

## Original Article

# Role of One Day Epidural Adhesiolysis in Management of Chronic Low Back Pain: A Randomized Clinical Trial

Laxmaiah Manchikanti, MD\*, Vidyasagar Pampati, M Sc\*\*, Bert Fellows, MA#, Jose Rivera, MD<sup>Ω</sup>,  
Carla D. Beyer, RN<sup>##</sup>, and Kim S. Damron, RN<sup>##</sup>

Epidural fibrosis is seen as a common phenomenon among postlumbar laminectomy syndrome patients, contributing to approximately 60% of symptom recurrence. Percutaneous epidural lysis of adhesions has been described as a modality to effectively manage chronic low back pain secondary to epidural fibrosis.

Forty-five patients were randomly assigned, with fifteen patients in the control group, or Group I, who were treated with conservative modalities of treatments, including medication, physical therapy, and an exercise program; and, thirty patients in Group II, who were treated with percutaneous epidural adhesiolysis and hypertonic saline neurolysis. The patients were evaluated over a period of 1 1/2 years to 3 years.

Results showed that cumulative relief, defined as relief greater than 50% with one to three injections, in the treat-

ment group was 97% at 3 months, 93% at 6 months, and 47% at 1 year. The study also showed that overall health status improved significantly in the treatment group in all parameters with average pain, physical health, mental health, functional status, psychological status and narcotic intake. Analysis also showed that this is a cost-effective treatment, with cost for 1-year improvement of quality of life at \$2693.

In conclusion, epidural adhesiolysis with hypertonic saline neurolysis performed on a 1-day basis is an effective modality of treatment in managing chronic low back pain in patients who failed to respond to fluoroscopically directed epidural steroid injections and also were demonstrated not to have facet joint mediated pain.

**Keywords:** percutaneous lysis of epidural adhesions, epidural fibrosis, hypertonic saline neurolysis, chronic low back pain

Among all the chronic painful conditions, low back pain is the most important clinical, social, economic, and public health problem affecting the population indiscriminately. Numerous modalities of therapeutic interventions are available for treatment of chronic low back pain: surgery, drugs, manipulation, physical therapy, behavior therapy, and neural blockade continue to spark debate among professionals, with regard to their effectiveness in managing chronic low back pain, even though there is an astonishing agreement among professionals with regard to the enormity of chronic low back pain and its impact on society (1-6).

Postlaminectomy syndrome, or pain following surgical procedures on the lumbar spine, is a common entity in modern medicine (7-21). Even though the exact incidence and prevalence of postlumbar laminectomy syndrome is not known, it is estimated that 20% to 30% of the spinal surgeries (occasionally as high as 40%), may not be successful.

Among postlumbar laminectomy syndrome patients epidural fibrosis is seen as a common phenomenon which contributes to 60% of the patients with recurring symptoms in conjunction with instability (9). However, the role of epidural fibrosis as a causative factor of chronic pain or a pain generator has been questioned (22-27). In spite of this debate, whether epidural fibrosis causes pain or not, it is widely accepted that postoperative scar tissue renders the nerve susceptible to injury (28). Ross et al (29), in a study of the relationship between peridural scar evaluated by magnetic resonance imaging (MRI) and radicular pain after lumbar discectomy, showed that, subjects with extensive peridural scarring were 3.2 times more likely to

---

From Pain Management Center of Paducah, Paducah, Kentucky. \*Medical Director, \*\*statistician, #psychologist, <sup>Ω</sup>interventional pain physician, and #clinical coordinators at the Pain Management Center of Paducah. Address correspondence: Laxmaiah Manchikanti, MD, 2831 Lone Oak Road, Paducah, KY 42003. E-mail: [drm@asipp.org](mailto:drm@asipp.org).

experience recurrent radicular pain. Parke and Watanabe (30) analyzed the frequency and location of lumbar dural adhesions in cadavers of lumbar disc herniation, showing significant evidence of adhesions in 40% at L4/5 levels, in 36% at L5/S1 levels, and in 16% at L3/4 levels. Berger and Davis (21) showed that in the group of 600 patients with a single operation, periradicular fibrosis was diagnosed preoperatively in 0.67% and postoperatively in 11%. They also showed that, in the 400 patients with multiple operations, at the time of the second operation, the incidence of periradicular fibrosis had risen to 47%. However, epidural adhesions have also been demonstrated without surgery. Leakage of the irritants of the nucleus pulposus into the epidural space has been documented to cause an inflammatory response, resulting in an increase in fibrocytic deposition, which results in epidural fibrosis (31-34).

Treatment of chronic back pain, specifically for postsurgical patients and patients with epidural fibrosis, continues to be a challenge. Effectiveness of epidural steroid injections in patients with epidural fibrosis has not been studied. Further surgery for peridural scarring has resulted in disappointing results, with success rates as low as 12% (12, 35). One of the techniques described to effectively manage chronic low back pain secondary to epidural fibrosis is adhesiolysis of epidural scar tissue. The purposes of percutaneous epidural lysis of adhesions are to eliminate deleterious effects of a scar which can physically prevent direct application of drugs to nerves or other tissues, and to assure delivery of high concentrations of injected drugs to the target areas.

Clinical effectiveness of percutaneous adhesiolysis was evaluated in one randomized, controlled trial (37), and four retrospective evaluations (34, 38-40). Racz et al (36), and Heavner et al (37) studied percutaneous epidural adhesiolysis in a prospective evaluation with 0.9% sodium chloride solution versus 10% sodium chloride solution with steroids, with a 1-year follow-up. They concluded that percutaneous epidural neuroplasty, as part of overall pain management, reduces pain in 25% or more of patients with radiculopathy plus low back pain refractory to conventional therapies. They also showed that the percent of patients requiring additional treatments during 1-year follow-up was approximately 70%, and on the average, patients required additional treatments at around 70 days. This percentage was approximately 60% in patients receiving hypertonic saline, and 80% in patients receiving normal saline. However, this was a 3-day protocol with injection of hypertonic saline on 3 consecutive days. In contrast, Manchikanti et al (38), evaluating 232 patients, retrospectively in

a randomized fashion with modification of the Racz protocol from a 3-day procedure to a 2-day procedure and a 1-day procedure, showed significant pain relief lasting at least 1 month in 52%, 2 months in 35%, 3 months in 11%, and 6 months in 7% of the patients with the first injection; and with better results with the second injection. However, no significant differences were noted between 1-day, 2-day, or 3-day procedures.

Thus, the appropriateness and effectiveness of the 1-day or 3-day procedure has been debated. Proponents of a 3-day procedure argue the fact of lack of prospective trials with a 1-day protocol, whereas opponents of a 3-day protocol argue that the 1-day protocol is as effective as a 3-day protocol with additional advantages of reduced cost and increased safety. These arguments were generated from the prospective study of Heavner et al (37), as well as retrospective, randomized studies of Manchikanti et al (38, 39) which showed similar results to the retrospective evaluations of Racz et al (34) with a 3-day protocol.

Hence, this randomized clinical trial was undertaken to evaluate the effectiveness of percutaneous adhesiolysis, and hypertonic saline neurolysis performed on a 1-day basis compared to the results of Heavner et al (37) from a 3-day protocol. This randomized clinical trial was also designed to compare patients undergoing epidural adhesiolysis with a control group of patients not receiving any type of injection therapy and managed conservatively. The patients in both groups were randomly selected from a group of patients who underwent comparative local anesthetic diagnostic facet joint blocks showing absence of facet joint mediated pain, who subsequently failed to respond to fluoroscopically directed epidural steroid injections.

## METHODS

The study was designed to evaluate 45 randomly assigned patients. Patients younger than 18 years or older than 90 years, those who exhibited progressive neurological deficits, those who had had pain for less than 6 months, those who had responded to epidural steroid injections, or those who tested positive for facet joint mediated pain were excluded. All patients were negative for facet joint mediated pain and failed to respond to fluoroscopically directed epidural steroid injections on one to three occasions. Failure was considered as response lasting less than 1 week with each injection or less than 1 month's cumulative relief with more than one injection. Fifteen patients were enrolled into Group I, considered as a convenient control group for whom we were unable to perform further injec-

tion therapy either due to the refusal of the insurer or the patient. The remaining 30 patients were assigned to Group II, the treatment group with percutaneous epidural adhesiolysis and hypertonic saline neurolysis. All patients provided informed choice and consent understanding the nature of the study and associated complications.

The study period lasted for 3 years, with a minimum of 18 months. All charts were reviewed, and patients were contacted by a physician who was not involved in their treatment during the treatment period and at the end of the study period. The evaluation included data collection as to the variables of age, gender, duration or pain in months, nature of onset, height, weight, and history of previous surgical interventions; overall health status in pre- and post-treatment phases; psychological status in pre and posttreatment phases; narcotic intake in pre- and posttreatment periods; and employment and work status in pre- and post-treatment periods in both groups. In Group II, data pertaining to the number of injections received by each patient. The quality and duration of pain relief were noted in both groups. The quality of pain relief was characterized as less than 50% relief, or greater than 50% relief. Pain relief greater than 50% was considered significant, and these patients were characterized as successful with "significant pain relief." Admission and discharge pain status was evaluated with a verbal pain rating scale in both groups. Patients in Group I were treated with conservative treatment including physical therapy, an exercise program and drug therapy.

All procedures were performed under fluoroscopy in an ambulatory surgery setting in sterile operating rooms by one physician. The procedure included appropriate preparation with intravenous access, antibiotic administration, sterile preparation, and appropriate sedation with small doses of midazolam and fentanyl. Access to the epidural space was obtained with an RK® needle (EpiMed International, Inc., Gloversville, NY). An epidurogram was obtained, identifying filling defects and/or epidural fibrosis. Adhesiolysis was carried out in all cases utilizing a Racz® catheter (EpiMed International, Inc.), with final positioning of the catheter on the side of the defect and the source of pain and an additional injection of contrast to identify successful adhesiolysis. Following the completion of the adhesiolysis and repositioning of the catheter, an injection of 5 mL of lidocaine 1% preservative free with 6 mg of betamethasone phosphate acetate mixture was injected. After waiting 10 to 15 minutes, provided that there was no evidence of subarachnoid blockade, 6 mL 10% sodium

chloride solution in two divided doses of 3 mL over 10 to 15 minutes was administered. Subsequently the catheter was removed and the patient was discharged home.

All data were collected during each visit. Each patient was evaluated for pain relief on the basis of a verbal 10-point pain scale, perceived physical health by the patient and physician, perceived mental health by the physician and patient, and perceived functional status by the patient and physician on a 10-point verbal rating scale. Patients were also evaluated as to narcotic intake with each visit. Any potential complications were also evaluated at each visit.

Demographic features of age, mode of onset of pain, pain characteristics, work status, history of surgery, and other historical features were obtained from the patient history and recorded. Average pain, physical health, mental health, and functional status were determined from multiple sources, including patient description of the pain, and patient perception of physical health, mental health and functional status, as well as objective evaluations performed with psychological evaluation and range-of-motion evaluation and ability to function and carry on important activities patients were unable to perform prior to the intervention. General psychological status and specific mood disorders of depression, generalized anxiety disorder, and somatization disorder were determined by a psychological questionnaire, as well as psychological evaluation utilizing Millon Clinical Multiaxial Inventory II (MCMI) or MCMI-III, Beck's Depression Inventory (BDI), and/or pain patient profile (P3). Symptom magnification was determined utilizing a set of signs and symptoms that included multiple items: strategy to control symptoms, control over environment, overt pain behavior, pain rating, pain diagram, nonphysiologic symptoms and signs, presence or absence of objective signs, laboratory evidence, coefficient of variation with functional testing, cooperation with evaluation and presence or absence of somatization.

Narcotic intake was determined as none, mild, moderate, or heavy based on the dosage, frequency and class of drug. Intake of class IV narcotics, ie, propoxyphene napsylate (pentazocine hydrochloride, tramadol hydrochloride up to a maximum of four times, or hydrocodone twice or less per day, was considered as mild; intake of class III narcotics, ie hydrocodone, up to four times was considered as moderate; and intake of class II narcotics, ie oxycodone, morphine, meperidine, transdermal fentanyl, and methadone, in any dosage was considered as heavy.

Employment and work status (employed, unemployed, housewife, disabled, and retired) were determined from the pretreatment and posttreatment work status. Only employed and unemployed patients were considered to be eligible for employment, whereas disabled patients and patients over 65 were considered not employable; however, data were tabulated if any of these patients returned to work.

Data were recorded on a database using Microsoft Access®. The SPSS Version 9.0 statistical package was used to generate the frequency tables, and the chi-squared statistic was used to test the significance difference between groups. Student's t test was used to test mean differences between groups. Paired t test was used to compare the pre- and posttreatment overall health status. Results were considered statistically significant if the *P* value was less than 0.05.

**RESULTS**

***Patient Characteristics***

Demographic data are shown in Table 1, with no significant differences noted among both groups in terms of gender, age, weight, height, mode of onset of pain, duration of pain, and history of previous surgical intervention.

***Injection Characteristics***

Table 2 illustrates the details of patients undergoing multiple procedures over a period of three years. Fifty percent of the patients underwent six procedures, which was reduced to 33% for eight procedures and 17% for 10 procedures, over a period of three years.

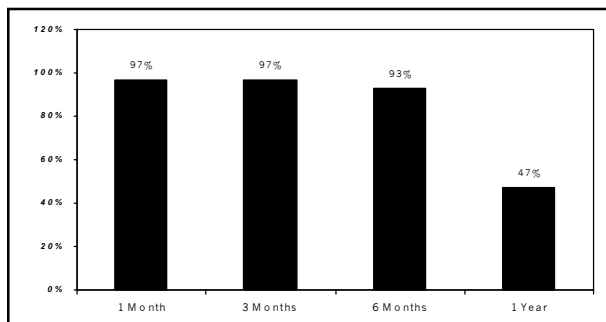
**Table 1. Patient characteristics**

		<b>Group I</b>	<b>Group II</b>
Number of patients		15	30
Gender	Male	40% (6)	57% (17)
	Female	60% (9)	43% (13)
Range	29 - 68	21 - 82	29 - 68
	≥ 65	13% (2)	10% (3)
	Mean ± SEM	47.0 ± 3.04	47.6 ± 2.48
Weight (lbs.)	Range	131 - 312	104 - 304
	Mean ± SEM	192.1 ± 13.65	188.7 ± 9.0
	Range	59 - 73	51 - 73
Height (inches)	Mean ± SEM	67.3 ± 1.01	68.0 ± 0.82
	Mean ± SEM	29.9 ± 2.11	28.7 ± 1.30
Body mass index	Occupational	33% (5)	43% (13)
Mode of onset of pain	Non-Occupational	0%	17% (5)
	Gradual onset	67% (10)	40% (12)
	Range	0.5 - 20+	0.5 - 20+
Duration of pain (yrs)	≤ 1	6% (1)	13% (4)
	1-4	47% (7)	47% (14)
	>4	47% (7)	40% (12)
History of previous laminectomy		40% (6)	70% (21)

**Table 2.** Significant relief (> 50%) with each injection in weeks in treatment group

Number of injections	Number of patients	Range of relief	Mean relief ± SEM
One	30	0 - 9	5.4* ± 0.46
Two	29	3 - 26	10.3# ± 1.17
Three	26	2 - 106	16.4 ± 3.89
Four	20	3 - 34	13.9 ± 1.60
Five	16	9 - 34	13.6 ± 1.47
Six	15	9 - 17	12.2 ± 0.58
Seven	14	9 - 17	13.0 ± 0.42
Eight	10	9 - 17	13.0 ± 0.60
Nine	8	9 - 17	13.0 ± 0.76
Ten	5	9 - 13	12.2 ± 0.80

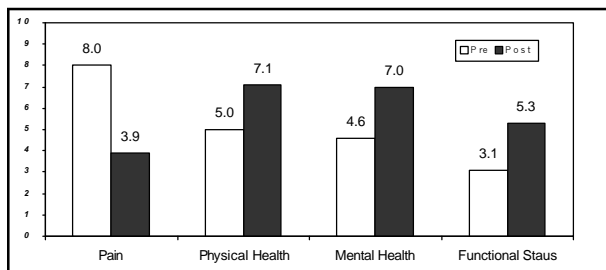
\* Indicates significant difference between injection one vs injections two to nine # Indicates significant difference between injection two vs injection three



**Fig. 1.** Cumulative relief (>50%) with one to three injections in the treatment group

**Pain Relief**

The duration of significant pain relief for the treatment group for all consecutive injections is illustrated in Table



**Fig. 2.** Change in pain status, physical health, mental health, and functional status post-treatment compared to pretreatment

2. Significant differences were noted between the first injection and injections two to nine, as well as between injections two and three. The relief ranged from 5.4 ± 0.46 weeks with the first injection to 16.4 ± 3.89 weeks with the third injection, with an overall range of 0 to 106 weeks.

Cumulative significant relief was evaluated with one to three injections in months (Fig. 1). This showed that 97% of the patients experienced significant relief at 1 month and 3 months, and 93% at 6 months; whereas this was variable after 6 months, with a decrease to 47% at 12 months.

**Overall Health Status**

Comparison of overall health status prior to treatment and after treatment as shown in Table 3 demonstrated that average pain, physical health, mental health, and functional status, which were all evaluated using a 10-point verbal scale, showed significant decrease in mean pain levels from 8.0 ± 0.15 to 3.9 ± 0.29; and significant improvement in physical health from 5.0 ± 0.23 to 7.1 ± 0.16, in mental health from 4.6 ± 0.22 to 7.0 ± 0.20, and in functional status from 3.1 ± 0.14 to 5.3 ± 0.13 in the treatment group, with no significant changes seen in the control group. Improvement was also significant from Group I to Group II in the post-treatment phase. Fig. 2 demonstrates the change seen in the treatment group.

**Table 3.** Comparison of overall health status pre and post treatment

	Group I		Group II	
	Pre Mean ± SEM	Post Mean ± SEM	Pre Mean ± SEM	Post Mean ± SEM
Average pain	7.7 ± 0.30	6.9 <sup>#</sup> ± 0.45	8.0 ± 0.15	3.9* ± 0.29
Physical health	5.7 ± 0.39	5.7 <sup>#</sup> ± 0.43	5.0 ± 0.23	7.1* ± 0.16
Mental health	5.4 ± 0.22	5.3 <sup>#</sup> ± 0.40	4.6 ± 0.22	7.0* ± 0.20
Functional status	4.3 ± 0.42	4.3 <sup>#</sup> ± 0.38	3.1 ± 0.14	5.3* ± 0.13

\* Indicates significant difference between pre and post treatment # Indicates significant difference between Group I and Group II

**Table 4.** Psychological status of patients in both groups pre and post treatment

Psychological Status	Group I		Group II	
	Pre	Post	Pre	Post
Depression	67% (10)	80% (12)	90% (27)	70% (21)
Generalized anxiety disorder	73% (11)	80% <sup>#</sup> (12)	80% (24)	50%* (15)
Somatization disorder	67% (10)	80% <sup>#</sup> (12)	50% (15)	20%* (6)
Symptom magnification	53% (8)	67% <sup>#</sup> (10)	37% (11)	20% (6)

( ) Number of patients \* Indicates significant difference between pre- and post treatment # indicates significant difference between Group I and Group II

Psychological status was evaluated, with evaluation of depression, anxiety, somatization, and symptom magnification (Table 4). There was improvement, with reduced levels of anxiety and somatization. Significant differences were noted among the groups during the posttreatment period in terms of generalized anxiety disorder, somatization disorder and symptom magnification.

**Narcotic Intake**

Narcotic intake was also compared pretreatment and post-treatment in all patients in both groups (Table 5). Clinical improvement with reduction in narcotic intake was seen in Group II, but with increased narcotic intake seen in Group I. Significant differences between the groups were in posttreatment periods. Heavy narcotic intake was re-

**Table 5.** Comparison of narcotic intake pre and post treatment

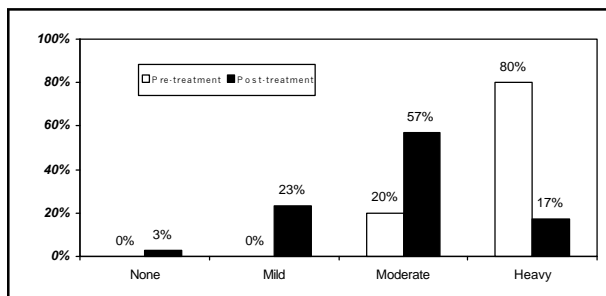
Narcotic Intake	Group I		Group II	
	Pre	Post	Pre	Post
None	20% (3)	20% (3)	0%	3% (1)
Mild	6% (1)	0%	0%	23% (7)
Moderate	27% (4)	6% <sup>#</sup> (1)	20% (6)	57% (17)
Heavy	47% (7)	74% <sup>#</sup> (11)	80% (24)	17%* (5)

( ) Number of patients \* Indicates significant difference between pre- and post treatment # indicates significant difference between Group I and Group II

**Table 6.** Employment or work status of patients in both groups pre and post treatments

Employment and Work status	Group I		Group II	
	Pre	Post	Pre	Post
Employed	27% (4)	20% (3)	10% (3)	17% (5)
Unemployed	40% (6)	7% (1)	7% (2)	0%
Housewife	7% (1)	7% (1)	3% (1)	3% (1)
Disabled	13% (2)	53% (8)	70% (21)	70% (21)
Over > 65 (retired)	13% (2)	13% (2)	10% (3)	10% (3)

( ) Number of patients



**Fig. 3.** Change in narcotic intake in treatment group

duced significantly in the treatment group. Fig. 3 illustrates the change in narcotic intake of patients in Group II.

**Employment Status**

Employment or work status is shown in Table 6. The patients who were employed and unemployed were considered as candidates for future employment or continued employment. Housewives, disabled patients, and patients

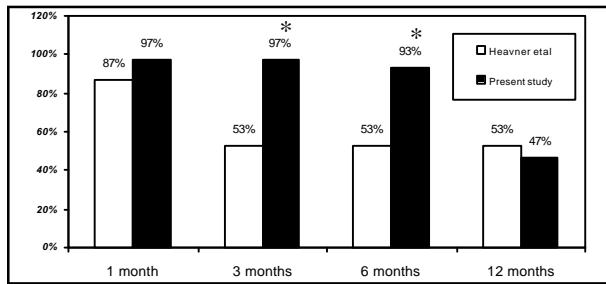
over 65 who were retired were considered not eligible for future employment. One-hundred percent of the patients (two) in Group II eligible for employment were employed after initiation of treatment. In contrast, none of the six patients in Group I eligible for employment were employed.

**Cost Effectiveness**

Cost effectiveness was analyzed, as shown in Table 7, for the treatment group only. The total cost was calculated for all procedures, including complications, in all patients. The total number of weeks with significant relief was calculated as 2,108, with a mean relief of  $11.8 \pm 0.69$  weeks per procedure. Total expenditures were calculated from net collections, or the patient’s expenses for the outpatient surgical center and physician fees as incurred by the insurer and/or the patient. The total cost per procedure was  $\$613 \pm 12.83$ . The total number of procedures was 178. Further calculations showed that significant pain relief was provided with a cost-per-1-week improvement of quality of life in Group II of \$52. Calculation of these cost figures with conversion to a 1-year improvement of quality of life

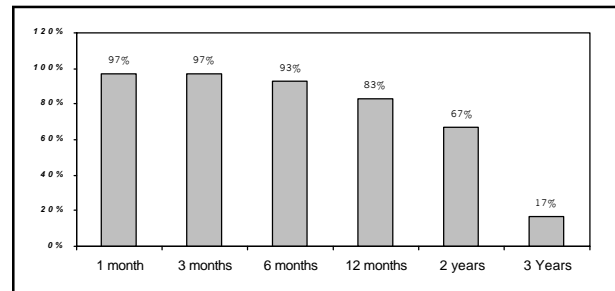
**Table 7.** Analysis of cost effectiveness of lysis of epidural adhesiolysis

Number of patients	30
Total number of procedures	178
Number of weeks with significant pain relief	2,108
Significant pain relief in weeks per procedure for all patients (Mean $\pm$ SEM)	$11.8 \pm 0.69$
Expenditure per procedure (Mean $\pm$ SEM)	$\$613 \pm 12.83$
Cost per 1 week improvement of quality of life	\$ 52
Cost per 1 year improvement of quality of life	\$2,693



**Fig. 4.** Comparison of treatment patients showing improvement with pain scales with Heavner et al's study (37)

\* Indicates significant difference



**Fig. 5.** Cumulative relief (>50%) with one to 10 injections in the treatment group

showed a cost of \$2,693 for Group II. However, this cost-effectiveness analysis did not take into consideration the patient's return to work and various other benefits; nor did the cost-benefit ratio consider the money spent outside therapy for drugs or other types of treatments. In addition, the cost of the diagnostic blocks was also not included in this analysis.

**Comparison Analysis**

Racz et al (36) and Heavner et al (37) reported patients with initial relief of 1 to 4 weeks as 83%, of 3 months as 49%, of 6 months as 43%, and of 12 months at 49%. Heavner et al (37) studied 15 patients receiving 10% sodium chloride solution, compared to other groups that also received hyaluronidase or isotonic saline. The results from the 15 patients were included in this comparison to provide the best benefit of the results, as these results showed a higher success rate than that for the patients receiving isotonic saline. These results were compared with the results of the present study, with the patients receiving multiple procedures assigned into the category of relief derived from one to three procedures, as shown in Fig. 4.

Cumulative relief with multiple injections was achieved 83% of patients at 1 year and 67% of patients at 2 years (Fig. 5).

**Complications**

Patients were evaluated for various types of complications, including infection, rash, reaction, and subarachnoid blockade. There were no instances of subarachnoid blockade or infection; However, suspicion of infection occurred in one patient. There were no reports of arachnoiditis, paralysis, weakness, bladder disturbances, or other serious complications. However, minor complications, which included rash, and itching, occurred in three patients, or 10%.

**DISCUSSION**

Epidural fibrosis is a progressive disease. It is an inflammatory reaction of the arachnoid, a fine nonvascular and elastic tissue enveloping the CNS (22). There are many possible etiologies of epidural fibrosis, including an annular tear, hematoma, infection, surgical trauma, or intrathecal contrast media. LaRocca and McNab (41) have demonstrated the invasion of fibrous connective tissue into the postoperative hematoma as a cause of epidural fibrosis. McCarron et al (31) 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 (33) 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.

Numerous authors (1, 34) identified the likely role of chemical irritation of the nerve root by the nucleus pulposus. In 1934, Mixter and Barr (42) demonstrated that a herniated disc could cause nerve root encroachment, ultimately producing back pain. Soon after that it was noticed that the removal of the disc did not always result in pain relief (43). In 1951, Barr (44) reported that a patient may have persistent low back pain, sciatica, or both, in spite of surgical intervention. Thus, the concept of noncompressive lesion and irritation of the nerve root, as well as definition of failed back surgery syndrome (FBSS) or postlumbar laminectomy syndrome with persistent or recurring low back pain, with or without radiculitis following one or more lumbar operations, evolved (7, 12). Fager and Freidberg (10), following the analysis of failures of lumbar surgery, re-



ported poor results, with conclusions that 51% of patients had more than one operation; among them 11% improved, 34% did not change, and 55% worsened. They also showed that only 32% improved following the initial operation, but the improvement was short-lived, at 6 months or less in 50% of the patients. Berger and Davis (21), in an evaluation of 1000 patients undergoing surgical interventions, with 600 patients undergoing single operation, reported that only 17% of the patients considered themselves improved; whereas 32% remained unchanged, and 51% were worse than prior to surgery. Waddell et al (18) documented that, the success of a second operation was only 50%, with an additional 20% considering themselves worse afterwards; with success further declining following a third operation to 30%, with 25% considering themselves worse and, after four operations, 20% success rate, with 45% of the patients considering themselves worse. Waddell et al (18) also noted that, in all studies of back pain, 10% to 15% of patients account for 80% to 90% of the total health-care compensation and cost for spinal disorders; and that the 1% to 2% of the patients who undergo surgery are the most expensive group.

Epidural fibrosis or arachnoiditis was a relatively rare entity prior to the introduction of lumbar spine surgery for degenerative conditions (23). Prior to 1935, the present condition of chronic adhesional arachnoiditis was generally described as chronic spinal meningitis (23). A multitude of reports in which epidural fibrosis was found at repeat surgery apparently led to the speculation of association of recurrent symptomatology with perineural scarring (23, 35, 45). The causes of failed back syndrome are epidural scarring, arachnoiditis, recurrent disc herniation with neural encroachment, mechanical instability, and facet degeneration.

Kuslich et al (46) concluded that the presence of scar tissue compounded pain associated with the nerve root by fixing it in one position and thus increasing the susceptibility of the nerve root to tension or compression. They also concluded that sciatica can only be reproduced by direct pressure or stretch on the inflammatory, stretched, or compressive nerve root. Even though considerable debate exists as to whether epidural fibrosis causes pain, it is widely accepted that postoperative scar tissue renders the nerves susceptible to injury (28). Scar tissue is generally found in the three compartments of the epidural space. Dorsal epidural scar tissue is formed by resorption of surgical hematoma and may be involved in pain generation (47). In the ventral epidural space, dense scar tissue is formed by ventral defects in the disc, which may persist despite sur-

gical treatment and continue to produce either chronic low back or lower extremity pain after the surgical healing phase (22). Finally, the lateral epidural space includes epiradicular structures out of the root canals, termed sleeves, containing the exiting nerve root and dorsal root ganglia, susceptible to lateral disc defects, facet overgrowth and neuroforaminal stenosis, etc. (48). Thus, it is postulated that various changes producing low back pain and lower extremity pain include inflammation, edema, fibrosis, venous congestion, mechanical pressure on the posterior longitudinal ligament, reduced or absent nutrient delivery to the spinal nerve or nerve root, and central sensitization. It is well known that inflammation may render nociceptors more sensitive to mechanical stimuli (49).

Intrathecal saline was used to relieve pain in cancer patients by Ventrafridda and Spreafico (50). Racz et al (34, 36, 40, 51-53) applied the technique of adhesiolysis and hypertonic saline neurolysis for refractory patients with chronic low back pain failing to respond to other modalities of treatments. The evidence of effectiveness of percutaneous lysis of adhesions with hypertonic saline neurolysis has been moderate (1). The controversy surrounding whether to perform a 3-day procedure or a 1-day procedure led not only to the evaluation of the clinical effectiveness and cost effectiveness, but also approval of the procedure itself (34-40, 51-56). Current Procedural Terminology (CPT) Assistant (55) published the opinion with regards to what involves adhesiolysis and contend that it has to be a multiday procedure, with multiple injections, even though evidence is equally favorable to either a 1-day or a 3-day procedure. However, several Medicare carriers, including Florida Medicare, have acknowledged that the procedure can be performed either or 1-, 2-, or 3-days (56).

The results of this study show that epidural lysis of adhesions with hypertonic saline neurolysis is effective in managing chronic low back and lower extremity pain in patients who were shown to be suffering with nonfacet joint mediated pain nonresponsive to fluoroscopically directed epidural steroid injections. This study showed that significant pain relief was seen with each injection, except in one patient who failed to report any pain relief at all. The study also showed that, at 3 months, 97% of the patients had significant pain relief, and at 6 months 93% had significant relief; whereas at 12 months, 47% of the patients had significant relief with one to three injections administered. With multiple injections, based on medical necessity, while the relief at 3 months continued to be 97% and at 6 months, 93%, at 12 months it decreased to 83%, and

at 2 years it decreased to 67%. Comparison of the overall health status, pre- and posttreatment, showed significant improvement, not only with average pain, but also with physical health, mental health and functional status. While psychological status with depression, generalized anxiety disorder, somatization disorder and symptom magnification showed improvement in posttreatment status compared to pretreatment status, these changes failed to reach statistical significance, even though there was significant worsening seen in Group I without adhesiolysis. Narcotic intake also increased in Group I, but decreased in Group II; however, there were no significant differences noted. While physical and functional status improved significantly, there was no significant difference noted in employment status in either group. This partly was due to 80% of the patients in the treatment group being either disabled or retired at the time of initiation of the treatment, even though only two patients employable in Group II, constituting 100% of the patients returned to work. Further, the current study also showed that adhesiolysis was cost effective compared to various other treatments in spite of the chronic nature of the pain, and failure of various other modalities of treatments; and most patients were disabled. Finally, the results of this study are either similar or superior to those for a 3-day procedure.

The current study is the first prospective study to have treated the patients without facet joint mediated pain confirmed with comparative local anesthetic diagnostic blocks who also failed to respond to fluoroscopically directed epidural steroid injections. Secondly, the current study is the first prospective, randomized clinical trial utilizing a 1-day rather than a 3-day protocol. Thirdly, this is the first study evaluating therapeutic effects of adhesiolysis and hypertonic saline neurolysis administered in a single day, utilizing low doses of lidocaine, betamethasone, and hypertonic saline, without hyaluronidase. Fourth, this is only the second study in the literature which has evaluated relief obtained with epidural adhesiolysis and hypertonic saline neurolysis in prospective and randomized analysis. Fifth, it is the only study in which multiple subjective and objective outcome measures were recorded during a prolonged follow-up period of 18 to 36 months. Sixth, this is again the only study with a control group without injection therapy receiving conservative management with medication and physical therapy. Finally, this is the only study in which cost effectiveness was calculated for epidural adhesiolysis performed on a 1-day basis in a prospective, randomized trial.

The study was prospective and randomized; even so, it

was not blinded. Thus, antagonists may jump on the band wagon to criticize for its nonblinded nature, as both the physician and patients were aware of the type of treatment, as well as the potential adverse effects. However, once again, the issues of ethics, feasibility, cost, and reliability pose challenges to a double-blind trial, which theoretically presents the gold standard at least in some circles (57-61). However, the reliability and the continuing belief in the gold standard of a randomized controlled trial continue to erode (62). In an analysis of various investigations, Concato et al (63) found that well-designed observational studies do not systematically overestimate the magnitude of effects of treatments as compared with those in randomized, controlled trials on the same topic, after analysis of numerous reports for five clinical topics. However, this is not to undermine the importance of randomized, double-blind, controlled studies; as flaws can exist in a study design or analysis, both in open as well as blinded trials (62-68). In addition, lack of randomization, rather than blinding of the treatment, is more important and allegedly leads to overestimation of the treatment effect by approximately 41%, whereas lack of blinding overestimates the treatment effect by 17% (69). However, this clearly may not be accurate in most neural blockades, specifically epidural adhesiolysis, as randomized clinical trials have actually yielded better results than observational or retrospective evaluations.

The cost-effectiveness analysis may also be criticized for various reasons. In the present environment confusion abounds over what is meant by the term *cost effectiveness*. Various economic evaluation designs describe cost-minimization analysis, cost-benefit analysis, cost-effectiveness analysis (CEA), or cost-utility analysis (CUA). In chronic low back pain CEA and CUA would be the most appropriate methods to use; since in these studies the effects are measured in natural units and quality of life (38, 39, 70-86). The outcome measures used in CEA studies in chronic pain research mainly include outcomes, such as disability days saved; pain-free days or improved quality of life, etc.; evaluation of quality of life, which is also known as functional status, health status, or health-related quality of life; well-being of the patient; satisfaction with care; health service utilization/economic analysis, and medical findings (81).

Thus, the quality-of-life assessment is designed to evaluate the patient's ability to function in his/her own world. Evaluation focuses on the patient's major perceived functional impairments, and improvement in areas such as playing with children/grandchildren, having sexual relations,

returning to work, going to school, homemaking, or performing other activities of daily living. Quality of life also measures social functioning, which determines whether health problems affect normal social activities, such as seeing friends or participating in group activities.

Cost of inpatient chronic pain programs ranges from \$17,000 to \$25,000, and the cost of outpatient treatment programs ranges from \$7,000 to \$10,000 (82). In addition, chronic pain patients may incur health-care bills in excess of \$20,000 annually for repetitive and, in some cases, redundant diagnostic workups, physical therapy, psychological interventions, and drugs. Guo et al (79) estimated that back pain accounted for 150 million lost work-days in the United States every year, which worked out to be about \$14 billion in wage costs alone. They also showed that even a 1% reduction in overall prevalence could considerably reduce morbidity and save billions of dollars considering the large magnitude of the back pain problem.

The cost effectiveness of lumbar discectomy for the treatment of herniated intervertebral discs has been based on the conclusion that surgery increased the average quality-adjusted life expectancy by 0.43 years during the decade following treatment compared to conservative treatment, a result comparable to extending a healthy life by 5 months (75). Malter et al (75) concluded that, for carefully selected patients with herniated discs, surgical discectomy is a cost-effective treatment at a discounted cost of \$12,000 per discectomy, or \$29,000 per life year adjusted for quality.

Kuntz et al (78) studied the cost effectiveness of fusion with and without instrumentation for patients with degenerative spondylolisthesis and spinal stenosis. They showed that the cost of laminectomy with a non-instrumented fusion was \$56,500 per quality-adjusted year of life compared laminectomy without fusion. The cost-effectiveness ratio of instrumented fusion compared with noninstrumented fusion was \$3,112,800 per quality-adjusted year of life (78). However, they also estimated that the cost-effectiveness ratio of instrumented fusion compared to with noninstrumented fusion would be \$82,400 per quality-adjusted year of life, if the proportion of patients experiencing symptom relief after instrumented fusion was 90%, as compared with 80% for patients with noninstrumented fusion.

Mueller-Schwefe et al (76) evaluated the cost effectiveness of intrathecal therapy in failed back surgery syndrome,

comparing it with alternative therapies for achieving a defined outcome, and reported the cost of medical management to be \$17,037 per year or \$1,420 per month. In comparison, they showed that intrathecal morphine delivery resulted in lower cumulative 60-month costs of \$16,579 per year, and \$1,382 per month (76).

The cost effectiveness evaluation for blind interlaminar, fluoroscopically directed caudal and transforaminal epidural injections for the management of low back pain showed the cost-effectiveness of caudal epidural steroids to be \$3,635 and that of transforaminal steroids to be \$2,927 per year, in stark contrast to blind interlaminar lumbar epidural steroid injections at \$6,024 per year (77). The cost effectiveness of lumbar facet joint nerve blocks in managing chronic low back pain was shown to be \$3,461 for 1-year improvement of quality of life (80).

In comparison, the cost effectiveness of medical treatment of hypertension was shown to be \$16,330 for a 60-year-old man in 1974 (81) and treatment of depression with medical therapy was \$11,766 per year of quality-adjusted life (83). Similarly, cost effectiveness of total hip arthroplasty was shown to be \$61,000 (84), that of coronary artery bypass grafting for patients with triple-vessel coronary artery disease and severe left ventricular function as \$41,800 (85), and that of for surgical repair of a 4-cm abdominal aortic aneurysm as \$21,800 with improvement per quality-adjusted year of life gained (86).

The cost effectiveness of percutaneous lysis of adhesions in this study for 1-year of improvement in the quality of life at \$2,693 is similar to the previous reports evaluating the cost effectiveness of percutaneous epidural adhesiolysis. The cost effectiveness of epidural adhesiolysis and hypertonic saline neurolysis was shown to be \$5,564 in chronic low back pain management in patients nonresponsive to numerous other modalities of treatment (38), whereas it was shown to be \$2,028 per year in postlumbar laminectomy patients (39). Thus, the results of the present study show the cost effectiveness to range between the previous two evaluations (38, 39); hence, lumbar epidural adhesiolysis in patients suffering with chronic low back pain who were shown to be negative for facet joint mediated pain and who also failed to respond to fluoroscopically directed epidural steroid injections, is not only in the same approximate range as that of other well-accepted modalities of treatments in managing chronic low back pain, but, also well within reasonable limits for present-day cost effective management of other medical conditions.

## CONCLUSION

Epidural adhesiolysis with hypertonic saline neurolysis is an effective modality of treatment in managing chronic low back pain in patients who failed to respond to fluoroscopically directed epidural steroid injections and who also were demonstrated not to have facet joint mediated pain. Epidural adhesiolysis is effective in providing significant pain relief, in improving functional status, overall psychological status, narcotic intake and return to work. The treatment also improved the patient's state of anxiety, and somatization. Hence, it is concluded that epidural adhesiolysis performed in a single day is an effective modality of treatment in managing chronic low back pain patients who were negative for facet joint mediated pain and also non-responsive to not only conservative modalities of treatments, but also to fluoroscopically directed epidural steroid injections.

## ACKNOWLEDGMENTS

We would like to thank Marla K. Neihoff and Lori A. Rose, medical records coordinators, for their assistance in collection of data. We would also like to thank Denise Pratt and Tonie Hatton, transcriptionists, for their assistance with transcription of the manuscript.

## REFERENCES

1. Manchikanti L, Singh V, Klothe D et al. Interventional techniques in the management of chronic pain: Part 2.0. *Pain Physician* 2001; 4: 24-96.
2. Cassidy D, Carroll L, Cote P: The Saskatchewan Health and Back Pain Survey. The prevalence of low back pain and related disability in Saskatchewan adults. *Spine* 1998; 23:1860-1867.
3. Manchikanti L. Epidemiology of low back pain. *Pain Physician* 2000; 3:167-192.
4. Bressler HB, Keyes WJ, Rochon PA et al. The prevalence of low back pain in the elderly. A systemic review of the literature. *Spine* 1999; 24:1813-1819.
5. Spitzer WO, Leblanc FE, Dupuis M (eds). Quebec Task Force on Spinal Disorders. Scientific approach to the assessment and management of activity-related spinal disorders: A monograph for clinicians. *Spine* 1987; (suppl) 12:1-59.6
6. Bigos SJ, Boyer OR, Braen GR et al. *Acute Low Back Problems in Adults*. Clinical Practice Guideline Number 4. AHCPR Publication No. 95-0642. Agency for Health Care Policy and Research, Public Health Service, US Department of Health and Human Services, Rockville, December 1994.
7. Wilkinson HA. Introduction: Etiology, diagnosis, and therapy. In *The Failed Back Syndrome. Etiology and Therapy*, ed 2. Springer-Verlag, New York, 1992, pp 1-3.
8. Waddell G, Kummel EG, Lotto WN et al. Failed lumbar disc surgery and repeat surgery following industrial injury. *J Bone Joint Surg (Am)* 1979; 61:201-207.
9. 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* 1996; 21:626-633.
10. Fager CA, Freidberg SR. Analysis of failures and poor results of lumbar spine surgery. *Spine* 1980; 5:87-94.
11. LaRocca H. Failed lumbar surgery. Principles of management. In Weinstein J, Wiesel S (eds). *The Lumbar Spine*. WB Saunders Company, Philadelphia, 1990, pp 872-881.
12. North RB, Campbell JN, James CS et al. Failed back surgery syndrome: 5 year follow-up in 102 patients undergoing repeated operation. *Neurosurgery* 1991; 28:685-691.
13. Hanley EN, Shapiro DE. The development of low back pain after excision of a lumbar disc. *J Bone Joint Surg* 1989; 71A:719-721.
14. Turner JA, Ersek, Herron L et al. Patient outcomes after lumbar spinal fusions. *JAMA* 1992; 268:907-911.
15. Davis H. Increasing rates of cervical and lumbar spine surgery in the United States, 1979-1990. *Spine* 1994; 19:1117-1124.
16. Postacchini F. Results of surgery compared with conservative management for lumbar disc herniations. *Spine* 1996; 21:1383-1387.
17. Nachemson AL. Failed back surgery syndrome is syndrome of failed back surgeons. *Pain Clinic* 1999; 11:271-284.
18. Waddell G, Gibson NA, Grant I. Surgical treatment of lumbar disc prolapse and degenerative lumbar disc disease. In Nachemson AL, Jonsson E (eds). *Neck and Back Pain*. Lippincott Williams & Wilkins, Philadelphia, 2000, pp 305-325.
19. Gibson JNA, Grant IC, Waddell G. The Cochrane review of surgery for lumbar disc prolapse and degenerative lumbar spondylosis. *Spine* 1999; 24:1820-1832.
20. Keskimaki I, Seitsalo S, Osterman H et al. Reoperations after lumbar disc surgery. A population-based study of regional and interspecialty variations. *Spine* 2000; 25:1500-1508.
21. Berger E, Davis JMB. Chronic pain following lumbar spinal surgery in 1000 patients. *Proceedings of 9<sup>th</sup> World Congress on Pain*, August 1999, pp181-182.
22. Anderson S. A rationale for the treatment algorithm of failed back surgery syndrome. *Curr Rev Pain* 2000; 4:395-406.
23. Pawl RP. Arachnoiditis and epidural fibrosis: The relationship to chronic pain. *Curr Rev Pain* 1998; 2:93-99.

24. Van Goethem JW, Van de Kelft E, Biltjes IG et al. MRI after successful lumbar discectomy. *Neuroradiology* 1996; 38:S90-96.
25. Grave P, Tullberg T, Rydberg J et al. Postoperative lumbar magnetic resonance imaging with contrast enhancement: Compression between symptomatic and asymptomatic patients. *Acta Radiol* 1996; 37:366-372.
26. Annertz M, Jonsson B, Stromquist B et al. No relationship between epidural fibrosis and sciatica in the lumbar postdiscectomy syndrome: A study with contrast-enhancement magnetic resonance imagery in symptomatic and asymptomatic patients. *Spine* 1995; 20:449-453.
27. Cervellini P, Curri D, Volpin L et al. Computed tomography of epidural fibrosis after discectomy. A comparison between symptomatic and asymptomatic patients. *Neurosurgery* 1988; 6:710-713.
28. Songer M, Ghosh L, Spencer D. Effects of sodium hyaluronate on peridural fibrosis after lumbar laminectomy and discectomy. *Spine* 1990; 15:550-554.
29. Ross JS, Robertson JT, Frederickson RCA et al. Association between peridural scar and recurrent radicular pain after lumbar discectomy: Magnetic resonance evaluation. *Neurosurgery* 1996; 38:855-863.
30. Parke WW, Watanable R. Adhesions of the ventral lumbar dura. Adjunct source of discogenic pain? *Spine* 1990; 15:300-303.
31. McCarron RF, Wimpee MW, Hudkins PG et al. The inflammatory effects of nucleus pulposus: A possible element in the pathogenesis of low back pain. *Spine* 1987; 12:760-764.
32. Cooper R, Freemont A, Hoyland J et al. Herniated intervertebral disc-associated periradicular fibrosis and vascular abnormalities occur without inflammatory cell infiltration. *Spine* 1995; 20:591-598.
33. McCarron RF. Epidural fibrosis: Experimental model and therapeutic alternatives. In Racz GB (ed). *Techniques of Neurolysis*. Kluwer Academic Publishers, Boston, 1989, pp 87-94.
34. Racz GB, Holubec JT. Lysis of adhesions in the epidural space. In Racz GB (ed). *Techniques of Neurolysis*. Kluwer Academic Publishers, Boston, 1989, pp 57-72.
35. Cook SD, Prewett AB, Dalton JE et al. Reduction in perineural scar formation after laminectomy with Polyactive<sup>®</sup> membrane sheets. *Spine* 1994; 19:1815-1825.
36. Racz GB, Heavner JE, Raj PP. Percutaneous epidural neuroplasty. Prospective one-year follow up. *Pain Digest* 1999; 9:97-102.
37. Heavner JE, Racz GB, Raj P. Percutaneous epidural neuroplasty. Prospective evaluation of 0.9% NaCl versus 10% NaCl with or without hyaluronidase. *Reg Anesth Pain Med* 1999; 24:202-207.
38. Manchikanti L, Pakanati RR, Bakhit CE et al. Role of adhesiolysis and hypertonic saline neurolysis in management of low back pain. Evaluation of modification of Racz Protocol. *Pain Digest*, 1999; 9:91-96.
39. Manchikanti L, Pakanati RR, Bakhit CE, et al. Non-endoscopic and endoscopic adhesiolysis in post lumbar laminectomy syndrome. A one-year outcome study and cost effectiveness analysis. *Pain Physician* 1999; 2:52-58.
40. Arthur J, Racz G, Heinrich R et al. Epidural space. Identification of filling defects in lysis of adhesions in the treatment of chronic painful conditions. In *Proceedings of the 7<sup>th</sup> World Congress of Pain*. Paris, IASP Publications, 1993, pp 557.
41. LaRocca H, Macnab I. The laminectomy membrane: Studies in its evolution, characteristics, effects and prophylaxis in dogs. *J Bone Joint Surg* 1974; 5613:545-550.
42. Mixter WJ, Barr JS. Rupture of the intervertebral disc with involvement of the spinal cord. *N Engl J Med* 1934; 211:210-215.
43. Ford LT, Lam RL. The psychiatric aspects of low back pain. *J Bone Joint Surg* 1952; 38:931-932.
44. Barr JS. Low back pain and sciatic pain. *J Bone Joint Surg* 1951; 33:633-649.
45. Barsa JE, Charlton JE. Diagnosis of epidural scarring and its possible contribution to chronic low back pain syndrome. *Pain* 1984; S4:376.
46. 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; 22:181-187.
47. Key JA, Ford LT. Experimental intervertebral disc lesions. *J Bone Joint Surg* 1948; 30:621-630.
48. Imai S, Hukuda S, Maeda T. Dually innervating nociceptive networks in the rat lumbar posterior longitudinal ligaments. *Spine* 1995; 19:2086-2092.
49. Racz GB, Noe C, Heavner JE. Selective spinal injections for lower back pain. *Curr Rev Pain* 1999; 3:333-341.
50. Ventrafridda V, Spreafico R. Subarachnoid saline perfusion. In Bonica JJ (ed). *Advances in Neurology*. New York, Raven Press, 1974, vol 4, pp 477-484.
51. Racz GB, Heavner JE, Diede JH. Lysis of epidural adhesions utilizing the epidural approach. In Waldman SD, Winnie AP (eds). *Interventional Pain Management*. WB Saunders, Philadelphia, 1996, pp 339-351.
52. Lou L, Racz GB, Heavner JE. Percutaneous epidural neuroplasty. In Waldman SD (ed). *Interventional Pain Management*, ed 2, WB Saunders Company, Philadelphia, 2000, pp 434-445.
53. Anderson SR, Racz GB, Heavner J. Evolution of epidural lysis of adhesions. *Pain Physician* 2000; 3:262-270.
54. Manchikanti L, Bakhit CE. Percutaneous lysis of epidural adhesions. *Pain Physician* 2000; 3:46-64.
55. Lysis of epidural adhesions (62263), *CPT Assistant*, 2000;10(8):7-9.

56. Percutaneous lysis of epidural adhesions: (62263) Florida Medicare Part 'B' Newsletter, First Coast Service Options, Inc. 2001; 14:55-56, website [www.floridamedicare.com](http://www.floridamedicare.com).
57. Weinstein JN. The tortoise and the hare. Is there a place in spine surgery for randomized trials? *Spine* 1999; 23:2548-2549.
58. Winter RB. The prospective, randomized, controlled clinical trial in spine surgery. Fact or fiction? *Spine* 1999; 23:2550-2552.
59. Carey TS. Randomized controlled trials in surgery. An essential component of scientific progress. *Spine* 1999; 23:2553-2555.
60. Fairbank J. Randomized controlled trials in the surgical management of spinal problems. *Spine* 1999; 23:2556-2563.
61. Tosteson TD. Point of view. *Spine* 1999; 24:2562-2563.
62. Manchikanti L, Kloth D, Singh V. The role of guidelines in interventional pain medicine: let us separate apples and oranges. *Pain Physician* 2001; 4: 13-23.
63. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. *N Engl J Med* 2000; 342:1887-1892.
64. Pocock SJ, Elbourne DR. Randomized trials or observational tribulations? *N Engl J Med* 2000; 342:1907-1909.
65. Kunz R, Khan KS, Neumayer H. Observational studies and randomized trials. *N Engl J Med* 2000; 343:1194.
66. Sacks HS. Observational studies and randomized trials. *N Engl J Med* 2000; 343:1195.
67. Liu PY, Anderson G, Crowley JJ. Observational studies and randomized trials. *N Engl J Med* 2000; 343:1195.
68. Friedman HS. Observational studies and randomized trials. *N Engl J Med* 2000; 343:1195-1996.
69. Schulz KF, Chambers I, Hayes RJ et al. Empirical evidence of bias: Dimensions of methodological quality associated with estimates of treatment effects on controlled trials. *JAMA* 1995; 273:408-412.
70. Goossens MEJB, Evers SMAA, Vlaeyen JWS et al. Principles of economic evaluation for interventions of chronic musculoskeletal pain. *Eur J Pain* 1999; 3:343-353.
71. Ferraz MB, Maetzel A, Bombardier C. A summary of economic evaluations published in the field of rheumatology and related disciplines. *Arthritis Rheum* 1997; 40:1587-1593.
72. Goossens MEJB, Evers SMAA. Economic evaluation of back pain interventions. *J Occup Rehab* 1997; 7:15-32.
73. Maetzel A, Ferraz MB, Bombardier C. A review of cost-effectiveness analyses in rheumatology and related disciplines. *Curr Opin Rheumatol* 1998; 10:136-140.
74. Ross Davies A, Doyle AT, Lansky D et al. Outcomes assessment in clinical settings: A consensus statement on principles and best practices in project management. *Joint Comm Quality Improvement* 1994; 20:6-16.
75. Malter AD, Larson EB, Urban N et al. Cost-effectiveness of lumbar discectomy for the treatment of herniated intervertebral disc. *Spine* 1996; 21:1048-1055.
76. Mueller-Schwefe G, Hassenbusch SJ, Reig E. Cost-effectiveness of intrathecal therapy for pain. *Neuromodulation* 1999; 2:77-84.
77. Manchikanti L, Pakanati RR, Pampati V. Comparison of three routes of epidural steroid injections in low back pain. *Pain Digest* 1999; 9:277-285.
78. Kuntz K, Snider R, Weinstein J et al. Cost-effectiveness of fusion with and without instrumentation for patients with degenerative spondylolisthesis and spinal stenosis. *Spine* 2000; 25: 1132-1139.
79. Guo HR, Tanaka S, Halperin WE et al. Back pain prevalence in US industry and estimates of lost work days. *Am J Public Health* 1999; 89:1029-1035.
80. Manchikanti L, Pampati V, Bakhit CE et al. Effectiveness of lumbar facet joint nerve blocks in chronic low back pain: A randomized clinical trial. *Pain Physician* 2001; 4: 101-117.
81. Hopwood M. Outcomes assessment in pain management. In Abram SE (ed). *Pain Management*. Churchill-Livingstone, Philadelphia, 1998; pp14.1-14.11.
82. Cicala RS, Wright H. Outpatient treatment of patients with chronic pain. Analysis of cost savings. *Clin J Pain* 1989; 5: 223-226.
83. Lave JR, Frank RG, Schulberg HC et al. Cost-effectiveness of treatments for major depression in primary care practice. *Arch Gen Psychiatry* 1998; 55:645-651.
84. Chang RW, Pellissier JM, Hazen GB. A cost-effectiveness analysis of total hip arthroplasty for osteoarthritis of the hip. *JAMA* 1996; 275:858-865.
85. Wong JB, Sonnenberg FA, Salem DN et al. Myocardial revascularization for chronic stable angina: Analysis of the role of percutaneous transluminal coronary angioplasty based on data available in 1989. *Ann Intern Med* 1990; 113:852-871.
86. Katz DA, Cronenwett JL. The cost effectiveness of early surgery versus watchful waiting in the management of small abdominal aortic aneurysms. *J Vasc Surg* 1994; 19:980-991.