication administration into the subarachnoid and subdural space, catheter shear, infection, and haemodynamic instability. Procedural complications are seen more immediately than adverse effects of the drugs administered.[70] A review of 250 PLOA cases resulted in the following adverse events: 39 patients had bleeding or aspiration from the epidural space, 25 had dermatomal numbness in the upper and lower extremities, 12 had hypotension during or after the procedure, and 11 had dural puncture.[71] Less commonly, patients experienced hypotension, epidural abscesses, and meningitis. Catheter-related issues in the review included torn catheter sheaths, catheter blockage, and catheter migration to the prevertebral space, epidural vein, and dura.

PLOA has been noted to cause can also have musculoskeletal complaints involving either the ipsilateral or contralateral side. One such

complication is detailed in a case report of a 19 year old who suffered acute motor weakness in the right lower leg after adhesiolysis on the left.[72] Authors suggest these symptoms resulted from increased pressure on the contralateral side to medication injection as emergency surgery subsequently demonstrated an inflamed right L5 nerve root. With this subsequent surgery, symptoms completely resolved. Further, it has also been reported that the catheter can become dislodged in the epidural space, putting the patient at risk for infection, fibrosis, or mechanical neural irritation. In a case of this particular complication, the patient complained of left-sided leg pain and numbness that completely resolved after repeat surgery was completed to retrieve the broken catheter.[73]

There have also been reports of neurological and cardiovascular sequelae of the procedure. Specifically, it has been specifically linked to stress induced cardiomyopathy. This phenomenon is hypothesized to result from catecholamine surge from the neurohumoral effects of hyperbaric anesthetics and adhesiolytics.[74] A separate neurologic report describes intracranial subdural hematoma after adhesiolyis that eventually required surgical treatment.[75] Authors suggest this was a sequelae of dural tear, which led to intracranial hypotension and resulting headache and neck pain with ultimately subdural hematoma formation. These authors cite a separate case of bilateral subacute subdural hematomas in a patient that underwent intrathecal catheter placement as supporting evidence of this presumed pathology mechanism.[76] In a separate case, a patient developed severe meningitis and neurologic complications following the procedure.[77] Although rare, these complications suggest that PLOA is best performed at centers of excellence under experienced hands.

Endoscopic Lysis of Adhesions

Background

Endoscopic lysis of adhesions, also known as epiduroscopy, is a procedural technique which has been shown to improve chronic back pain in one-third to one-half of patients with clinically symptomatic fibrous adhesions, which is generally a sequelae of repeated back surgery.[4] The procedure involves use of a flexible spinal endoscope to deliver medications, typically ozone and ciprofloxacin, and mechanically lyse adhesions under direct visualization of target sites.[6] Candidates for therapy include patients with chronic refractory low back pain not responsive to less invasive remedies including physical therapies, oral and topical medications, and epidural injections. Compared to percutaneous lysis

of adhesions, epiduroscopy offers clinicians direct visualization of the epidural space and pathologic adhesions. Endoscopic lysis of adhesions is a newer technique than the percutaneous approach, and as such, there is less evidence supporting its use.[8] The following content summarizes the latest available evidence investigating the use of endoscopic lysis of adhesions.

Effectiveness

The development of painful adhesions in post lumbar surgery syndrome is one of the most researched indications of spinal endoscopy. A 2013 systematic review by Helm et al. which included one randomized controlled trial and two observational studies, suggested endoscopic lysis of adhesions as both a safe and effective method in the treatment of post lumbar surgery syndrome.[78] Pereira et al. made a similar conclusion in a 2016 prospective study of 24 patients who developed postoperative fibrosis following lumbar discectomy, where 71%, 63%, 63%, and 38% of patients achieved at least 50% pain reduction at one, three, six, and twelve months of follow up, respectively. Mean patient satisfaction scores with the treatment were 80%, 75%, 70%, and 67% at one, three, six, and twelve months of follow-up, respectively.[79]

Past studies have indicated endoscopic epidurolysis may also be an effective tool in degenerative chronic low back pain management. Manchikanti et al. demonstrated in a randomized controlled trial of 83 patients with chronic degenerative low back pain that endoscopic lysis of adhesions provided at least 50% chronic low back pain relief in more patients and for longer durations compared to control, who received spinal endoscopy without adhesiolysis. Specifically, 90% of patients receiving the procedure had at least 50% pain reduction one month later compared to 33% in control. The same trend held true at three months post-op, with 48% who received the procedure experiencing at least 50% pain reduction compared to 0% in control. Following endoscopic lysis of adhesions, patients also exhibited significant improvements in functionality, range of motion, depression, and anxiety compared to control up to the total length of follow-up at 12 months.[80] Findings by Donato et al. in a prospective study investigating the effectiveness of endoscopic epidurolysis in the treatment of 234 patients with degenerative chronic lower back pain showed similar results, with significant improvements in visual analog pain scores through 48 months of follow-up and disability index scores, particularly at 3 months of follow-up, but also throughout long-term follow-up intervals.[81]

Most recently, a 2019 systematic review by Brito-Garcia and other authors including methodologists, researchers, and clinicians specializing

in low back pain challenged the efficacy, safety, and cost-effectiveness of epidural adhesiolysis in the treatment of Failed Back Surgery Syndrome, stating there are far more reviews covering the topic than actual randomized controlled trials, which may be leading to underpowered conclusions about this procedure. Furthermore, they concluded the studies that do exist are a heterogenous mix of poor methodology, lacking evidence, or having a high risk of bias with publications in a journal the senior author founded. The authors concluded there is currently no sufficient evidence for the effectiveness or safety of epidurolysis, and high quality RCTs are needed to make unbiased conclusions concerning efficacy, safety, and cost-effectiveness of this procedure.[82]

Currently, there are no retrospective studies or randomized controlled trials comparing outcomes of percutaneous versus endoscopic lysis of epidural adhesions, making it difficult to recommend one treatment over the other. Overall, the indicated level of evidence for endoscopic adhesiolysis in post-surgery syndrome-related back pain is currently II-1 or II-2 based on USPTF criteria.[83]

Sedative Selection During Endoscopic Adhesiolysis

Suzuki et al. conducted a single-site retrospective study in 2018 of 45 patients undergoing endoscopic adhesiolysis to see how usage of different sedatives during the procedure affected fentanyl requirement during the procedure and postoperative nausea and vomiting. With comparative values between treatment groups in sex, age, and BMI, the use of dexmedetomidine with fentanyl was associated with a significantly lower fentanyl dose during surgery when compared to droperidol and fentanyl (126 ± 14 vs 193 ± 21 ug, respectively). Only one patient receiving dexmedetomidine experienced postoperative nausea and vomiting compared to three who received droperidol.[84] The findings of this study may be especially pertinent to consider when treating elderly patients with spinal endoscopic adhesiolysis to prevent apnea.

Safety

Based on currently available evidence, endoscopic adhesiolysis is generally regarded as a safe, well-tolerated procedure with rare adverse effects, most commonly involving localized pain and transient nerve root irritation. Perhaps the most significant potential adverse effect from epidural adhesiolysis is potentially transient blindness as a result of excess epidural hydrostatic pressure during the procedure.[8]

A recent systematic review by Brito-Garcia et al. reported several adverse effects seen in both percutaneous and epidural adhesiolysis

including: infection, postoperative weakness, sensory deficit, rash, weight increase, head and neck pain, wound pain, sciatic pain, low back pain, dural puncture, bleeding, and apnea. No occurrence rates were reported with any of these adverse effects. Due to failure of current literature to dependably report adverse effect rates in endoscopic adhesiolysis, Brito-Garcia et al. suggest more high quality RCTs are needed before fully informed recommendations for this therapy can be made.[82]

Surgical Prophylaxis

Background

Epidural fibrosis and adhesions are two major causes of failed back surgery syndrome, giving some patients chronic back pain, leg pain, and radiculopathy after subsequent attempts at correction of pre-existing back pain with laminectomy, etc.[85] Percutaneous and endoscopic lysis of these adhesions are viable options for patients who fail conservative therapy; however, adhesions and scar tissue are likely to recur, limiting these procedures' therapeutic value.[86] This has prompted the research of potential therapeutics aimed to reduce the initial occurrence of epidural adhesion formation status post lumbar back surgery.

Membrane Therapies

In 2018, Wang et al. published data on a bacterial cellulose anti-adhesion membrane they developed containing exosomes from human umbilical cord mesenchymal stem cells investigating its ability to prevent postoperative epidural fibrosis and peridural adhesions in New Zealand White rabbits. L6 laminectomies were performed on 270 rabbits, with some receiving no treatment over the exposed dura and others receiving the bacterial cellulose membrane with human-derived exosomes over the dural space. Blood tests and MRI were performed on the rabbits 90 days after the procedure, and the animals were sacrificed for gross appearance and histological analysis one year after the procedure. Blood tests and histological analysis confirmed the membrane didn't cause any tissue necrosis or change in normal physiology of heart, kidney, and liver tissue, suggesting in vivo compatibility. On gross examination there was significant epidural fibrosis and adhesion formation between the spinal cord and neighboring muscle in control group rabbits. However, the authors report no observed adhesion between muscle and spinal cord in the groups receiving the therapeutic membrane. Additionally, almost no scar formation was observed on MRI in the membrane-treated group compared to control.[85]

These results build off a similar 2009 study by Tao et al. assessing the prevention of epidural fibrosis in 24 canines receiving either amniotic membranes or no intervention over the dural space status post laminectomy. Similar to Wang et al.'s findings, there was grossly less epidural fibrosis observed and histologically less fibroblast infiltration in canines receiving the amniotic membrane compared to control at 1, 6, and 12 weeks postoperatively.[86] The results of both these studies encourage further efforts for the development of a membrane preventative therapy for human application.

Injection Therapies

Several recent studies have investigated the role of locally applied medications to laminectomy sites and their abilities to reduce post-operative epidural fibrosis formation. In 2016, Dai J et al. displayed significantly reduced epidural fibrosis formation, fibroblast proliferation, and expression of cyclin D1, cyclin E, and PCNA in rats injected with 300 mg/mL suramin at laminectomy sites.[87] Similar reductions in post-laminectomy epidural fibrosis formation have been shown in rat models receiving several other locally applied medications including: rapamycin, artesunate, and all-trans retinoic acid.[88–90]

A 2018 experimental study by Demirel et al. compared platelet rich fibrin, hyaluronic acid, and Adcon® gel in their abilities to prevent epidural fibrosis status post laminectomy in 28 Sprague-Dawley rats. There were no statistically significant differences in acute inflammation cell density, angiogenesis, and new bone formation levels in all groups including control. However, rats receiving platelet rich fibrin did have significantly lower levels of epidural fibrosis and chronic inflammation cell density.[91]

Conclusion

The literature concerning epidurolysis in the management of epidural adhesions is insufficient. Prospective studies, including randomized controlled trials and observational studies, have suggested epidurolysis to be effective in terms of pain reduction, functional improvement, and patient satisfaction scores. However, the validity and methodological integrity of the studies supporting the benefit of epidurolysis has been questioned, and there remains a need for unequivocally unbiased, higher-quality randomized control trials to determine the effectiveness of the procedure.

Regarding safety, observational studies report epidurolysis as a well-tolerated, safe procedure. Adverse events are reported in the literature,

although studies investigating frequency and associated risk factors surrounding the adverse events are nonexistent. Similarly to effectiveness, high-quality studies must be done before the safety of epidurolysis can be confidently determined.

Current evidence suggests that epidurolysis may be used as an effective treatment modality for epidural adhesions. Nonetheless, further high quality randomized controlled studies assessing the safety and efficacy of epidurolysis in the management of epidural adhesions is needed. ✤

References

• Of Importance: 5, 16, 29

5. A review of literature of epidural adhesiolysis suggesting that the evidence supporting this procedure are rather weak, however, it is likely safe and slightly more effective than epidural injection therapy.
16. An economical-perspective review of FBSS and the cost incurred with this syndrome.
29. An important imaging review showing that there is little imaging differences between symptomatic and asymptomatic epidural fibrosis patients, suggesting the mechanism is more than just structural.

• Of Major Importance: 59, 68, 79

59. A large retrospective review into the factors associated with long term outcomes of epidural adhesiolysis identifying "MRI High Intensity Zone" as a predictor for success.
68. An RTC supporting the use of epidural steroid injections in post-discectomy patients, providing evidence of a shorter hospital stay and symptomatic relief.
79. An RTC examining epidurolysis with local administration of anesthetics and steroids providing evidence to the effectiveness of this procedure and its safety.

1. Masopust V, Häckel M, Netuka D, Bradáč O, Rokyta R, Vrabec M. Postoperative Epidural Fibrosis. *Clin J Pain*. 2009;25(7):600–606.
2. Sandoval MA, Hernandez-Vaquero D. Preventing peridural fibrosis with nonsteroidal anti-inflammatory drugs. *Eur Spine J*. 2008;17(3):451–455.
3. Bosscher HA, Heavner JE. Incidence and Severity of Epidural Fibrosis after Back Surgery: An Endoscopic Study. *Pain Pract*. 2010;10(1):18–24.
4. Vymazal J, Kříž R. Vertebroplasty and epiduroscopy as seen by interventional radiologist. *Cas Lek Cesk*. 157(4):203–207.
5. Jamison DE, Hsu E, Cohen SP. Epidural adhesiolysis: an evidence-based review. *J Neurosurg Sci*. 2014;58(2):65–76.
6. Lee F, Jamison DE, Hurley RW, Cohen SP. Epidural lysis of adhesions. *Korean J Pain*. 2014;27(1): 3–15.
7. Racz GB, Holubec JT. Lysis of Adhesions in the Epidural Space. In Springer, Boston, MA; 1989. p. 57–72.
8. Helm S, Racz GB, Gerdesmeyer L, Justiz R, Hayek SM, Kaplan ED, El Terany MA, Knezevic NN. Percutaneous and Endoscopic Adhesiolysis in Managing Low Back and Lower Extremity Pain: A Systematic Review and Meta-analysis. *Pain Physician*. 2016;19(2):E245–E282.
9. Ross JS, Obuchowski N, Modic MT. MR evaluation of epidural fibrosis: proposed grading system with intra- and inter-observer variability. *Neurol Res*. 1999;21 Suppl 1:S23–S26.
10. Urits I, Burshtein A, Sharma M, Testa L, Gold PA, Orhurhu V, Viswanath O, Jones MR, Sidransky MA, Spektor B, Kaye AD. Low Back Pain, a Comprehensive Review: Pathophysiology, Diagnosis, and Treatment. Vol. 23, Current Pain and Headache Reports. Current Medicine Group LLC 1; 2019.
11. Nygaard OP, Jacobsen EA, Solberg T, Kloster R, Dullerud R. Postoperative nerve root displacement and scar tissue. A prospective cohort study with contrast-enhanced MR imaging one year after microdiscectomy. *Acta Radiol*. 1999;40(6):598–602.
12. Ross JS, Robertson JT, Frederickson RC, Petrie JL, Obuchowski N, Modic MT, deTribolet N. Association between peridural scar and recurrent radicular pain after lumbar discectomy: magnetic resonance evaluation. ADCON-L European Study Group. *Neurosurgery*. 1996;38(4):855–61; discussion 861–863.

13. Maroon JC, Abla A, Bost J. Association between peridural scar and persistent low back pain after lumbar discectomy. *Neurol Res*. 1999;21 Suppl 1:S43–S46.
14. Gray DT, Deyo RA, Kreuter W, Mirza SK, Heagerty PJ, Comstock BA, Chan L. Population-Based Trends in Volumes and Rates of Ambulatory Lumbar Spine Surgery. *Spine (Phila Pa 1976)*. 2006;31(17):1957–1963.
15. Deyo RA, Gray DT, Kreuter W, Mirza S, Martin BI. United States trends in lumbar fusion surgery for degenerative conditions. *Spine (Phila Pa 1976)*. 2005;30(12):1441–1445.
16. Weinstein JN, Lurie JD, Olson PR, Bronner KK, Fisher ES. United States' Trends and Regional Variations in Lumbar Spine Surgery: 1992–2003. *Spine (Phila Pa 1976)*. 2006;31(23):2707–2714.
17. Taylor RS, Taylor RJ. The economic impact of failed back surgery syndrome. *Br J Pain*. 2012;6(4):174–181.
18. Mohi Eldin MM, Abdel Razek NM. Epidural Fibrosis after Lumbar Disc Surgery: Prevention and Outcome Evaluation. *Asian Spine J*. 2015;9(3):370–385.
19. Fritsch EW, Heisel J, Rupp S. The failed back surgery syndrome: reasons, intraoperative findings, and long-term results: a report of 182 operative treatments. *Spine (Phila Pa 1976)*. 1996;21(5):626–633.
20. Jönsson B, Strömqvist B. Repeat decompression of lumbar nerve roots. A prospective two-year evaluation. *J Bone Joint Surg Br*. 1993;75(6):894–897.
21. Jayson MI. The role of vascular damage and fibrosis in the pathogenesis of nerve root damage. *Clin Orthop Relat Res*. 1992;(279):40–48.
22. Hurme M, Katevuo K, Nykvist F, Aalto T, Alaranta H, Einola S. CT five years after myelographic diagnosis of lumbar disk herniation. *Acta Radiol*. 1991;32(4):286–289.
23. Sen O, Kizilkilic O, Aydin MV, Yalcin O, Erdogan B, Cekinmez M, Caner H, Altinors N. The role of closed-suction drainage in preventing epidural fibrosis and its correlation with a new grading system of epidural fibrosis on the basis of MRI. *Eur Spine J*. 2005;14(4):409–414.
24. Rodgers KE, Robertson JT, Espinoza T, Oppelt W, Cortese S, diZerega GS, Berg RA. Reduction of epidural fibrosis in lumbar surgery with Oxiplex adhesion barriers of carboxymethylcellulose and polyethylene oxide. *Spine J*. 3(4):277–283; discussion 284.
25. Songer MN, Ghosh L, Spencer DL. Effects of sodium hyaluronate on peridural fibrosis after lumbar laminotomy and discectomy. *Spine (Phila Pa 1976)*. 1990;15(6):550–554.
26. Kemaloğlu S, Ozkan U, Yilmaz F, Nas K, Gur A, Acemoglu H, Karasu H, Cakmak E. Prevention of spinal epidural fibrosis by recombinant tissue plasminogen activator in rats. *Spinal Cord*. 2003;41(8):427–431.
27. Häckel M, Masopust V, Bojar M, Ghaly Y, Horínek D. The epidural steroids in the prevention of epidural fibrosis: MRI and clinical findings. *Neuro Endocrinol Lett*. 2009;30(1):51–55.
28. Gunaldi O, Erdogan S, Guclu G, Tugcu B, Ofluoglu E, Baydin S, Emel E. Honey can prevent epidural fibrosis development after laminectomy: an experimental study. *Turk Neurosurg*. 2013;24(6): 849–854.
29. Dinç C, Tuncer C, Türkoğlu ME, Tokmak M, Ocak P, Er U. Effect of topical rifamycin application on epidural fibrosis in rats. *Turk J Phys Med Rehab*. 2019;65(1):24–29.
30. Cervellini P, Curri D, Volpin L, Bernardi L, Pinna V, Benedetti A. Computed Tomography of Epidural Fibrosis after Discectomy: A Comparison between Symptomatic and Asymptomatic Patients. *Neurosurgery*. 1988;23(6):710–713.
31. KEY JA, FORD LT. Experimental intervertebral-disc lesions. *J Bone Joint Surg Am*. 1948;30A(3):621–630.
32. LaRocca H, Macnab I. The laminectomy membrane. Studies in its evolution, characteristics, effects and prophylaxis in dogs. *J Bone Joint Surg Br*. 1974;56B(3):545–550.
33. Long DM. Failed back surgery syndrome. *Neurosurg Clin N Am*. 1991;2(4):899–919.
34. Rydevik B, Lundborg G, Bagge U. Effects of graded compression on intraneural blood blow. An in vivo study on rabbit tibial nerve. *J Hand Surg Am*. 1981;6(1):3–12.
35. Waguespack A, Schofferman J, Slosar P, Reynolds J. Etiology of Long-term Failures of Lumbar Spine Surgery. *Pain Med*. 2002;3(1):18–22.
36. Ozer AF, Oktenoglu T, Sasani M, Bozkus H, Canbulat N, Karaarslan E, Sungurlu SF, Sarioglu AC. Preserving the Ligamentum Flavum in Lumbar Discectomy: A New Technique that Prevents Scar Tissue Formation in the First 6 Months Postsurgery. *Oper Neurosurg*. 2006;59(1 Suppl 1): ONS-126-ONS-133.
37. Cinotti G, Roysam GS, Eisenstein SM, Postacchini F. Ipsilateral recurrent lumbar disc herniation. A prospective, controlled study. *J Bone Joint Surg Br*. 1998;80(5):825–832.
38. Lee YS, Choi ES, Song CJ. Symptomatic Nerve Root Changes on Contrast-Enhanced MR Imaging after Surgery for Lumbar Disk Herniation. *Am J Neuroradiol*. 2009;30(5):1062–1067.
39. Jinkins JR, Osborn AG, Garrett D, Hunt S, Story JL. Spinal nerve enhancement with Gd-DTPA: MR correlation with the postoperative lumbosacral spine. *AJNR Am J Neuroradiol*. 14(2):383–394.
40. Guyer RD, Patterson M, Ohnmeiss DD. Failed back surgery syndrome: diagnostic evaluation. *J Am Acad Orthop Surg*. 2006;14(9):534–543.
41. Racz G, Holubec J. *Techniques of neurolysis*. Boston: Kluwer Academic; 1989. p. 57–72.

42. Kuslich SD, Ulstrom CL, Michael CJ. The tissue origin of low back pain and sciatica: a report of pain response to tissue stimulation during operations on the lumbar spine using local anesthesia. *Orthop Clin North Am*. 1991;22(2):181–187.
43. Austin PJ, Moalem-Taylor G. The neuro-immune balance in neuropathic pain: Involvement of inflammatory immune cells, immune-like glial cells and cytokines. *J Neuroimmunol*. 2010;229(1–2):26–50.
44. Scuderi GJ, Cuellar JM, Cuellar VG, Yeomans DC, Carragee EJ, Angst MS. Epidural Interferon Gamma-Immunoreactivity. *Spine (Phila Pa 1976)*. 2009;34(21):2311–2317.
45. Murata Y, Olmarker K, Larsson K, Takahashi K, Rydevik B. Production of tumor necrosis factor-α from porcine nucleus pulposus cells at various time points in cell culture under conditions of nutritional deficiency. *Cytokine*. 2006;34(3–4):206–211.
46. Lee F, Jamison DE, Hurley RW, Cohen SP. Epidural Lysis of Adhesions. *Korean J Pain*. 2014;27(1):3.
47. Rabinovitch DL, Peliowski A, Furlan AD. Influence of lumbar epidural injection volume on pain relief for radicular leg pain and/or low back pain. *Spine J*. 2009;9(6):509–517.
48. Chan C, Peng P. Failed back surgery syndrome. *Pain Med*. 2011;12(4):577–606.
49. Hsu HC, Wu JJ, Jim YF, Chang CY, Lo WH, Yang DJ. Calcific tendinitis and rotator cuff tearing: A clinical and radiographic study. *J Shoulder Elbow Surg*. 1994;3(3):159–164.
50. Kalichman L, Cole R, Kim DH, Li L, Suri P, Guermazi A, Hunter DJ. Spinal stenosis prevalence and association with symptoms: the Framingham Study. *Spine J*. 2009;9(7):545–550.
51. Yabe Y, Hagiwara Y, Ando A, Tsuchiya M, Minowa T, Takemura T, Honda M, Hatori K, Sonofuchi K, Kanazawa K, Koide M, Sekiguchi T, Itoi E. Chondrogenic and Fibrotic Process in the Ligamentum Flavum of Patients With Lumbar Spinal Canal Stenosis. *Spine (Phila Pa 1976)*. 2015;40(7):429–435.
52. Okada K, Oka S, Tohge K, Ono K, Yonenobu K, Hosoya T. Thoracic myelopathy caused by ossification of the ligamentum flavum. Clinicopathologic study and surgical treatment. *Spine (Phila Pa 1976)*. 1991;16(3):280–287.
53. Safak AA, Is M, Sevinc O, Barut C, Eryoruk N, Erdogmus B, Dosoglu M. The thickness of the ligamentum flavum in relation to age and gender. *Clin Anat*. 2009;23(1):NA–NA.
54. Racz GB, Sabonghy M, Gintautas J, Kline WM. Intractable pain therapy using a new epidural catheter. *JAMA*. 1982;248(5):579–581.
55. Chun-jing H, Hao-xiong N, jia-xiang N. The application of percutaneous lysis of epidural adhesions in patients with failed back surgery syndrome. *Acta Cir Bras*. 2012;27(4):357–362.
56. Manchikanti L, Singh V, Cash KA, Pampati V. Assessment of effectiveness of percutaneous adhesiolysis and caudal epidural injections in managing post lumbar surgery syndrome: 2-year follow-up of a randomized, controlled trial. *J Pain Res*. 2012;5:597.
57. Moon SH, Park JY, Cho S-S, Cho H-S, Lee J-Y, Kim YJ, Choi S-S. Comparative effectiveness of percutaneous epidural adhesiolysis for different sacrum types in patients with chronic pain due to lumbar disc herniation: A propensity score matching analysis. *Medicine (Baltimore)*. 2016;95(37):e4647.
58. Choi SS, Joo EY, Hwang BS, Lee JH, Lee G, Suh JH, Leem JG, Shin JW. A novel balloon-inflatable catheter for percutaneous epidural adhesiolysis and decompression. *Korean J Pain*. 2014;27(2):178–185.
59. Racz GB, Heavner JE, Trescot A. Percutaneous Lysis of Epidural Adhesions—Evidence for Safety and Efficacy. *Pain Pract*. 2008;8(4):277–286.
60. Moon SH, Lee J Il, Cho HS, Shin JW, Koh WU. Factors for Predicting Favorable Outcome of Percutaneous Epidural Adhesiolysis for Lumbar Disc Herniation. *Pain Res Manag*. 2017;2017:1494538.
61. Helm S, Knezevic NN. A review of the role of epidural percutaneous neuroplasty. *Pain Manag*. 2019;9(1):53–62.
62. Akbas M, Elawamy AR, Salem HH, Fouad AZ, Abbas NA, Dagistan G. Comparison of 3 Approaches to Percutaneous Epidural Adhesiolysis and Neuroplasty in Post Lumbar Surgery Syndrome. *Pain Physician*. 2018;21(5):E501–E508.
63. Chang HO, Ji G, Cho P, Choi W, Shin D, Keung NK, Kang H. The catheter tip position and effects of percutaneous epidural neuroplasty in patients with lumbar disc disease during 6-months of follow-up. - PubMed - NCBI. 2014. p. 599–608.
64. Foulkes GD, Robinson JS. Intraoperative dexamethasone irrigation in lumbar microdiskectomy. *Clin Orthop Relat Res*. 1990;(261):224–228.
65. Cenic A, Kachur E. Lumbar discectomy: a national survey of neurosurgeons and literature review. *Can J Neurol Sci*. 2009;36(2):196–200.
66. Asomugha EU, Miller JA, McLain RF. Surgical Site Infections in Posterior Lumbar Surgery. *Spine (Phila Pa 1976)*. 2017;42(1):63–69.
67. Akinduro OO, Miller BA, Haussen DC, Pradilla G, Ahmad FU. Complications of intraoperative epidural steroid use in lumbar discectomy: a systematic review and meta-analysis. *Neurosurg Focus*. 2015;39(4):E12.
68. Hu A, Gu X, Guan X, Fan G, He S. Epidural versus intravenous steroids application following percutaneous endoscopic lumbar discectomy. *Medicine (Baltimore)*. 2018;97(18):e0654.

69. Rasmussen S, Krum-Møller DS, Lauridsen LR, Jensen SEH, Mandøe H, Gerlif C, Kehlet H. Epidural Steroid Following Discectomy for Herniated Lumbar Disc Reduces Neurological Impairment and Enhances Recovery. *Spine (Phila Pa 1976)*. 2008;33(19):2028–2033.
70. Erdine SK, Talu G. Precautions During Epidural Neuroplasty. *Pain Pract*. 2002;2(4):308–314.
71. Talu GK, Erdine S. Complications of Epidural Neuroplasty: A Retrospective Evaluation. *Neuromodulation Technol Neural Interface*. 2003;6(4):237–247.
72. Lim YS, Jung KT, Park CH, Wee SW, Sin SS, Kim J. Acute Motor Weakness of Opposite Lower Extremity after Percutaneous Epidural Neuroplasty. *Korean J Pain*. 2015;28(2):144.
73. Kim TH, Shin JJ, Lee WY. Surgical treatment of a broken neuroplasty catheter in the epidural space: a case report. *J Med Case Rep*. 2016;10(1):277.
74. Lee C-H, Son J-W, Kim U. Reverse Takotsubo Cardiomyopathy following Inadvertent Intrathecal Injection during Percutaneous Epidural Neuroplasty. *Hear Lung Circ*. 2015;24(9):e148–151.
75. Kim SB, Kim MK, Kim KD, Lim YJ. Unintended complication of intracranial subdural hematoma after percutaneous epidural neuroplasty. *J Korean Neurosurg Soc*. 2014;55(3):170–172.
76. Magro E, Remy-Neris O, Seizeur R, Allano V, Quinio B, Dam-Hieu P. Bilateral Subdural Hematoma Following Implantation of Intrathecal Drug Delivery Device. *Neuromodulation Technol Neural Interface*. 2011;14(2):179–182.
77. Wagner K, Sprenger T, Pecho C, Kochs E, Tölle T, Berthele A, Gerdesmeyer L. Schwerwiegende Risiken und Komplikationen der epiduralen Neurolyse nach Racz. *ains · Anästhesiologie · Intensivmed · Notfallmedizin · Schmerztherapie*. 2006;41(4):213–222.
78. Helm S, Hayek SM, Colson J, Chopra P, Deer TR, Justiz R, Hameed M, Falco FJE. Spinal endoscopic adhesiolysis in post lumbar surgery syndrome: an update of assessment of the evidence. *Pain Physician*. 2013;16(2 Suppl):SE125–150.
79. Pereira P, Severo M, Monteiro P, Silva PA, Rebelo V, Castro-Lopes JM, Vaz R. Results of Lumbar Endoscopic Adhesiolysis Using a Radiofrequency Catheter in Patients with Postoperative Fibrosis and Persistent or Recurrent Symptoms After Discectomy. *Pain Pract*. 2016;16(1):67–79.
80. Manchikanti L, Boswell MV, Rivera JJ, Pampati VS, Damron KS, McManus CD, Brandon DE, Wilson SR. A randomized, controlled trial of spinal endoscopic adhesiolysis in chronic refractory low back and lower extremity pain [ISRCTN 16558617]. *BMC Anesthesiol*. 2005;5(1):10.
81. Donato A Di, Fontana C, Pinto R, Beltrutti D, Pinto G. The effectiveness of endoscopic epidurolysis in treatment of degenerative chronic low back pain: a prospective analysis and follow-up at 48 months. *Acta Neurochir Suppl*. 2011;108:67–73.
82. Brito-García N, García-Pérez L, Kovacs FM, del Pino-Sedeño T, Pérez-Ramos J, Imaz-Iglesia I, Serrano-Aguilar P. Efficacy, Effectiveness, Safety, and Cost-effectiveness of Epidural Adhesiolysis for Treating Failed Back Surgery Syndrome. A Systematic Review. *Pain Med*. 2019;20(4):692–706.
83. Hayek SM, Helm S, Benyamin RM, Singh V, Bryce DA, Smith HS. Effectiveness of spinal endoscopic adhesiolysis in post lumbar surgery syndrome: a systematic review. *Pain Physician*. 12(2):419–435.
84. Suzuki T, Inokuchi R, Hanaoka K, Suka M, Yanagisawa H. Dexmedetomidine use during epiduroscopy reduces fentanyl use and postoperative nausea and vomiting: A single-center retrospective study. *SAGE open Med*. 2018;6:2050312118756804.
85. Wang B, Li P, Shangguan L, Ma J, Mao K, Zhang Q, Wang Y, Liu Z, Mao K. A novel bacterial cellulose membrane immobilized with human umbilical cord mesenchymal stem cells-derived exosome prevents epidural fibrosis. *Int J Nanomedicine*. 2018;13:5257–5273.
86. Tao H, Fan H. Implantation of amniotic membrane to reduce postlaminectomy epidural adhesions. *Eur Spine J*. 2009;18(8):1202–1212.
87. Dai J, Li X, Yan L, Chen H, He J, Wang S, Wang J, Sun Y. The effect of suramin on inhibiting fibroblast proliferation and preventing epidural fibrosis after laminectomy in rats. *J Orthop Surg Res*. 2016;11(1):108.
88. Zhang C, Kong X, Ning G, Liang Z, Qu T, Chen F, Cao D, Wang T, Sharma HS, Feng S. All-trans retinoic acid prevents epidural fibrosis through NF-κB signaling pathway in post-laminectomy rats. *Neuropharmacology*. 2014;79:275–281.
89. Wan Q, Chen H, Li X, Yan L, Sun Y, Wang J. Artesunate inhibits fibroblasts proliferation and reduces surgery-induced epidural fibrosis via the autophagy-mediated p53/p21waf1/cip1 pathway. *Eur J Pharmacol*. 2019;842:197–207.
90. Sun Y, Zhao S, Li X, Yan L, Wang J, Wang D, Chen H, Dai J, He J. Local application of rapamycin reduces epidural fibrosis after laminectomy via inhibiting fibroblast proliferation and prompting apoptosis. *J Orthop Surg Res*. 2016;11(1):58.
91. Demirel E, Yildiz K, Çadirci K, Aygün H, Şenocak E, Gündoğdu B. Effect of platelet-rich fibrin on epidural fibrosis and comparison to ADCON® Gel and hyaluronic acid. *Acta Orthop Traumatol Turc*. 2018;52(6):469–474.