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Review Article

Percutaneous Lysis of Epidural Adhesions

Laxmaiah Manchikanti, MD*, and Cyrus E. Bakhit, MD#

Percutaneous epidural adhesiolysis, lysis of epidural adhesions, percutaneous neuroplasty, or epidural neurolysis is an interventional pain management technique which emerged during the latter part of the 1980s. It is becoming established as a common treatment modality in managing chronic low back pain that is nonresponsive to other modalities of treatment. While epidural adhesions most commonly result following surgical intervention of the spine, leakage of disc material into the epidural space following an annular tear, or an inflammatory response can also result in the formation of epidural adhesions. Even though advanced technology, including computerized tomography and magnetic resonance imaging, have made significant advances in the diagnosis of epidural fibrosis, it is believed that epidural adhesions are best diagnosed by performing an epidurogram.

Percutaneous lysis of epidural scar tissue, followed by the injection of hypertonic saline neurolysis, has been shown to be cost effective in multiple studies. This review discusses various aspects of percutaneous nonendoscopic adhesiolysis and hypertonic saline neurolysis including clinical effectiveness, complications, rationale, and indications.
Keywords: Epidural fibrosis, percutaneous lysis of epidural adhesions, hypertonic saline neurolysis, chronic low back pain

While neural blockade in the management of spinal pain continues to be one of the most contentious interventional modalities, percutaneous epidural adhesiolysis, with or without hypertonic saline neurolysis, has attracted an even greater prominence and controversy (1, 2). Among all the chronic painful conditions, spinal pain is the most common, with low back pain taking prominence, burdening approximately 15% to 39% of the population with serious financial and social consequences (3-14). Apparently, low back pain ranks first among musculoskeletal disorders (3). In a recent study, Cassidy and colleagues (5), in assessing the prevalence of chronic low back pain in the general population and its impact on general health, divided the patients into four categories, with 28% of the patients reporting Grade 0 or pain-free status, 47% of the patients reporting Grade 1 pain with low pain intensity and low disability, 12% with Grade 2 pain with high pain intensity and low disability, and 13% of the patients reporting Grade 3 or Grade 4 pain and disability with high pain intensity and either moderate or severe disability.

Duration of back pain and its chronicity have long been topics of controversy and some of the most misunderstood issues. It is widely believed that most episodes of low back pain are short-lived and 90% of patients recover in about 6 weeks, irrespective of the administration or type of treatment (8). This widely held misbelief and myth was dispelled in multiple studies (6, 7, 11, 12). In these studies, the authors showed that 79% of patients continue to suffer with chronic low back pain at 3 months, with no significant change at 12 months in the number of patients with continued low back pain. While disorders of the disc and joints play a major role in causation of low back pain, failed low back surgery syndrome, also known as failed management syndrome or postlumbar laminectomy syndrome, is a growing entity in modern medicine (15-34). An estimated 20% to 50% of lumbar surgeries result in failed back surgery syndrome (15, 16, 20, 26-34). Though

From Pain Management Center of Paducah, Paducah, KY. *Dr. Manchikanti is the medical director of Pain Management Center of Paducah. #Dr. Bakhit is an interventional pain specialist at the Roanoke Pain Center in Roanoke, VA. Address correspondence: Laxmaiah Manchikanti, M.D., 2831 Lone Oak Road, Paducah, KY 42003.

these often result from surgery that was inadequate, incorrect, or unnecessary, this syndrome also results following a well-indicated and well-performed surgical intervention. Fritsch and coworkers (22) reported that, in 80% of the patients, results were satisfactory in short-term evaluation, decreasing to 22% in long-term follow-up after lumbar surgical intervention. Epidural fibrosis and instability were present in more than 60% of the patients evaluated for recurring symptoms (22). Similarly, Fager and Freidberg (26), following the analysis of failures of lumbar surgery, reported poor results, with conclusions that 51% of the 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, with 6 months or less in 50% of the patients. Even in appropriately selected patients, disc excision is not universally successful, as almost 40% will have some symptomatology, with 15% presenting with persistent disabling symptoms leading to further evaluation, treatment, and often surgery (20, 26, 27, 29-31). In fact, Waddell and colleagues (20) 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 procedure to 30%, with 25% considering themselves worse and, after four operations, a 20% success rate, with 45% of the patients considering themselves worse.

Ross and coworkers (21), in the study of the relationship between peridural scar evaluated by magnetic resonance imaging (MRI) and recurrent radicular pain after lumbar discectomy, showed that subjects with extensive peridural scarring were 3.2 times more likely to experience recurrent radicular pain. Even modern developments in spinal surgery with microsurgical approaches also have added new categories of treatment failure (34). Analysis of the frequency and location of lumbar and ventral dural adhesions in elderly cadavers showed significant evidence of adhesions in 40% at L4/5 levels, in 36% at L5/S1 levels, and in 16% at L3/4 levels (23).

While epidural adhesions are most commonly observed following surgical intervention of the spine, leakage of disc material into the epidural space following an annular tear was also reported to cause fibrocyte deposition and an inflammatory response that can also result in the formation of epidural adhesions (35, 36). It has been presumed that inflammation and compression of nerve roots by epidural adhesions is the mechanism of persistent pain in patients (35-38). Epidural fibrosis or arachnoiditis was a relatively rare entity prior to the introduction of lumbar spinal surgery for degenerative conditions (38). Prior to 1935, the present condition of chronic adhesional arachnoiditis was generally described as chronic spinal meningitis (38). A multitude of reports in which epidural fibrosis was found on repeat surgery apparently led to the speculation of association of recurrent symptomatology with perineural scarring (38-40). The causes of failed back syndrome are epidural scarring, arachnoiditis, recurrent disc herniation with neural encroachment, mechanical instability, and facet degeneration. While it is largely agreed that perineural scarring contributes to a considerable amount of morbidity and mortality following lumbar surgery, further surgery is not a solution, as results showed disappointing success rates as low as 12% (34, 40).

It has been stated that epidural adhesions are not readily diagnosed by conventional studies such as myelography, computerized tomography, and MRI, even though modern technology has made significant improvements in this area (36). It is believed that epidural adhesions are best diagnosed by performing an epidurogram, which is most commonly performed via the caudal route, followed by the other routes, including the lumbar interlaminar route, and thoracic and cervical interlaminar routes (36, 37, 41-50). Epidural filling defects have also been seen in a significant number of patients with no history of prior surgery (44).

While peridural scarring in itself is not painful, it can produce pain by "trapping" spinal nerves so that movement places tension on the nerves, thus eliciting pain in an inflamed nerve (47, 50, 51). Kuslich and coworkers (51) reported that back pain was produced by stimulation of several lumbar tissues. However, the outer layer of the annulus fibrosis and posterior longitudinal ligament innervated by synovial vertebral nerves were the most common tissues of this origin (51).

LYSIS OF EPIDURAL ADHESIONS

Adhesiolysis of epidural scar tissue, followed by the injection of hypertonic saline, has been described by Racz and coworkers in multiple publications (36, 37, 47, 48, 50). The technique described by Racz and colleagues involved epidurography, adhesiolysis, and injection of hyaluronidase, bupivacaine, triamcinolone diacetate, and 10% sodium chloride solution on day 1, followed by injections of bupivacaine and hypertonic sodium chloride solution on days 2 and 3. Manchikanti and colleagues (49) modified the Racz protocol from a 3-day procedure to a 1-day procedure.

The purpose of percutaneous epidural lysis of adhesions is to eliminate deleterious effects of scar formation, which can physically prevent direct application of drugs to nerves or other tissues to treat chronic back pain with or without radiculopathy (47). 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.

HISTORICAL CONSIDERATIONS

Epidural injection for chronic low back pain was performed by Pasquier and Leri in 1901 (52). Eight years later, reports on cures of sciatica with epidural anesthesia were made by Caussade and Queste (53). The initial epidurography was performed in 1921 by Sicard and Forestier (54). Hitchcock (55) administered cold hypertonic saline in 1967 for the treatment of chronic pain intrathecally. Ventrafridda and Spreafico (56) reported the use of intrathecal saline to relieve pain in cancer patients. Hitchock (57) also reported that the determining factor in the therapeutic effect of this solution was its hypertonicity rather than the temperature. Racz and Holubec (36) reported the first use of epidural hypertonic saline to facilitate lysis of adhesions. Payne and Rupp (58) used hyaluronidase in an attempt to alter the rapidity of onset, extent, intensity, and duration of caudal anesthesia. Moore (59) also described the addition of hyaluronidase to caudal blocks to enhance the spread of local anesthetic. Cyriax (60) reported his extensive experience with 20,000 patients who showed significant improvement with large volumes of caudal epidural anesthetic. Brown (61) also injected large volumes ranging from 40 to 100 mL of normal saline, which was followed by the injection of 80 mg of methylprednisolone in an attempt to mechanically disrupt and prevent preformation of presumably fibrotic lesions in patients with sciatica. Hyaluronidase was introduced as an alternative agent by Stolker and colleagues (62). Over the years, Racz and coworkers (36, 47, 50), Heavner and colleagues (48), Arthur and coworkers (63), and Manchikanti and colleagues (49, 64) have studied the effectiveness of adhesiolysis and hypertonic saline neurolysis with or without hyaluronidase.

TECHNICAL CONSIDERATIONS

The technique of adhesiolysis involves accessing the lumbar epidural space either caudally, utilizing an interlaminar approach, or by a transforaminal approach. Thoracic and cervical entry have been described by interlaminar means. Entry is performed with a 16-gauge RK® needle (Epimed International Inc, Gloverville, NY), followed by advancement of a Racz® catheter (Epimed International Inc, Gloverville, NY) into the epidural space, with appropriate lysis of adhesions under radiographic control utilizing nonionic contrast medium. Subsequently, a combination of local anesthetic and steroid is injected into the epidural space through the catheter, following which hypertonic saline neurolysis is carried out by slow and intermittent injection of hypertonic saline, either by infusion or in incremental doses. In classic Racz technique (36, 37, 47, 48, 50), the procedure is repeated without steroids on day 2 and day 3; whereas, with other modifications, the catheter is removed after the initial procedure is performed. Racz and his followers also recommend hyaluronidase with these injections (36, 47, 48, 50, 63).

RATIONALE

The rationale for adhesiolysis and hypertonic saline neurolysis in the management of spinal pain stems from the fact that epidural adhesions are a common source of chronic low back pain. The epidural space restricted by adhesions is safely accessible utilizing a special catheter. Removal or correction of structural abnormalities of the lumbar spine may fail to cure and may even worsen painful conditions; degenerative processes of the lumbar spine and the origin of spinal pain are complex; the effectiveness of a large variety of therapeutic interventions in managing low back pain has not been demonstrated conclusively; and the reasonable effectiveness of adhesiolysis and hypertonic saline neurolysis has been demonstrated (2).

Racz and coworkers (50) rationalized percutaneous lysis of epidural adhesions on the basis 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 chronic back pain and/or radiculopathy. Hence, it is reasonable to treat back pain with or without radiculopathy with local application of anti-inflammatory medication (eg, corticosteroids), agents aimed at reducing edema (eg, hypertonic sodium chloride solution, corticosteroids), local anesthetics, and hyaluronidase to promote lysis. Percutaneous lysis of adhesions is indicated only with appropriate diagnostic evaluation and after failure or ineffectiveness of conservative

modalities of treatment has been proven.

While most commonly used methods involve entry into the epidural space through the sacral hiatus, medication placed in the posterior or posterolateral epidural space may not reach pathology in an intravertebral foramen or in the anterior epidural space (65-75). The rationale for transforaminal approach is based on lesion-specific adhesiolysis and delivery of medication to fulfill the aim of reaching the primary site of pathology, thus improving the ultimate outcome. In fact, present evidence evaluating the effectiveness of transforaminal steroids is encouraging compared to interlaminar and caudal epidural steroid injections (2, 66-76).

CLINICAL EFFECTIVENESS

Racz and Holubec (36), in their earliest publication, reported favorable results with good-to-excellent pain relief for up to 1 month in 65% of the patients, for 1 to 3 months in 43% of the patients, and for 3 to 6 months in 13% of the patients. Similarly, Arthur and colleagues (63), in studying 100 patients, concluded that when hyaluronidase was added to the injectate, 82% reported initial pain relief compared to 68% in those without the hyaluronidase. However, no significant difference was seen in long-term improvement (14% vs 12%). Manchikanti and coworkers (49), evaluating 232 patients, 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. Racz and colleagues (47), and Heavner and coworkers (48), in the study of percutaneous epidural adhesiolysis, which was described as epidural neuroplasty, with a prospective evaluation of 0.9% sodium chloride solution versus 10% sodium chloride solution with steroids, with or without hyaluronidase, with prospective 1-year follow-up, concluded that percutaneous epidural neuroplasty, as part of an overall pain management strategy, reduces pain in 25% or more of the patients with radiculopathy plus low back pain refractory to conventional therapies. They also noted that the use of hypertonic saline and hyaluronidase may reduce the number of patients that require additional treatments. However, adhesiolysis was effective even in the patients receiving normal saline. They also showed that the percent of patients requiring additional treatments during 1-year follow-up was approximately 70%, on average around 70 days. This percentage was approximately 60% in patients receiving hypertonic saline, and 80% in patients receiving normal saline. Finally, Racz and colleagues (48) concluded that the most significant finding of the study was that at 1-year follow-up 49% of the patients had pain relief in the body area targeted for the lesion-specific therapy. In contrast to the above reports, Devulder and coworkers (46) concluded that epidurography might confirm epidural filling defects, but a better contrast spread assuming scar lysis does not guarantee sustained pain relief, as filling defects were confirmed in 88% of the patients with epidurography, but significant pain relief was seen in only 33% of the patients at 1 month, 13% at 3 months, and 0% at 12 months. However, the problem with this study was that lysis of adhesions was not lesion specific. Consequently, the delivery of drugs was also nonspecific (77, 78).

In a study evaluating the effectiveness of nonendoscopic adhesiolysis in postlumbar laminectomy syndrome in 60 patients, Manchikanti and colleagues (64) reported relief of 12 ± 3.2 weeks' (mean $\pm$ SEM) relief with the first procedure, whereas with the second procedure it was 13 ± 2.9 weeks using a modified 1-day adhesiolysis. This study also showed 1-year relief in 52% of patients, with repeat procedures of 2.98 ± 0.16 over a 1-year period per patient. Tables 1 and 2 show the results of published reports of non-endoscopic adhesiolysis and hypertonic neurolysis with their effectiveness or lack thereof.

COMPLICATIONS

The most common and worrisome complications of neural blockade in the lumbar spine are related to dural puncture, spinal cord compression, catheter shearing, infection, steroids, hypertonic saline, and hyaluronidase (1, 2, 36-38, 47-50, 64, 66, 79-102). Unintended subarachnoid or subdural puncture with injection of local anesthetic or hypertonic saline is one of the major complications of the procedure. Hypertonic saline injected into the subarachnoid space has been reported to cause cardiac arrhythmias, myelopathy, paralysis, and loss of sphincter control (36, 81). In fact, Aldrete and colleagues (79) attributed incidences of arachnoiditis following epidural adhesiolysis with hypertonic saline to subarachnoid leakage of hypertonic saline. However, the technique utilized in these cases was criticized (103-105). Even though subarachnoid blockade was noted in 2% of the patients, no such complications were recorded by others (49, 64, 103-105). Kim and coworkers (81) reported a case of myelopathy after intrathecal administration of hypertonic saline of 15%, 10 mL, diluted with CSF to a volume of 12 mL, preceded by

TABLE 1. RESULTS OF PUBLISHED REPORTS OF PERCUTANEOUS ADHESIOLYSIS AND HYPERTONIC SALINE NEUROLYSIS FOR A SINGLE PROCEDURE

Author(s)	Study Characteristics	No. of Patients	Drugs Used	No. of Days of Procedure	Initial Relief 1-4 weeks	Long-Term Relief		
						3 months	6 months	12 months
Racz and Holubec (36)	R, RA	72	B, T, H, HS	3	65%	43%	13%	N/A
Arthur et al (63)	R	50	B, T, HS	3	68%	N/A	14%	N/A
Arthur et al (63)	R	50	B, T, H, HS	3	82%	N/A	12%	N/A
Manchikanti et al (49)	R, RA	103	M, L, HS	2	74%	37%	21%	4%
Manchikanti et al (49)	R, RA	129	M, L, HS	1	79%	26%	14%	4%
Manchikanti et al (64)	R	60	L, HS, CS	1	100%	10%	7%	5%

R=retrospective; C=controlled; RA=randomized; B=bupivacaine; L=lidocaine; T=triamcinolone; M=methylprednisolone; CS=celestone soluspan; H=hyaluronidase; HS=hypertonic saline; NS=normal saline; +=positive; -=negative; N/A=not available

an injection of 1 mL of an aqueous solution of morphine sulfate without preservative, 10 mg/mL, diluted with CSF to a volume of 10 mL, and 1 mL of which was slowly administered intrathecally. Autopsy findings of this patient, who died 16 months after intrathecal administration of hypertonic saline, showed peripheral accentuated loss of myelinated fibers within the spinal cord from T12 downward, as well as dense collagenous thickening of the dorsal leptomeninges from T9 to T11. Admittedly, this case report by Kim and colleagues (81) was a devastating complication. However, Hitchcock and Prandini (82), in managing 108 patients suffering from intractable pain with intrathecal hypertonic saline, reported sphincter disorders in 8% of the patients, with 2.7% experiencing cauda equina syndromes with paraplegia. They (82) also reported rapid recovery in one patient, but quite slow and incomplete recovery in the others, attributing the cauda equina syndromes to pre-existing arachnoiditis in one patient and arteriovascular disease in the others. Lucas and colleagues (83), in a survey of 648 neurosurgeons, reported that 31.2% had used intrathecal hypertonic saline to treat pain in 1,943 patients. They reported adverse reactions in 11.2% of the

TABLE 2. RESULTS OF 1-YEAR FOLLOW-UP OF PATIENTS UNDERGOING PERCUTANEOUS EPIDURAL ADHESIOLYSIS

Author(s)	Study Characteristics	No. of Patients	No. of Days of Procedure	Percent of Patient with Significant Relief			
				1 month	3 months	6 months	12 months
Racz et al (47), Heavner et al (48)	P, C, RA	59	3	83%	49%	43%	49%
Manchikanti et al (64)	R	60	1	100%	90%	72%	52%

R=retrospective; P=prospective; RA=randomized; C=controlled

patients treated by injection of hypertonic saline and 7.6% of those treated with normal or diluted saline injections. However, only 22 patients, or 1%, suffered significant morbidity. Paraplegia or tetraplegia was seen in 16 or 0.76%, of the patients; while monoparesis of the leg affected one patient (0.05%). They also reported two patients who died as a result of myocardial infarction, whereas two others had loss of hearing and transient ipsilateral facial weakness after cisternal injection. In retrospect, the statistics of administration of intrathecal hypertonic saline do not suggest that the procedure was inordinately hazardous. Commenting on the report by Kim and coworkers (81), Dagi (84) postulated that these events were very unusual even for intrathecal hypertonic saline injection of 15%, wondering whether hypertonic saline was the cause of paraplegia or whether the paraplegia possibly resulted from the inadvertent substitution of morphine with preservative for morphine without preservative before the administration of saline. Other reports of spinal cord lesions by subdural injection of neurolytic agents and local anesthetics were also with exuberant pachymeningitis reaction in dogs (85). However, the other postmortem examinations in humans after saline injections were more sobering (83).

The second specific complication of percutaneous epidural adhesiolysis is related to catheter shearing and its retention in the epidural space. Even though the RK needle and Racz catheter have been specifically designed for this procedure, catheter shearing has been reported. Racz and colleagues (36) reported this problem to occur in five such cases. Manchikanti and Bakhit (80) also reported a torn Racz catheter in the lumbar epidural space, which was successfully removed. This complication has also been reported following epidural injections with catheters utilized for anesthesia. 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, even though no such complications have been reported following adhesiolysis and hypertonic saline neurolysis. Kushner and Olson (91) evaluated patients who complained of visual-field defects or blurred vision after receiving epidural steroid injections and concluded that retinal hemorrhage is uncommon but significant. Retinal hemorrhages mainly have been attributed to rapid epidural injections of high volumes, causing a sudden increase in intracranial pressure, resulting in the increase of retinal venous pressure (91-97). However, it is extremely difficult to decisively conclude whether this complication has any relation to the steroid administration, or the administration of any other adjuvant drugs, as it may be precipitated either with the administration of normal saline, local anesthetic, hypertonic saline, or any other type of drug. Hence, it appears that there is no causal relationship between these complications and adhesiolysis, epidural injection, or administration of various agents.

Epidural infection following this procedure is a distinct possibility due to the procedure itself, as well as potential immunosuppression secondary to steroid injection. Racz and colleagues (36, 47, 48, 50) have reported no incidences of epidural abscess in their patient population. Similarly, Manchikanti and coworkers (49), though noting serious infection in one patient with the development of an abscess, saw no involvement of the spinal canal. Manchikanti and colleagues (49) also reported a suspicion of infection in 2% of the cases. Sampath and Rigamonti (98), in a review of epidemiology, diagnosis, and treatment of spinal epidural abscess, noted that spinal nerve block was responsible for 7% of the patients, whereas a multitude of predisposing factors included intravenous (IV) drug use, diabetes mellitus, multiple medical illnesses, trauma, prior spinal surgery, morbid obesity, HIV disease, and end-stage renal disease in a descending order of frequency. Wang and coworkers (99), in a 1-year study of the incidence of spinal epidural abscess after epidural analgesia, reported nine cases of epidural abscess formation from a total of 17,372 epidural catheters. No arachnoiditis, paralysis, weakness, bladder disturbances, or other serious complications were seen with percutaneous lysis of epidural adhesions in any of the reports.

Direct trauma to the spinal cord following cervical, thoracic, and lumbar epidural injections has been reported, resulting in disastrous complications, even though none of the case reports involved percutaneous lysis of epidural adhesions (100-102). The potential of spinal cord trauma is more likely with percutaneous adhesiolysis with hypertonic saline injection than with other epidural procedures, as the injection of adjuvant agents with preservatives may be unforgiving.

Occasional sensitivity to hyaluronidase may be a problem. Moore (59) reported a 3% sensitivity reaction in a series of 1,520 epidural administrations of hyaluronidase. However, Racz and colleagues (36, 50) reported no such incidences of hyaluronidase sensitivity and postulated that the steroid leaves the space more slowly than hyaluronidase, which may help protect against allergic reaction

TABLE 3. PHARMACOLOGICAL PROFILE OF COMMONLY USED STEROIDS IN PERCUTANEOUS EPIDURAL ADHESIOLYSIS

Name of Drug	Equivalent Dose	Epidural Dose	Anti-inflammatory Potency	Sodium Retention Capacity	Duration of Adrenal Suppression		
					IM	Single Epidural	Three Epidurals
Triamcinolone acetonide (Kenalog)	4 mg	40-80 mg	5	0	2-6 weeks	N/A	2-3 months
Betamethasone (Celestone Soluspan)	0.6 mg	6-12 mg	25	0	1-2 weeks	N/A	N/A
Triamcinolone diacetate (Aristocort)	4 mg	40-80 mg	5	0	1-2 weeks	1-5 weeks	N/A
Methylprednisolone acetate (Depo-Medrol)	4 mg	40-80 mg	5	0.5	1-6 weeks	1-3 weeks	N/A

Data adapted and modified from Mikhail et al (117, 118), Melby (119), Schimmer and Parker (120), McEvoy et al (121)

as the steroid is placed exactly at the site where the hyaluronidase is also deposited.

Other side effects are related to the administration of steroids, and are generally attributed to the chemistry or pharmacology of the steroids. The most commonly used agents in adhesiolysis and hypertonic saline neurolysis by Racz and colleagues (36, 47, 48, 50, 63) have been triamcinolone acetonide (Kenalog®), whereas Manchikanti and coworkers (49, 64) utilized either methylprednisolone (Depo-Medrol®), or Celestone® Soluspan®. The safety of steroids and preservatives at epidural therapeutic doses has been demonstrated in both clinical and experimental studies (2, 66, 106-113). The major theoretical complications of corticosteroid administration include suppression of the pituitary-adrenal axis, hypocorticism, Cushing's syndrome, osteoporosis, avascular necrosis of bone, steroid myopathy, weight gain, fluid retention, and hyperglycemia (2, 66, 114-123). 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 (92-94, 119-123). However, the use of corticosteroids repeatedly for days or even a few weeks does not lead to adrenal insufficiency upon cessation of treatment; but prolonged therapy with corticosteroids occasionally may result in the suppression of pituitary-adrenal function that can be slow in returning to normal. Rare hypothalamic-pituitary-adrenal suppression during corticosteroid administration with epidural injections and after its withdrawal has been reported (114-116). However, no such reports have implicated percutaneous adhesiolysis and hypertonic saline neurolysis. After a single, clinically used dose of steroid, Mikhail and colleagues (117, 118) reported that maintenance of adequate endogenous adrenal function was influenced by the length of the interval between steroid injections. They showed that adrenal suppression with 50 mg of triamcinolone diacetate (Aristocort®) or 9 mg of betamethasone acetate – phosphate mixture (Celestone Soluspan) lasted only 1 week, in contrast to triamcinolone acetonide (Kenalog), with which adrenal suppression lasted for 6 weeks. Finally, the effect of serial epidurals was studied by Slucky and colleagues (113) on the material properties of the lumbar dura mater, as steroids, apart from their anti-inflammatory effect, also are known to affect collagen synthesis, material strength, and tissue healing. Slucky and coworkers (113) showed that three serial epidural injections of saline or methylprednisolone at 2-week intervals produced no significant material or matrix changes in the lumbar dura in canines. Table 3 illustrates the comparative phar-

macology of commonly used steroids in neural blockade in general and adhesiolysis and hypertonic saline neurolysis in particular.

INDICATIONS

Percutaneous epidural adhesiolysis and hypertonic saline neurolysis are indicated in patients with chronic low back pain who have failed to respond to conservative modalities of treatments including epidural injections administered under fluoroscopic guidance, and other well-documented therapeutic modalities. Various conditions in which epidural lysis of adhesions is indicated include post-laminectomy syndrome, epidural adhesions, disc disruption, traumatic or pathologic vertebral body compression fracture, and resistant multilevel degenerative arthritis (36, 50).

In the past, a multitude of investigators have attempted to identify predictors of outcome of epidural injections, as well as facet-joint injections (2). However, these have been proven to be futile. No such attempts have been made with regards to percutaneous adhesiolysis and hypertonic saline neurolysis.

COST EFFECTIVENESS

Fortunately, cost effectiveness of percutaneous epidural adhesiolysis was determined in two separate groups of patients (49, 64). Manchikanti and colleagues (49), utilizing the principles of functional improvement extrapolated to quality-adjusted life-years (QALYs) calculated the cost effectiveness of either 1-day or 2-day adhesiolysis and hypertonic saline neurolysis in 232 patients with complaints of low back and lower-extremity pain in a heterogenous group of patients that included postsurgical and nonsurgical patients, who had failed to improve with any other modalities of treatment. They showed that significant relief was provided with a determination of 1-year QALY improvement for $7,332 for patients undergoing the 2-day procedure, and for $5,564 for patients who were on a 1-day basis.

Using a 1-day procedure, Manchikanti and coworkers (64) also studied 60 post-lumbar laminectomy patients who failed to respond to any and all conservative modalities of treatment. This study showed one QALY improvement at a cost of $2,080.

CONTROVERSIES

The evolution of percutaneous epidural adhesiolysis and hypertonic saline neurolysis has been associated with some controversy since its introduction, though it was received with enthusiasm and has been accepted as part of medical practice by many physicians specializing in pain management (1, 2, 36, 45, 47-50, 63, 64, 77-81, 103-105, 124). Various aspects of the evolution and occasional controversy of percutaneous adhesiolysis and hypertonic neurolysis in managing low back pain include its rationale and efficacy; type of local anesthetic; frequency and number of injections; and, finally, cost effectiveness.

Rationale and Efficacy

The rationale and efficacy have been established with reasonable probability (47-50, 64). However, detractors of percutaneous epidural adhesiolysis do exist (1, 45, 79). Most of the criticism is based on lack of understanding of the technique, improper application of the technique, and inability to review the recent literature available on percutaneous epidural adhesiolysis. The indications for percutaneous epidural adhesiolysis are straightforward, and include postlaminectomy syndrome, epidural adhesions, disc disruption, traumatic or pathologic vertebral body compression fracture, and resistant multilevel degenerative arthritis. However, some would like to limit this procedure only to postlumbar laminectomy syndrome with demonstrated epidural scar tissue on MRI.

Type and Dosage of Drugs

With regard to the type and dosage of drugs, the major developments involve not only the steroids but also hypertonic saline, as well as hyaluronidase.

Steroids: The significant attention focused in the literature on the complications attributed to the use of epidural steroids arises from false impressions and misunderstandings. Based on the available literature and scientific application, all four formulations of long-acting steroids appear to be safe and effective. Various modes of action of corticosteroids include membrane stabilization, inhibition of peptide synthesis or action, blockade of phospholipase A_2 activity, prolonged suppression of ongoing neuronal discharge, suppression of sensitization of dorsal horn neu-

rons, and reversible local anesthetic effect (2). Epidural injections of betamethasone in a model of lumbar radiculopathy showed a significant effect on thermal analgesia, while administration of IV methylprednisolone dramatically reduced the nerve-root injury produced by epidural application of autologous nucleus pulposus in a pig experimental model (125, 126). In addition, Minamide and colleagues (127), in an experimental study in the rabbit, showed that, while lipopolysaccharide accelerated the process of herniated intervertebral disc resorption, high-dose steroids suppressed the process. Kingery and coworkers (128), while examining the effects of systemic methylprednisolone on acute nociception and pain behavior in hyperalgesia in normal and neuropathic rats, reported that chronic steroid treatment prevented neuropathic edema and blocked neurogenic extravasation. Johansson and Bennett (129) demonstrated that local application of methylprednisolone in a nerve-injury model showed that the heat hyperalgesia and mechanoallodynia were depressed in the animals receiving the corticosteroids, but not in those treated with saline, with the effect remaining for 11 days after the test.

Racz and colleagues (36, 50) have recommended triamcinolone, as it is a more specific glucocorticoid agonist than methylprednisolone. However, the differences between triamcinolone acetonide (Kenalog), which is recommended by Racz and coworkers (36, 50), and triamcinolone diacetate (Aristocort), which is also substituted for triamcinolone acetonide, are significant (Table 3). Both have similar anti-inflammatory potencies with no sodium retention capacity, even though adrenal suppression is vastly different, with a relatively short period of 2 weeks with triamcinolone diacetate (Aristocort) and a longer period of 6 weeks with triamcinolone acetonide (Kenalog) (117, 118). However, Delaney and colleagues (106) reported that triamcinolone diacetate (Aristocort) was preferred due to its excellent anti-inflammatory effect, low potential for sodium retention, and ability to remain in suspension in local anesthetic mixture for longer periods of time.

Kepes and Duncalf (130), however, in their review concluded that methylprednisolone was the least irritating, the most beneficial, and the longest acting. The disadvantage quoted for methylprednisolone (Depomedrol) was that of its sodium retention capacity (124). In addition, all three drugs, (ie, methylprednisolone acetate [Depomedrol], triamcinolone diacetate [Aristocort], and triamcinolone acetonide [Kenalog]) contain benzyl alcohol as a preservative. However, methylprednisolone acetate (Depomedrol) is available in generic form without benzyl alcohol.

In contrast, betamethasone acetate – phosphate mixture (Celestone Soluspan) has been shown to be the least irritating with an excellent anti-inflammatory effect, along with rapid onset and superior dissolution in the diluent. Latham and coworkers (112) demonstrated that Celestone in doses equivalent to either 1 mL or 6 mg, and probably doses up to 2 mL or 12 mg, is safe when injected intrathecally, and, therefore, should not constitute a hazard when used epidurally in humans. No studies compare the effectiveness of all four drugs or any of the drugs either in neural blockade or following adhesiolysis.

Unintended intrathecal administration of steroids always poses a serious problem; even though Abram and O'Connor (89), after reviewing 65 published series of epidural steroid injections, which included 7,000 patients, found no reports of neurological complications other than one case of transient foot drop. Tanner (131) published the results of a questionnaire assessing the safety of epidural steroid injections which involved 41 physician responses and included experience with approximately 75,000 procedures, with only one report of persistent neurologic dysfunction.

However, there have been several reports of arachnoiditis among patients treated with multiple intrathecal steroid injections. Nelson and colleagues (132) reported two cases of adhesional arachnoiditis that occurred among 23 patients treated for multiple sclerosis. This group had received 83 subarachnoid injections of methylprednisolone acetate. Ryan and Taylor (133) also reported a case of adhesional arachnoiditis among 180 patients treated with a combination of 40 mg each of intrathecal and epidural methylprednisolone acetate. Sclerosing patchy spinal meningitis was also reported in one patient (134). Calcific arachnoiditis was reported in a case with a patient with multiple sclerosis (MS) who received numerous injections of intrathecal methylprednisolone acetate and methylprednisolone sodium succinate over a 2-year period (135). In another retrospective review of 80 patients who had myelographic changes compatible with arachnoiditis, Roche (136) attributed only one case to intrathecal steroid injections. Most cases have occurred in patients with pre-existing, severe neurologic symptoms as-

sociated with MS. In addition, aseptic meningitis also has been documented after intrathecal injections of long-acting steroids (66, 132, 137); other reported complications associated with intrathecal steroid injections include cauda equina syndrome, tuberculous meningitis, streptococcal meningitis, and cerebral thrombosis (138-142).

Hypertonic Saline: The next issue in the evolution of percutaneous adhesiolysis surrounds injection of hypertonic saline. Early experiments on hypertonic saline and nerve conduction showed that osmolar depletion of water content within peripheral axons resulted in decreased nerve conduction (143). However, later work demonstrated attenuation of transmitter release from neuromuscular junctions exposed to hypertonic solutions (144). In 1967, the first application of hypertonic saline in the treatment of chronic back pain by intrathecal injection of cold saline was described by Hitchcock (55). However, subsequently it was shown that the efficacy of hypertonic saline was due to the hypertonicity of the solution rather than to any thermal effect (57). In another study, the mechanism of action of hypertonic saline was demonstrated to be selective C-fiber blockade in cat dorsal rootlets with increased concentration of chloride ion (145). Subsequently, it was shown that hypertonic saline decreased spinal-cord water content and depressed lateral column-evoked ventral root response (86). However, this response was observed with all hyperosmolar agents and was not chloride-ion dependent (86). Kukita and Yamagishi (146) also suggested that there were at least two changes produced by increasing extra-axonal osmolality, which may have an effect on axonal function. These changes include volume change due to outflow of water across the membrane, and ionic concentration changes. They also showed that when the volume is eliminated, hypertonic saline increased the peak action potential, but did not greatly change the resting potential. Benefits of hypertonic saline were explained by reducing cell swelling or by causing an osmotically induced fluid shift, consequently reducing pressure on the nerve, and producing a local anesthetic effect of the hypertonic solution (147). Racz and colleagues (148) showed that the study of dural permeability in dogs demonstrated transdural equilibration of hypertonic saline to occur very slowly, but doubling cerebrospinal sodium concentration 20 minutes after extradural placement of 10% sodium chloride solution. Hence, the anesthetic effects of epidural hypertonic saline not only remain controversial and lack definition, but also cast doubt on the hypothesis that it achieves its therapeutic effect by shrinking the mass. In fact, Wittenberg and coworkers (149) showed an actual increase in tissue mass in the case of intravertebral tissue incubated in 10% sodium chloride solution.

Further controversy over the mechanism of action of hypertonic saline surrounds the question of marked alteration of intracellular sodium. In an experimental setting, it was noted that, following the injection of hypertonic saline following a period of hyponatremia, myelin sheaths surrounding oligodendrocytes underwent not only vesicular disruption, but also disintegration (86). However, it was also shown that corticosteroids protected against such changes (87). Nevertheless, the clinical relevance of these findings is not known, as these authors specifically excluded the spinal cord and the peripheral nervous system from their examination. Therefore, any attempt to extrapolate these findings to epidural hypertonic saline neurolysis would be a stretch of the imagination and inappropriate.

Type of Local Anesthetic: The type of local anesthetic, either bupivacaine or another type of local anesthetic, has also been controversial, evolving from description of the technique by Racz and colleagues, recommending bupivacaine as an ideal agent (36, 47, 48, 50, 124). Racz and coworkers based this recommendation on their experience that bupivacaine has a more rapid onset of action in the subarachnoid space than in the epidural space (36, 47, 48, 50, 124, 150). Racz and colleagues (36, 47, 48, 50, 124, 150) considered the issue of prolonged block from local anesthetic by 0.25% bupivacaine as less of a problem than the issue of differentiating between epidural, subdural, and subarachnoid spread. Further, their assertions include that bupivacaine causes motor block in the subdural space, but will not cause a motor block in the epidural space. However, Manchikanti and coworkers (49, 64, 152) showed no significant differences utilizing 1% lidocaine in contrast to 0.25% bupivacaine. Racz and colleagues (50, 124, 150) are concerned that lidocaine does not have such marked difference between subarachnoid and epidural onset of action and that one may see a motor block in the epidural space as well. They consider this as a major disadvantage with lidocaine that will interfere with one of the key parameters used to guard against iatrogenic damage. However, Manchikanti and coworkers (49, 64, 151) believe that there is no significant difference in motor blockade of either 0.25% bupivacaine or 1% lidocaine. In addition, they have reported no deterioration in relief with 1% lidocaine, with the added benefit of fewer side effects, an extremely important issue in an outpatient setting as inadvertent intrathecal administration of bupivacaine may result in sensory and motor blockade lasting over 12 hours. Another clinical advantage of lidocaine is its rapid onset

of blockade. It is also important to note that every attempt must be made by prior injection with local anesthetic and by waiting for an appropriate time before injection of hypertonic saline and/or by not exceeding the volume of local anesthetic by the volume of hypertonic saline.

An additional discussion surrounds hyaluronidase. The rationale for the use of hyaluronidase in percutaneous adhesiolysis relates to its ability to disrupt epidural adhesions. The therapeutic importance of such disruptions by hyaluronidase is controversial, even though Racz and colleagues (36, 47, 48, 50, 63, 124) believe that it is supported by a number of their investigations. Basically, hyaluronidase appears to be safe, even if administered intrathecally. The first reported use of the protein enzyme hyaluronidase was in 1929 by Duran-Reynals (152), which was termed *the spreading factor*. The safety of hyaluronidase injected into the epidural space has been documented in the literature with significant clinical experience (36, 47, 48, 50, 58, 59, 153, 154). However, the controlled studies performed by Racz and coworkers (47) and Heavner and colleagues (48) failed to show any statistically significant difference in results with addition of hyaluronidase. Considering the safety of hyaluronidase and potential improvement in the quality of adhesiolysis, though not statistically significant, one may consider using hyaluronidase in selected cases requiring extensive adhesiolysis.

Technique

Although the technical aspects of the procedure, have continued to focus on lesion-specific adhesiolysis and delivery of the steroid, local anesthetic, and hypertonic saline to the target specific area others have attempted nonspecific adhesiolysis (36, 45, 47, 48, 50, 77, 78, 124). Lesion-specific adhesiolysis and delivery of the medication to the target area are important; volume-dependent fluid dissection has been shown to be controversial, as larger volumes of epidural solutions increase cephalad spread, but fail to facilitate lateral spread across the areas of adhesions (155). In addition, it was also shown that increase in the volumes of epidural solutions failed to improve filling patterns (44). Further evolution of the technology also is incorporating modification of the original technique with site-specific lateral and ventral epidural catheter placement.

Frequency and Number of Injections

Frequency and total number of injections are key issues in any type of neural blockade, even though quite controversial and poorly addressed. They are of paramount importance in percutaneous adhesiolysis. Racz and coworkers (36, 47, 48, 50, 124) strongly believe that a 3-day rigid protocol is essential for good results. However, Manchikanti and colleagues (49, 64) have shown that a modified alternative 1-day protocol was as effective as a 3-day or a 2-day protocol and reduced the cost of the procedure with improvement in cost effectiveness. Thus far, the studies have shown that average relief ranged, with a single injection, to approximately 70 days, with the need for additional treatments around this time (47-50, 64). Further controversy with regards to the number of injections is based not only on adhesiolysis, but also on the discrepancy between various recommended protocols for the frequency, time interval, and steroid dosage of epidural injections. These range from three injections in a series, a course of three injections followed by a repeat course of an additional three injections after 3-, 6-, and 12-month intervals, to an unlimited number of injections with no established goals or parameters, as well as the limitation of 3 mg/kg body weight of steroid or 210 mg per year (in an average person) of steroids, or a lifetime limitation of a total dose of 420 mg of steroid. However, it is not only unrealistic but also unfair to presume that nonendoscopic adhesiolysis performed either on a 1-day, 2-day, or 3-day basis will provide permanent relief with one treatment. Hence, it should be based on each individual's experience either to follow a traditional 3-day approach or a modified 1-day approach, with the frequency of injections based on the pharmacology of the drugs administered in conjunction with relief of pain and functional improvement. Based on the available evidence, it appears reasonable to continue percutaneous epidural adhesiolysis at increasing intervals of 4 to 6 weeks, leading to stabilization and continued increasing duration of relief between blocks to a maintenance status with intervals of at least 2 to 3 months.

Cost Effectiveness

Finally, cost effectiveness is a contentious issue in pain management in general and interventional pain management in particular. Generally, outcome research in chronic pain management remains a collection of documents that describe and provide examples of methodologies, instruments, and philosophies that have guided its development. The entire medical field is full of controversy and ambiguity. Clinical efficacy and outcome assessment are pivotal in the modern health care environment in the United States, with growing calls for accountability in medicine and for research that measures the end result of treatment rather than the process or treatment itself (156-160). Out-

comes research differs from traditional clinical research in that focuses on issues of a broader scope and on effectiveness versus efficacy (156-165).

While outcomes may be assessed by numerous means, the quality-of-life/functional status is the most important aspect of outcomes assessment in pain management (156). The quality-of-life assessment is designed to evaluate a patient's abilities to function in his/her own world, with physical functioning measuring the ability to perform physical activities such as walking, climbing stairs, or carrying things or in a separate domain where evaluation consists of the patient's major perceived functional impairments, and improvement in the patient's major perceived impairments such as playing with children/grandchildren, having sexual relations, returning to work, performing activities of daily living, going to school, or homemaking. Hopwood (156), in discussing quality-adjusted life-years (QALYs), proposed that, for pain patients, the trade-off of one year of pain for 0.5 years of pain-free status (thus equaling improvement of 0.5 QALYs) may be reasonable.

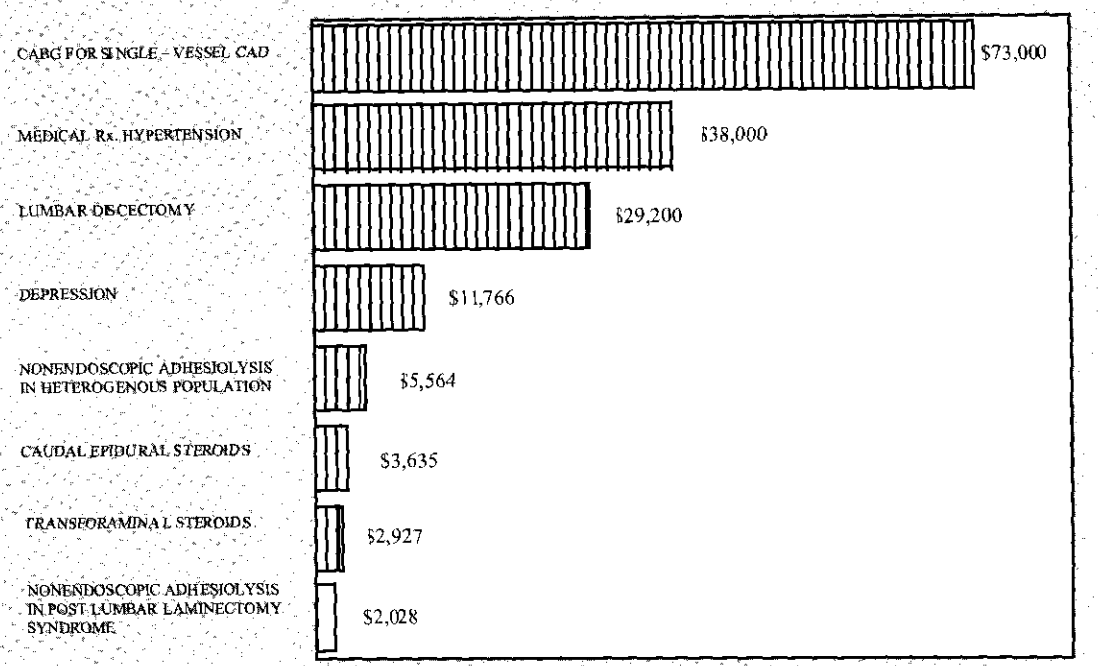
It is often too easy for academicians to retreat into criticism and it is fashionable and cost effective to be a therapeutic nihilist, but the clinician is faced with the daily task of advising patients, with or without outcomes and cost effectiveness analyses. In practice, taking care of the patient requires individualizing from the general to the specific person being treated. While waiting for better data to emerge, it would be unwise for anyone to be dogmatic and dismiss percutaneous epidural adhesiolysis and hypertonic neurolysis.

The 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 (166). In addition, chronic pain patients may incur health-care bills in excess of $20,000 annually for repetitive and in some cases redundant diagnostic and therapeutic interventions. Malter and colleagues (167) evaluated the cost effectiveness of lumbar discectomy for the treatment of herniated intervertebral discs and concluded that surgery increased the average quality-adjusted life-expectancy by 0.43 years during the decade following treatment, a result comparable to extending a healthy life by 5 months compared to conservative treatment. They 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. However, this study does not take into consideration whether the initial surgical treatment for herniated disc fails. Waddell (20) has reported declining relief from 50% for a second operation to 20% for a fourth operation, and the worsening of symptomatology in 20% of the patients following the second operation and increasing to 45% of the patients with the fourth operation. In a recent study, Mueller-Schwefe and colleagues (168), in evaluating the cost effectiveness of intrathecal therapy for pain secondary to failed back surgery syndrome by comparing alternative therapies for achieving a defined outcome, reported the cost of medical management to be $85,186 per 5 years, $17,037 per year, and $1,420 per month. They also showed that intrathecal morphine delivery resulted in lower cumulative 60-month costs of $82,893 per five years, $16,579 per year, and $1,382 per month. Cost effectiveness of percutaneous adhesiolysis and hypertonic saline neurolysis utilizing a modified technique on a 1-day basis was demonstrated to be $5,564 for improvement of each year of quality of life for patients with chronic low back pain, nonresponsive to numerous other modalities of treatment in a heterogenous population; and $2,080 in postlumbar laminectomy syndrome patients (49, 64).

Thus far, the published evidence is mixed for epidural steroid injections in general, with the evidence more in favor of caudal epidural steroids, even though it does not support the use of interlaminar lumbar epidural steroids (2, 66, 169). However, other studies performing meta-analysis (69, 170-173) showed both caudal and lumbar epidural injections to be efficacious, even though the caudal approach was somewhat superior. Manchikanti and coworkers (69) have shown transforaminal epidurals to be superior in cost effectiveness, followed by caudal epidurals, and blind interlaminar epidurals were the least cost effective. In fact, the costs of this procedure actually exceeded those of non-endoscopic adhesiolysis and hypertonic saline neurolysis (69). Fig. 1 illustrates the cost effectiveness of selective therapies per QALY gained utilizing various modalities of treatment in managing low back pain, as well as for treatment of single-vessel coronary artery disease, medical treatment of hypertension, and depression.

Recommendations for any procedure are based either on evidence or consensus. Essentially, these recommendations are based on the evidence, as well as consensus. However, evidence, as well as consensus, has been criticized in the literature (174, 175). The issues of ethics, feasibility, cost, and reliability pose challenges to the randomized trial in percutaneous epidural adhesiolysis and hypertonic saline neurolysis, which theoretically represents the gold standard (176-183). Such a published, randomized clinical trial of the efficacy of percutaneous epidural

Figure 1. *Cost effectiveness of selective therapies per quality-adjusted year of life gained*



Data adapted and modified from Malter et al (167), Manchikanti et al (49, 64, 69), and Lave et al (173).

adhesiolysis has been criticized (1, 48). It has been suggested that the methodological quality of a large number of published, randomized clinical trials on the efficacy of interventions in the management of low back pain have been poor (176). Thus, well-controlled, randomized trials continue to be recommended and strongly urged. Until then, the present available literature must be considered based on its merits.

CONCLUSION

Chronic low back pain is a major health-care and social problem. Much of the confusion surrounding nonendoscopic adhesiolysis and hypertonic saline neurolysis in managing refractory low back pain results from overemphasis on biopsychosocial problems and inappropriate selection of patients for this treatment modality. Considering the cumulative evidence available in the literature on percutaneous epidural adhesiolysis and hypertonic neurolysis, the efficacy of this procedure is similar, if not superior, to various other modalities of treatments available in managing chronic low back pain, including surgical intervention.

While this is a very effective technique in managing chronic low back pain, caution must be exercised with application in the cervical, as well as thoracic spine, as there are significant risks of spinal-cord trauma. While a pain practitioner needs to individualize the choice of treatment to each patient and personal experience, we recommend percutaneous adhesiolysis with hypertonic saline neurolysis on a 1-day basis, which was proven to be a valuable, safe, and cost-effective technique for relieving chronic intractable pain when performed in an outpatient setting, with reasonable and customary charges for the facility and physician services.

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