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Therapeutic Trial Protocol

Protocol for Evaluation of the Comparative Effectiveness of Percutaneous Adhesiolysis and Caudal Epidural Steroid Injections in Low Back and/or Lower Extremity Pain without Post Surgery Syndrome or Spinal Stenosis

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Background: Treatment of chronic low back pain with or without lower extremity pain continues to be a challenge. Epidural steroids are commonly utilized in patients after the failure of conservative treatment. The results of epidural steroid injections have been variable based on the pathophysiology, the route of administration, injected drugs, and utilization of fluoroscopy. In patients resistant to fluoroscopically directed epidural injections, percutaneous epidural adhesiolysis and percutaneous targeted delivery of injections with or without adhesiolysis has been recommended. Percutaneous adhesiolysis has been studied in chronic pain syndromes related to post laminectomy syndrome and spinal stenosis with encouraging results.

There is a paucity of literature regarding the effectiveness of the targeted delivery of medications with or without epidural adhesiolysis in patients recalcitrant to epidural steroid injections without a history of surgery and spinal stenosis.

Study Design: A randomized, equivalence trial of percutaneous lumbar adhesiolysis and caudal epidural steroid injections in patients with low back and/or lower extremity pain without post surgery syndrome or spinal stenosis.

Setting: An interventional pain management practice setting in the United States.

Objective: The study is designed to evaluate the effectiveness of percutaneous epidural adhesiolysis in managing chronic low back and/or lower extremity pain in patients without post lumbar surgery syndrome or spinal stenosis and compare it with fluoroscopically directed caudal epidural steroid injections

Methods: The study design includes 120 patients randomly assigned into 2 groups. Group I (60 patients), the control group, will receive caudal epidural injections with catheterization up to S3 with local anesthetic, steroids, and 0.9% sodium chloride solution; Group II (60 patients), the intervention group, will receive percutaneous adhesiolysis with target delivery of lidocaine, 10% hypertonic sodium chloride solution, and non-participate betamethasone. Randomization will be performed by computer-generated random allocation sequence by simple randomization.

Outcome Measures: Multiple outcome measures will be utilized including numeric rating scale (NRS), the Oswestry Disability Index 2.0 (ODI), employment status, and opioid intake with assessment at 3, 6, 12, 18 and 24 months post treatment.

Significant pain relief is considered as 50% or more, whereas significant improvement in the disability score is defined as a reduction of 40% or more.

Results: The results will be analyzed to show significant relief as well as improvement in functional status.

Limitations: This study is limited by potentially inadequate double blinding and the lack of a placebo group.

Conclusion: This protocol describes a comparative effectiveness evaluation of percutaneous adhesiolysis and epidural steroid injections in managing chronic low back and lower extremity pain in patients without post surgery syndrome or spinal stenosis utilizing a randomized, equivalence trial design.

Clinical Trial Registration: NCT01053273

Key words: Chronic low back pain, disc herniation, post lumbar surgery syndrome, spinal stenosis, epidural steroid injections, percutaneous adhesiolysis, randomized trial, comparative effectiveness

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Despite advances in biomedical knowledge and the highest per capita health care expenditures in the world, the quality and outcome of health care vary dramatically across the United States (1-8). Accordingly, the trend to develop and implement research and support of evidence-based practice has been a focus of medical practice for the past decade. As an emerging specialty, interventional pain management faces multiple problems which may be disproportionate compared to established medical specialties. Interventional pain management is faced with the task of increasing appropriate utilization of effective, safe techniques due to its emerging nature, as well as eliminating potentially inappropriate care that may be ineffective or unsafe (5,6,8-16). The available evidence at the present time documents a wide degree of variance in the definition and the practice of medicine in general and interventional pain management in particular (8-16). Numerous developments, questions and issues have been reported in recent years with regard to multiple interventional techniques, including percutaneous adhesiolysis.

It has become an essential part of medicine to provide randomized comparative effectiveness or efficacy trials to prove the clinical, as well as cost effectiveness, of multiple treatments provided (1,2).

1.0 Introduction

Treatment of chronic low back pain with or without lower extremity pain continues to be a challenge. Epidural steroids are commonly utilized in patients after the failure of conservative management (5,9-29). The results of epidural steroid injections have been variable based on the pathophysiology, the route of administration, injected drugs, and utilization of fluoroscopy (5,9-29). In patients resistant to fluoroscopically directed epidural injections, percutaneous targeted delivery of injected drugs with or without adhesiolysis has been recommended (30-44). A number of studies have reported the effectiveness of percutaneous adhesiolysis in post laminectomy syndrome and spinal stenosis (33-43). However, patients who are recalcitrant to epidural steroid injections without a history of post surgery syndrome or spinal stenosis have not been studied separately using targeted delivery of medication with or without percutaneous lumbar epidural adhesiolysis.

1.1 Targeted Delivery of Steroids, Adhesiolysis, and Hypertonic Saline Neurolysis

Adhesiolysis of epidural scar tissue, followed by the injection of hypertonic saline, has been described by Racz and coworkers in multiple publications. The technique described by Racz and colleagues involved epidurography, adhesiolysis, and injection of hyaluronidase, bupivacaine, triamcinolone diacetate, and 10% sodium chloride solution on day one, followed by injections of bupivacaine and hypertonic sodium chloride solution on days 2 and 3. Manchikanti and colleagues modified the Racz protocol from a 3-day procedure to a one-day procedure.

The goal of percutaneous lysis of epidural adhesions is to assure delivery of high concentrations of injected drugs to the target areas. Thus, percutaneous epidural lysis of adhesions is the first and most commonly used treatment to incorporate multiple therapeutic goals (31,32).

A number of studies have demonstrated the efficacy of percutaneous adhesiolysis. The majority of the studies used a heterogeneous population, which also included a non-surgical population and a spinal stenosis population. Thus, it is very difficult to interpret the results specific to non-surgical and non-spinal stenosis patients with either disc herniation or degenerative disc disease.

Manchikanti et al (34) evaluated the role of adhesiolysis, specifically with a control group receiving epidural steroid injection only where the catheter was inserted without adhesiolysis, followed by an injection of epidural steroid and local anesthetic injection with so-

dium chloride solution injection with a catheter in place in the sacral region (S2 or S3), and with Group II and Group III undergoing adhesiolysis. Also, Manchikanti et al (42) evaluated the effectiveness of adhesiolysis only in post lumbar surgery syndrome patients with publication of the preliminary results. These results showed 73% of patients responding positively in the intervention group. The protocol was similar to the one described above (34). Manchikanti et al (43) also evaluated the effectiveness of adhesiolysis in spinal stenosis. All 6 studies (33,34,40-43) showed positive results for short-term and long-term improvement with adhesiolysis, either over the control group or with patients as their own controls.

1.2 Pathophysiology

Epidural fibrosis is a progressive disease. There are many possible etiologies of epidural fibrosis, including annular tear, hematoma, infection, surgical trauma, or intrathecal contrast media (45). LaRocca and Macnab (46) have demonstrated the invasion of fibrous connective tissue into the postoperative hematoma as a cause of epidural fibrosis. McCarron et al (47) investigated the irritative effect of material from the nucleus pulposus upon the dural sac, adjacent nerve roots, and nerve root sleeves independent of the influence of direct compression upon these structures. McCarron (48) further explored epidural fibrosis in an experimental model in adult mongrel dogs. He reported an inflammatory reaction in the spinal cord sections taken from dogs sacrificed after the initial injection of homogenized nucleus pulposus, whereas the spinal cord was grossly normal after the initial injection of normal saline.

Lumbosacral radicular syndrome is known by a range of terms in the literature, such as "sciatica," "radiculitis," "radiculopathy," "nerve root pain," and "nerve root entrapment" or "irritation" (49). Radicular pain is readily recognized in most cases in clinical practice in low back pain. It is generally defined as pain radiating to the leg, normally below the knee and into the foot and toes. The first to create widespread interest in the disc as a source of radicular pain in American literature were Mixter and Barr (50) with their 1934 hallmark description of the herniated nucleus pulposus. However, the pathophysiology of lumbar radicular pain is a subject of ongoing research and controversy with only a limited causative role for disc herniation and radiculitis, with non-specific or discogenic and facet joint pain assuming major roles (51-74). The pathophysiology of radicular pain assumes not only a mechanical component, but also multiple other factors including inflammation of the compressed nerve root, vascular compromise, and neurotoxicity (47,74-85).

Kuslich et al (69) identified intervertebral discs, facet joints, ligaments, fascia, muscles, and nerve root dura as tissues capable of transmitting pain in the low back. The human intervertebral disc in the lumbar spine has been known to cause low back and lower extremity pain secondary to disc disruption, disc herniation, and nerve root compression (49,50,68-95). Nerve root compression may be caused by disc herniation, spinal stenosis, and osteoarthritis. Chemical radiculitis and residual pain after surgical interventions, also known as post surgery syndrome, are also common factors in the causation of low back and lower extremity pain related to the disc (91-95).

1.3 Rationale

It has been reasoned that inflammation, edema, fibrosis, and venous congestion; mechanical pressure on posterior longitudinal ligaments, annulus fibrosus, and spinal nerve; reduced or absent nutrient delivery to the spinal nerve or nerve root; and central sensitization may be present in patients with radiculitis with disc herniation, stenosis, and epidural fibrosis. Hence, it has been postulated as reasonable to treat back pain with or without radiculopathy with the local application of anti-inflammatory medication agents (e.g., corticosteroids) aimed at reducing edema (e.g., hypertonic sodium chloride solution, corticosteroids), local anesthetics, and hyaluronidase to promote lysis (32,33). Thus, percutaneous lysis of adhesions is indicated in patients with appropriate diagnostic evaluation and after the failure or ineffectiveness of conservative modalities of treatment have been proven.

The underlying mechanism of action of epidurally administered steroid and local anesthetic injections is still not well understood. It is believed that the achieved neural blockade alters or interrupts nociceptive input, reflex mechanism of the afferent fibers, self-sustaining activity of the neurons, and the pattern of central neuronal activities (5,21,68,96,97). Further, corticosteroids have been shown to reduce inflammation by inhibiting either the synthesis or release of a number of pro-inflammatory mediators and by causing a reversible local anesthetic effect (97-105). In contrast, local anesthetics have been described to provide short- to long-term symptomatic relief by suppression of nociceptive discharge (106-108), the block of axonal transport (109,110) of the sympathetic reflex arch

(111), the block of sensitization (112), and anti-inflammatory effect (113). The long-lasting effect of local anesthetics in nerve blocks has been demonstrated in multiple studies (17-20,113-119). Sato et al (116) evaluated the prolonged analgesic effect of epidural bupivacaine in a rat model of neuropathic pain and concluded that repetitive administration of bupivacaine into the epidural space in rats exerts an analgesic effect, possibly by inducing a plastic change in nociceptive input. Further, Tachihara et al (120) showed in rats that nerve root infiltration prevented mechanical allodynia, however, no additional benefit from using corticosteroid was identified, suggesting that corticosteroid may be unnecessary for nerve root blocks.

1.4 Complications

The most common and worrisome complications of adhesiolysis in the lumbar spine are related to dural puncture, spinal cord compression, catheter shearing, infection, steroids, hypertonic saline, and hyaluronidase (121-138).

Spinal cord compression following rapid injections into the epidural space, which may cause large increases in intraspinal pressure with a risk of cerebral hemorrhage, visual disturbance, headache, and compromise of spinal cord blood flow, has been mentioned. However, the only complication reported following epidural injection has been vision loss; no such complications have been reported following adhesiolysis and hypertonic saline neurolysis.

Epidural infection following this procedure is a distinct possibility due to the procedure itself, as well as potential immunosuppression secondary to steroid injection.

The potential of spinal cord trauma is more likely with percutaneous adhesiolysis with hypertonic saline injection than with other epidural procedures including epidural injections, as the injection of adjuvant agents with preservatives may be unforgiving. Additional issues with transforaminal epidural adhesiolysis include intravascular penetration and neural trauma that may be higher than caudal or intralaminar. The incidence of vascular epidural injections documented by contrast-enhanced fluoroscopic imaging and negative blood aspiration has varied from 5% to 11%.

Neural trauma is a potential complication even though there are no such case reports either with caudal or transforaminal epidural adhesiolysis.

Other side effects are related to the administration of steroids, and are generally attributed to the chemistry or pharmacology of the steroids. The major theoretical complications of corticosteroid administration include arachnoiditis, suppression of the pituitary-adrenal axis, hypocorticism, Cushing's syndrome, osteoporosis, avascular necrosis of bone, steroid myopathy, weight gain, fluid retention, and hyperglycemia. Other potential complications include hypertension, hypokalemia, epidural lipomatosis, retinal hemorrhage, increased intraocular pressure, subcapsular cataract formation, insomnia, mood swings, psychosis, facial flushing, headache, gastrointestinal disturbances, and menstrual disturbances. Manchikanti et al (138) evaluated the effect of neuraxial steroids on weight and bone mass density prospectively. The results of serial determination of weight and bone mass density showed no significant change at any interval or at the end of one year. They concluded that low-dose administration of neuraxial steroids is safe in patients suffering with chronic pain who have failed to respond to conservative modalities of treatments with a favorable risk-benefit ratio, without any deleterious effects either on body weight or bone mass density.

2.0 Investigational Methodology

2.1 Site and Location

The study will be conducted in an interventional pain management practice and a specialty referral center in a private practice setting in the United States. The study will be performed based on Consolidated Standards of Reporting Trials (CONSORT) guidelines and an extension of the CONSORT statement reporting non-inferiority and equivalence in randomized trials (139,140).

2.2 IRB Approval of Study Protocol

The study protocol has been approved by the Institutional Review Board (IRB) and has been registered in the U.S. Clinical Trial Registry with an assigned number of NCT01053273.

2.3 Informed Consent

All patients will be provided with the IRB-approved protocol and informed consent which will describe in detail all aspects of the study and withdrawal process.

Patients considered suitable by the investigator for participation in this clinical investigation will be given a verbal explanation of the nature of their clinical condition and this investigation and supplied with written informed consent. Each patient will be allowed sufficient time to decide whether they wish to participate in this investigation. The investigator or another member

of the investigative team will address any questions regarding this investigation appropriately.

Patients will be instructed that they are free to obtain further information from the investigator at any time, that they are free to withdraw their consent, and to discontinue their participation in the study at any time without prejudice. If the patient is willing to participate in this investigation, written informed consent will be obtained. Written informed consent from the subject must be obtained before any of the screening procedures are performed. In addition, the consent must be written in a language in which the patient is literate.

2.4 Participants

The study is designed to assign 120 patients into 2 groups: Group I will receive caudal epidural injections with catheterization up to S3 with local anesthetic, steroids, and 0.9% sodium chloride solution; Group II will receive percutaneous adhesiolysis with targeted delivery of lidocaine, 10% hypertonic sodium chloride solution, and non-particulate betamethasone.

2.4.1 Participant Flow

Participant flow will be described utilizing schematic presentation of patient flow with a flow diagram as recommended by CONSORT (139,140).

2.5 Interventions

The summary of steps of the procedure are illustrated in Table 1.

2.5.1 Description of Interventions

All procedures will be performed in a sterile operating room under sterile conditions utilizing fluoroscopy and a specially designed RK needle and a Racz® catheter 19 gauge Brevi-STF.

2.5.1.1 Procedure

The procedure will include appropriate preparation with intervenous access, antibiotic administration, and appropriate sedation.

An RK needle will be introduced into the sacral epidural space under intermittent fluoroscopy. Once the needle placement is confirmed to be in the epidural space, a lumbar epidurogram will be carried out, utilizing approximately 5 mL of contrast (Omnipaque® 240). Identification of the filling defects will be carried out by examining the contrast flow into the nerve roots. Intravascular or subarachnoid placement of the needle or contrast will be avoided; if such malpositioning occurs, the needle will be repositioned.

In Group I, after appropriate determination of epidurography, a Racz catheter will be passed through the RK needle up to S3 and additional Omnipaque 240, 3 mL, will be injected. Following this, 5 mL of 2% preservative-free Xylocaine will be injected into the epidural space through the catheter.

In Group II, after identification of the filling defects, the Racz catheter will be advanced through the RK needle to the area of the filling defect or the site of pathology as determined by magnetic resonance imaging (MRI), computed tomography (CT), or symptomatology.

Adhesiolysis will be carried out and the final positioning will be achieved in the epidural space laterally and ventrally. After satisfactory positioning, at least 3 mL of contrast will be injected. If there is no subarachnoid, intravascular, or other extra epidural filling and

Table 1. *Summary of steps and procedural considerations.*

GROUP I (Control Group)	GROUP II (Intervention Group)
1. Preparation	1. Preparation
2. Epidurography	2. Epidurography
3. Introduction of catheter up to S3 or S2	3. Introduction of catheter to level of defect
4. No adhesiolysis	4. Adhesiolysis and/or targeted catheter positioning
5. Repeat epidurography	5. Epidurography with confirmation of ventral and lateral filling
6. Injection of 5 mL of 2% lidocaine	6. Injection of 5 mL of 2% lidocaine
7. Transfer to recovery room	7. Transfer to recovery room
8. Injection of 6 mL of normal saline	8. Injection of 6 mL of 10% sodium chloride solution
9. Injection of 6 mg of non-particulate betamethasone	9. Injection of 6 mg of non-particulate betamethasone
10. Injection of 1 mL of normal saline and removal of catheter	10. Injection of 1 mL of normal saline and removal of catheter

satisfactory filling is obtained with epidural and targeted nerve root filling, 5 mL of 2% preservative-free Xylocaine will be injected.

2.5.1.2 Recovery Room

After 10 to 15 minutes of monitoring, the injection of sodium chloride solution (0.9% in Group I or 10% in Group II) will be carried out by repeat injection in doses of 2 to 3 mL, followed by injection of 6 mg of non-particulate Betamethasone and 1 mL of sodium chloride solution and then removal of the catheter.

The patient will be ambulated if all parameters are satisfactory. Intravenous access will be removed and the patient will be discharged home with appropriate instructions.

Repeat percutaneous adhesiolysis injections will be provided based on the response to the prior injections evaluated by improvement in physical and functional status followed by subsequent increased levels of pain being reported and deteriorating relief below 50% and with deterioration in functional status.

2.5.1.3 Devices

In order to perform the percutaneous adhesiolysis procedure, RK #15-gauge coude needle and Racz catheter #19 gauge XL STF and other items are required. These items are manufactured by:

Epimed Inc.
3100 Premiere Drive, Suite 232
Irving TX 75063
Telephone: 800-727-1201

2.5.1.4 Additional Interventions

All the patients will undergo the treatments as assigned. A patient will be unblinded on request or if an emergency situation exists. If a patient requires additional procedures, they will be provided based on the response to the previous injections, either after unblinding or without unblinding. If the patient chooses not to be unblinded, the prior treatment will be repeated as assigned. Patients who are non-responsive, but continue with conservative management, will be followed without further study procedures with medical management, unless they request unblinding. In addition, all patients who are unblinded at any time and those who are lost to follow-up at one year will be considered withdrawn.

2.5.1.5 Co-Interventions

It is expected that most patients will be receiving opioid and non-opioid analgesics, as well as adjuvant analgesics; some will be involved in a therapeutic exercise program. If patients improve significantly and the medical necessity for these drugs is lacking, medications will be stopped or dosages will be decreased. In addition, dosages will also be increased based on medical necessity. All patients will continue previously directed exercise programs, as well as their work. Thus, no specific physical therapy, occupational therapy, bracing, or other interventions are offered other than the study intervention.

2.6 Pre-Enrollment Evaluation

The pre-enrollment evaluation will include collection of demographic data, medical and surgical history listing co-existing disease(s), radiologic investigations, physical examination, pain rating scores using the numeric rating scale (NRS), work status, opioid intake, and functional status assessment by the Oswestry Disability Index (ODI).

2.6.1 Inclusion Criteria

Patients with a history of chronic function-limiting low back pain with or without lower extremity pain of at least 6 months duration; and patients who are competent to understand the study protocol and provide voluntary, written informed consent and participate in outcome measurements.

Inclusion criteria will also include no evidence of facet joint pain and failure to improve substantially with conservative management including but not limited to physical therapy, chiropractic manipulation, exercises, drug therapy, bedrest, and fluoroscopically directed caudal or transforaminal epidural injections.

Exclusion criteria will include post surgery syndrome, central spinal stenosis, and facet joints as sole pain generators, unstable or heavy opioid use (400 mg of morphine equivalents daily), uncontrolled psychiatric disorders, uncontrolled medical illness, any conditions that could interfere with the interpretation of the outcome assessments, pregnant or lactating women, and patients with a history or potential for adverse reaction(s) to local anesthetic, steroids, or hypertonic sodium chloride solution.

2.6.2 Subject Eligibility and Identification

Once signed informed consent has been obtained from the patient, the eligibility checklists contained in the case report form (CRF) will be completed.

Where a patient fails to fulfill any element of the inclusion and exclusion criteria, the failure will be documented in the patient source notes. The investigator will retain the signed consent form and completed eligibility. These patients will not be enrolled into this clinical investigation.

2.6.3 Contraindications

Contraindications include, but are not limited to, coagulopathy, pregnancy, renal insufficiency, chronic liver dysfunction, history of adverse reaction to local anesthetic or anti-inflammatory drugs, history of gastrointestinal bleeding or ulcers, urinary sphincter dysfunction, progressive neurological deficit, infection, increased intracranial pressure, pseudotumor cerebri, intracranial tumors, unstable angina, severe chronic obstructive pulmonary disease, inability to achieve appropriate positioning, and inability to understand informed consent and protocol. The procedure should never be performed under general anesthesia. Other minor or related contraindications include generalized symptomatology as well as active untreated or resistant psychiatric disorders affecting physical condition, and visual deficiencies.

2.7 Objectives

The study is designed to evaluate the effectiveness of percutaneous epidural adhesiolysis in managing chronic low back and/or lower extremity pain in patients without post lumbar surgery syndrome or spinal stenosis and compare it with fluoroscopically directed caudal epidural steroid injections.

2.8 Outcomes

Multiple outcome measures will be utilized including the NRS (0 – 10 scale), the ODI on a 0 – 50 scale, employment status, and opioid intake in terms of daily intake of morphine equivalents, with assessment at 3, 6, 12, 18, and 24 months post treatment. The value and validity of the NRS and ODI have been reported (141-145). Thresholds for the minimum clinically important difference for the ODI varied from a 4 to 15 point change from a total score of 50. Significant pain relief is described as 50% or more reduction in the NRS from baseline, whereas significant improvement in function is described as at least a 40% reduction in the ODI (26-29,42,43,117-119).

Based on the dosage frequency and schedule of the drug, the opioid intake will be converted into morphine equivalents (146).

Employment and work status will be determined based on employability at the time of enrollment rather than including all patients in the study as employable. Employment and work status will be classified into multiple categories such as employable, housewife with no desire to work outside the home, retired, or over the age 65. Patients who are unemployed due to pain or employed but on sick leave or laid off will be considered as employable.

2.9 Data Management and Analysis

2.9.1 Sample Size

Sample size was calculated based on reduction of NRS. A 25% clinical difference change of 1.15 (d) was set from a previous study (34). With standard deviation (σ) of the NRS of 2.3, $\delta = d/\sigma$, $\delta = 0.50$, to achieve an alpha of 0.05 and beta of 0.20 with 80% power (147), it will require 60 patients in each group of the trial. One hundred patients in each group would provide 95% power (i.e., alpha and beta of 0.05).

Previous studies of interventional techniques have confirmed that 50 to 60 patients is acceptable (26-29,42,43,117-119,148).

2.9.2 Statistical Methods

Statistical analysis will include chi-squared statistic, Fisher's exact test, t-test, and paired t-test. Results will be considered statistically significant if the *P* value is less than 0.05.

Chi-squared statistic will be used to test the differences in proportions. Fisher's exact test will be used wherever the expected value is less than 5; a paired t-test will be used to compare the pre- and post-treatment results of average pain scores and ODI measurements at baseline versus 3, 6, 12, 18, and 24 months. For comparison of mean scores between groups, a t-test will be performed.

2.9.3 Intent-to-Treat-Analysis

An intent-to-treat-analysis will be performed. Either the last follow-up data or initial data will be utilized in the patients who drop out of the study and no other data is available.

2.10 Randomization

A total of 120 patients with 60 patients randomly assigned into 2 groups.

2.10.1 Sequence Generation

Randomization will be performed by computer

generated random allocations sequence by simple randomization.

2.10.2 Allocation Concealment

The operating room nurse assisting with the procedure will randomize the patients and prepare the drugs appropriately.

2.10.3 Implementation

Participants will be invited to enroll in the study if they meet inclusion criteria. One of 3 nurses assigned as coordinators of the study will enroll the participants and assign participants to their respective groups.

2.10.4 Blinding (Masking)

Participants and those administering the interventions will be blinded to the group assignment. The blinding will be assured by mixing the patients with other patients receiving routine treatment and not informing the physician performing the procedure of the inclusion of the patients in the study.

3.0 Safety Assessments

3.1 Adverse Event Occurrence

At each follow-up assessment (3, 6, 12, 18, and 24 months post-treatment), details of any adverse event or adverse device effect reported by the subject will be recorded in the CRF. Details to be recorded include the nature, onset, duration, severity, and relationship to the invasive procedure and outcome of the event.

The occurrence of adverse events (including new illnesses, worsening symptoms of coexisting diseases, or additional symptoms) will be identified by spontaneous reports from the subject or by clinical/radiological assessment.

3.2 Adverse Event Reporting

According to the FDA's Clinical Investigation of Medical Devices for Human Subjects, an adverse event is defined as "any undesirable clinical occurrence in a subject whether it is considered device related or not." In addition, an adverse device effect or undesirable side effect, is defined as "a device related adverse event."

A record of all adverse events, as well as details of the nature, onset, duration, severity, and relationship to the device, will be recorded on the relevant section(s) of the subject's CRF. The subject will be questioned about any adverse event(s) at each subsequent follow-up assessment visit.

An adverse event or an adverse device effect may be mild, moderate, or severe, and is usually unexpected. A serious adverse event or adverse device effect is defined as any experience that:

1) Is fatal or life-threatening;
2) Is permanently incapacitating or disabling;
3) Requires in-patient hospitalization because of a potential disability, danger to life, or an intervention has been necessitated;
4) Malignancy results.

All serious adverse events or serious adverse device effects, which occur during this investigation, must be reported immediately by telephone or facsimile to the IRB.

The investigator should institute appropriate therapeutic and follow-up measures in accordance with good medical practice but should notify the study monitor of such actions and record them in the subject's CRF.

4.0 Results

4.1 Participant Flow

An illustration of the participant flow will be as shown in Fig. 1.

4.2 Recruitment

The recruitment period is from February 1, 2010, to January 31, 2012.

4.3 Baseline Data

Baseline demographic and clinical characteristics of each group will be illustrated as shown in Table 2. Significant differences will be assessed between the groups.

4.4 Analysis of Data

4.4.1 Numbers Analyzed

A schematic illustration of patient flow will be provided in Fig. 1. The duration of the study is proposed from February 1, 2010, to January 31, 2012, with selection of 120 patients with 60 patients in each group.

4.5 Outcomes and Estimation

4.5.1 Pain Relief

Table 3 will illustrate the NRS scores and changes at 3, 6, 12, 18, and 24 months in all groups, with significant differences assessed between the groups at baseline and at all follow-up periods.

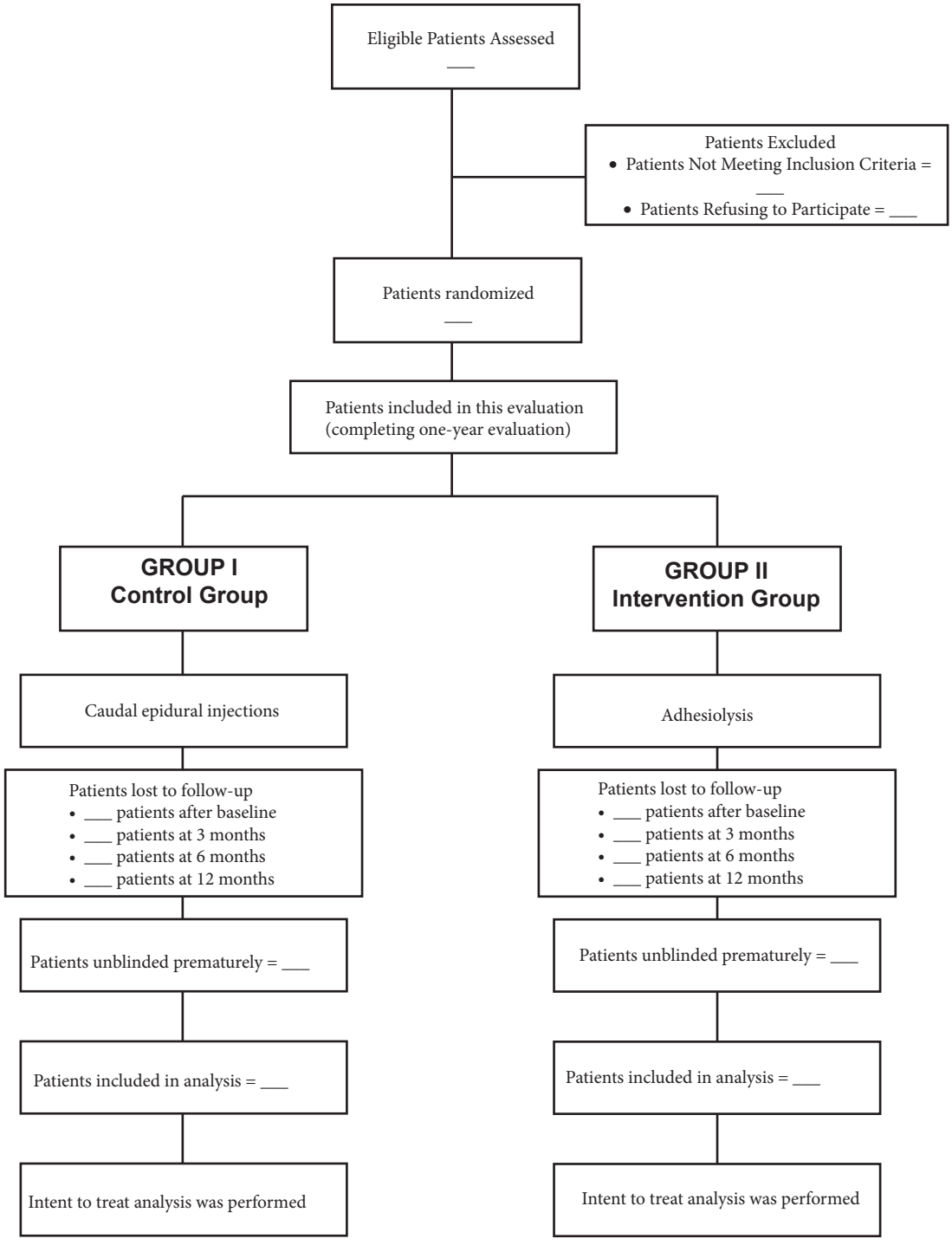

Fig. 1. *Schematic presentation of patient flow.*

Table 2. *Demographic characteristics.*

		Group I (N = 60)	Group II (N = 60)	*P* value
Gender	Male			
	Female			
Age	Mean ± SD			
Height (inches)	Mean ± SD			
Weight (lbs.)	Mean ± SD			
Duration of pain (months)	Mean ± SD			
Mode of onset of pain	Non-traumatic			
	Traumatic			
Leg pain Distribution	Bilateral			
	Left only			
	Left worse			
	Right only			
	Right worse			

Table 3. *Pain relief characteristics.*

		Group I (N = 60)	Group II (N = 60)	*P* value
Average pain scores (mean ± SD)	Baseline			
	3 months			
	6 months			
	12 months			
	18 months			
	24 months			

# indicates significant difference with baseline values

Table 4. *Functional assessment evaluated by Oswestry Disability Index.*

		Group I (N = 60)	Group II (N = 60)	*P* value
Average Oswestry Disability Index (Mean ± SD)	Baseline			
	3 months			
	6 months			
	12 months			

# indicates significant difference with baseline values

In addition, the proportion of patients with significant pain relief (≥ 50%) will be illustrated in a figure format.

4.6 Functional Assessment

Functional assessment results will be assessed by the ODI and will be illustrated as shown in Table 4 and in a figure format.

Table 5. *Employment characteristics.*

Employment status	Group I		Group II	
	Baseline	12 months	Baseline	12 months
Employed part-time				
Employed full-time				
Unemployed				
Total employed				
Eligible for employment				
Housewife				
Disabled				
Over 65 year of age				
Total number of patients	60	60	60	60

4.7 Employment Characteristics

Table 5 demonstrates the characteristics of employment to be evaluated in both groups.

4.8 Opioid Intake

Table 6 illustrates the methodology to be utilized for opioid intake between both groups and at various follow-up periods and statistical analysis.

4.9 Therapeutic Procedural Characteristics

Therapeutic procedural characteristics with average pain relief per procedure and average overall relief per year and differences between the groups will be

Table 6. Daily opioid (morphine equivalents).

	Group I	Group II	*P* value
Baseline			
3 months			
6 months			
12 months			

# indicates significant difference ($P < 0.01$) with baseline values

Table 7. Illustration of procedural characteristics with procedural frequency, average relief per procedure, and average total relief in weeks over a period of one-year.

	Back Pain		Leg Pain	
Procedure number	Group I (N = 60)	Group II (N = 60)	Group I (N = 60)	Group II (N = 60)
1st injection relief				
2nd injection relief				
3rd injection relief				
4th injection relief				
Number of injections per year				
Total relief per year (weeks)				
Average relief per procedure				

* indicates significant difference between groups ($P < 0.05$)

illustrated as shown in Table 7.

4.10 Adverse Events

Adverse events will be reported.

5.0 Conclusion

This article describes the protocol for evaluation of the comparative effectiveness of percutaneous adhesiolysis and caudal epidural steroid injections in low back and/or lower extremity pain without post surgery syndrome or spinal stenosis, in an interventional pain management center and a referral center in the United States. The protocol utilizes CONSORT guidelines and all the prerequisites for randomized equivalence trials and comparative effectiveness evaluation. Further, the protocol utilizes approved methodology with appropriate consent, and the Health Insurance Portability and Accountability Act (HIPAA) and ethical regulations. This study is the first of its nature in the United States to evaluate the role of targeted delivery of drugs in recalcitrant low back pain with or without adhesiolysis.

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APPENDIX I
Protocol for Evaluation of the Comparative Effectiveness of Percutaneous Adhesiolysis and Caudal Epidural Steroid Injections in Low Back and/or Lower Extremity Pain without Post Surgery Syndrome or Spinal Stenosis: A Randomized, Equivalence Trial of Percutaneous Lumbar Adhesiolysis and Caudal Epidural Steroid Injections

Technique

Prior to undergoing adhesiolysis, all patients will be assessed with a comprehensive physical and psychological evaluation. All less invasive and conservative modalities of treatment, including fluoroscopically directed epidural steroid injections, should be exhausted. In addition, appropriate laboratory studies should be considered to rule out bleeding disorders. Anticoagulants should be discontinued to avoid unusual bleeding.

Procedure Environment: The procedure is performed in a sterile operating room under appropriate sterile precautions utilizing fluoroscopy.

Preparation: After the initial evaluation, the patient is transferred to the holding area where appropriate preparation is carried out with preoperative evaluation, checking of vital signs and establishment of intravenous access as well as antibiotic administration.

Consent: An appropriate detailed consent is obtained from all the patients.

Operating Room: The procedure will include appropriate preparation with intervenous access, antibiotic administration, and appropriate sedation.

An RK needle will be introduced into the sacral epidural space under intermittent fluoroscopy. Once the needle placement is confirmed to be in the epidural space, a lumbar epidurogram will be carried out, utilizing approximately 5 mL of contrast (Omnipaque® 240). Identification of the filling defects will be carried out by examining the contrast flow into the nerve roots. Intravascular or subarachnoid placement of the needle or contrast will be avoided; if such malpositioning occurs, the needle will be repositioned.

In Group I, after the epidurography, a Racz catheter will be passed through the RK needle up to S3 and additional Omnipaque 240, 3 mL, will be injected. Following this, 5 mL of 2% preservative-free Xylocaine will be injected into the epidural space through the catheter.

In Group II, after identification of the filling defects, the Racz catheter will be advanced through the RK needle to the area of filling defect or the site of pathology as determined by MRI, CT, or symptomatology.

Adhesiolysis will be carried out and the final positioning will be achieved in the epidural space laterally and ventrally. After satisfactory positioning, at least 3 mL of contrast will be injected. If there is no subarachnoid, intravascular, or other extra epidural filling and satisfactory filling is obtained with epidural and targeted nerve root filling, 5 mL of 2% preservative-free Xylocaine will be injected either as a single dose in patients without hardware or fusion or will be injected intermittently in other cases.

APPENDIX II

Informed Consent to Participate in a Clinical Research Study

Study Title: Protocol for evaluation of the comparative effectiveness of percutaneous adhesiolysis and caudal epidural steroid injections in low back and/or lower extremity pain without post surgery syndrome or spinal stenosis: A randomized, equivalence trial of percutaneous lumbar adhesiolysis and caudal epidural steroid injections

Principal Investigator: Laxmaiah Manchikanti, MD

Study Site: Ambulatory Surgery Center

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand.

Introduction

The following information will describe the study and your role as a participant. This document is intended to inform you about the nature and risks of the clinical study in which you have been invited to participate. The principal investigator or a member of the study team will answer any questions you may have about this consent form and about the study. Please read this consent form carefully and do not hesitate to ask any questions you may have about the information provided below.

Description and Purpose of the Study

You have been invited to take part in this research study because you have been diagnosed with chronic low back pain, and previous treatment with fluoroscopically directed epidural injections has failed.

This is a randomized double-blind study which means that both you and the study doctor will not know which treatment is provided.

A total of 120 patients will be studied in 2 groups with 60 patients in each group: Group I will receive caudal epidural injections with catheterization up to S3 with local anesthetic, steroids, and 0.9% sodium chloride solution; Group II will receive percutaneous adhesiolysis with targeted delivery of lidocaine, 10% hypertonic sodium chloride solution, and non-particulate betamethasone.

Objectives of This Study

1) To evaluate the effectiveness of percutaneous epidural adhesiolysis in managing chronic low back and/or lower extremity pain in patients without post lumbar surgery syndrome or spinal stenosis and compare with fluoroscopically directed caudal epidural steroid injections.
2) To evaluate and compare the adverse event profile in all groups.

Study Procedures

All patients will be unblinded at 12 months.

Length of the Study

Patients will return for follow-up visits at 3, 6, 12, 18, and 24 months post-treatment. The recruitment period is estimated as 24 months with an anticipated study duration of 48 months.

APPENDIX II (cont.)

Evaluations

Evaluations will be conducted prior to starting the study procedures and each follow-up time at 3, 6, 12, 18, and 24 months. These evaluations will include pain evaluation, disability questionnaire, medication use, and employment status.

Risk/benefit Analysis

Percutaneous adhesiolysis with or without hypertonic saline neurolysis, like any invasive procedure, poses potential risks and/or complications. Risks or complications associated with adhesiolysis procedure using the Racz catheter include but are not limited to: transient post-operative pain; sensory or motor deficit; and in rare instances, neural trauma, subarachnoid blockade, epidural hematoma, steroid side effects, infection, or neurologic injury.

The anticipated benefits to subjects with chronic low back pain who participate in this study include: 1) amelioration of chronic back pain without the risks of major surgery or general anesthesia, and 2) subjects may also have an improvement in function and quality of life as a result of the diminution in pain. In addition, the information gained from this investigation may help to improve the future developments of minimally invasive techniques for treating chronic low back pain.

The risks involved with this procedure include, but are not limited to, numbness, weakness, reaction to local anesthetics, steroids, and/or other medications, dural puncture with subsequent complications, hematoma formation, urinary retention, muscle spasm, and increase in pain following injection therapy, injection into the blood vessels or around the spinal cord with complications, and infection.

Other consequences include failure of the procedure to be effective and also increased levels of pain.

Discontinuation of the Study

You may discontinue or withdraw from the study for the following reasons:

1. You may like to withdraw prematurely from the study.
2. You want to proceed to another nonsurgical or surgical intervention such as spinal endoscopy or surgery.
3. Investigator's judgment.
4. A complication directly related to the procedure or device that requires withdrawal from the study.

Pregnancy and Breastfeeding (For Women Only)

Pregnant women and nursing mothers will not be allowed to enter this study. Women who are at least 2 years postmenopausal, sterilized, or who are willing to use a medically acceptable form of birth control (e.g., oral or implanted contraceptive, IUDs, sterilization, or barrier plus spermicide) may participate in this study; women who can become pregnant and who are not using a medically acceptable form of birth control may not participate in this study.

If you suspect you are pregnant at any time during the study, you must notify your study doctor immediately. If you become pregnant, no further procedures will be performed. It is important that you do not participate in the study if you have a positive pregnancy test or if you think you may be pregnant. If you plan to become pregnant during the course of this study, you should not enroll in the study. By signing this document, you are agreeing not to become pregnant while participating in the study.

The effects of drugs and procedures on human fetuses are unknown and may be harmful. In addition, x-rays may be harmful.

If you do become pregnant during your participation in this study, all costs for care related to your pregnancy, childbirth, and postpartum/newborn care will be your responsibility. However, you should provide all information in follow-up.

Special Precautions

You should exercise special caution when driving or using machinery for 24 hours after the procedure due to sedation.

Benefits of the Study

There is no guarantee of benefit as a result of your participation in this study. You may or may not respond to treatment with the study procedure. Taking part in this study may reduce the severity of your symptoms; however, you may experience either no improvement or a worsening of your condition. Future patients may, however, benefit from the overall conclusions drawn from the results of the study.

New Information

As with any procedure, there is the possibility of complications and undesirable side effects which are unknown at this time and could possibly occur. You will be told of any significant new findings that develop during the course of this study that may affect your willingness to continue your participation.

APPENDIX II (cont.)

Alternative Treatment

You understand that if you do not wish to participate in this study, there are other procedures available for treatment of chronic low back pain. Standard treatments include non-drug therapies (physical therapy, chiropractic manipulation, acupuncture, TENS, laser therapy, and surgery), drug treatments including anti-inflammatories (NSAIDs), muscle relaxants, narcotic analgesics, antidepressants, anti-seizure medications, steroids, and other procedures such as epidural steroid injections. However, you have determined that these have failed in the past. If you withdraw your participation or if you are terminated, the study doctor will recommend an alternative treatment for your condition. You do not have to participate in this study to receive treatment for your condition.

Participation Information

Your participation in this study is voluntary. You may refuse to participate or you may discontinue participation at any time during the study without penalty or loss of benefits to which you are otherwise entitled. If you wish to voluntarily withdraw from the study, please notify your study doctor immediately and arrange for a final visit.

Confidentiality

Every reasonable effort will be made to keep your medical records confidential.

Persons To Contact

If you have any questions about this study or your rights, please call Dr. Manchikanti or the study staff at (270) 554-8373, Ambulatory Surgery Center, 2831 Lone Oak Road, Paducah, KY 42003.

Consent

I have read or someone has read this informed consent to me in a language I can understand. I have fully discussed and understand the purpose and procedures of this study which have been explained to me, in a layman's language. I have been given the chance to ask any questions that I have about the study, and all my questions have been answered to my satisfaction. I acknowledge that I will be given a signed copy of this consent form.

Having thoroughly read and understood all of the above information, I voluntarily agree to participate in this research study. I understand that I have not given up any of my legal rights by signing this informed consent.

_____
Printed Name of Study Participant

_____ _____
Signature of Study Participant Date

_____
Printed Name of Witness

_____ _____
Signature of Witness Date

To the best of my knowledge, the information contained in this document was fully and carefully explained to the study participant.

_____
Printed Name of Investigator or Designee

_____ _____
Signature of Investigator or Designee Date