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Editorial

Refinement in Evidence Synthesis of Percutaneous Adhesiolysis

Standiford Helm II, MD[1], Ramsin M. Benyamin, MD[2], and Frank J.E. Falco, MD[3]

The Institute of Medicine report on relieving pain in America (1,2) showed the magnitude of pain in the United States and pain's astounding financial costs, which range from $560 billion to $630 billion per year. Martin et al (3) estimated that treatment for back and neck pain problems accounted for $86 billion in health care expenditures in the United States in 2005, with a 65% increase in expenditures and a 49% increase in the number of patients seeking spine-related care from 1997 through 2006. However, exploding health care costs in managing chronic pain are not an isolated issue for the United States; rather it is a global issue. Almost all countries continue to face escalating health care costs. Among various reasons for exploding costs in managing spinal pain, interventional techniques have been implicated (4). In fact, the growth of interventional techniques for managing spinal pain continues to surprise, especially policy-makers. The increasing utilization of interventional techniques is often considered to be inappropriate and occasionally unsafe, resulting in inappropriate care (4-12). Ironically, the criticism continues despite significant advances with multiple randomized, controlled trials, systematic reviews, and evidence-based guidelines (4,13-83). Even then, the available evidence documents a wide degree of variation in the definition of the practice of medicine in general and interventional pain management in particular. Manchikanti et al (5), in an assessment of all interventional techniques, except for implantables, continuous epidurals, intraarticular injections, trigger point and ligament injections, peripheral nerve blocks, and vertebroplasty procedures, showed an increase of 177% per 100,000 Medicare beneficiaries from 2000 to 2011 with an annual average increase of 11.4%. This assessment showed the increases were significantly higher for facet joint interventions and sacroiliac joint blocks with an increase of 310% per 100,000 Medicare beneficiaries, whereas the increases for epidural and adhesiolysis procedures was 127%. The geometric average of annual increase was also higher for facet joint interventions with 13.7% and 7.7% for epidural and adhesiolysis procedures. Of these, percutaneous adhesiolysis procedures constitute 1% of epidural injections and less than 0.5% of all interventional procedures (5-7).

American Society of Interventional Pain Physicians guidelines have demonstrated the evidence available for interventional techniques is fair or above for only 47% of the therapeutic interventions assessed (4). These guidelines illustrate a rigorousness of assessment and the paucity of literature for interventional techniques. Even then, all interventional techniques have been questioned for their efficacy and cost effectiveness. This issue of Pain Physician dispels some of the myths and demonstrates the effectiveness of placebo controlled percutaneous adhesiolysis in managing chronic radiculitis (83) and cost utility analysis of caudal epidural injections in managing chronic low back and lower extremity pain due to various pathologies (84). However, these are not the first studies to specifically show the effectiveness of spinal interventional techniques (4), including percutaneous adhesiolysis, and related cost utility analysis. In fact, Helm et al (56), in a systematic review of percutaneous adhesiolysis, and Manchikanti et al (4) in

From: [1]The Helm Center for Pain Management, Laguna Hills, CA; [2]Millennium Pain Center, Bloomington, IL, and University of Illinois, Urbana-Champaign, IL; [3]Mid Atlantic Spine & Pain Physicians, Newark, DE and Temple University Hospital, Philadelphia, PA.

Dr. Helm is Medical Director, The Helm Center for Pain Management, Laguna Hills, CA. Dr. Benyamin is Medical Director, Millennium Pain Center, Bloomington, IL and Clinical Assistant Professor of Surgery, College of Medicine, University of Illinois, Urbana-Champaign, IL. Dr. Falco is Medical Director of Mid Atlantic Spine & Pain Physicians, Newark, DE; Director, Pain Medicine Fellowship Program, Temple University Hospital, Philadelphia, PA; and Associate Professor, Department of PM&R, Temple University Medical School, Philadelphia, PA.

Address Correspondence:
Standiford Helm II, MD
24902 Moulton Parkway, Suite 200
Laguna Hills, CA 92637
E-mail: drhelm@thehelmcenter.com

Conflicts of Interest on page 180
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a comprehensive review of evidence for percutaneous adhesiolysis in guideline preparation, have concluded that the evidence for percutaneous adhesiolysis in post lumbar surgery syndrome and lumbar central spinal stenosis to be fair, based on a total of 6 randomized, controlled trials (32,33,85-90). Even then, these studies have been chastised for not having pure placebo controls, for utilizing active-control designs, for utilizing highly selective criteria in their enrollment, for the high number of withdrawals in the control group thus invalidating the entire study, and for the studies originating from the developers or those practicing interventional pain management with high levels of interest in the procedures.

Even though none of the criticism offered is valid, clinically relevant, and methodologically appropriate, Gerdesmeyer et al (83) in a placebo-controlled, randomized assessment of the efficacy of percutaneous adhesiolysis, answered the call for such a trial. Above all, Gerdesmeyer et al (83) utilized a true placebo instead of other impure placebos or fake placebos, which have been misinterpreted by methodologists without consideration for the effects of placebos when injected into active structures such as the epidural space, over nerves, intraarticular injections, or even worse, consideration of local anesthetics as placebo (4,9,11-40,91-96).

The study by Gerdesmeyer et al (83) provides high quality evidence in support of percutaneous adhesiolysis. The study is multi-centered and is methodologically sound; it has sufficient size (about 45 patients in each arm compared to the minimum required of 25 patients) and has sufficiently high benchmarks for success (50% reduction in both Oswestry Disability Index [ODI] and Visual Analog Scale [VAS] to easily meet the criteria to be considered high quality. The study is placebo controlled, with the placebo being the injection of normal saline into the soft tissue: it meets the criteria for a placebo study rather than an active control, such as happens when local anesthetic or saline is injected around a nerve root. This is only the second study of its nature in interventional pain management with appropriate placebo, with the first study having been conducted by Ghahreman et al (40).

This study by Gersmeyer et al (83) is coupled with a previous comparative effectiveness study by the same group, showing that adhesiolysis is more effective than physical therapy in treating this population group (88).

Gerdesmeyer et al's study (83) mirrored all previous studies in having a low complication rate. There was one case of catheter shearing, which could have been caused by manipulation of the RK needle without the stylet in place, so that the tip got bent and snagged the catheter. The risk of this complication is removed by the use of Coudé® needles. While there is risk with the injection of hypertonic saline, this study confirms what other studies have found, which is that experienced operators can detect when the dura is punctured, either by dye spread or response to local anesthetic injection, and not inject hypertonic saline into the subarachnoid space.

Placebo controlled studies have the ability to show the presence of an effect and to measure the absolute size of the effect. Gerdesmeyer found that the placebo effect was about 2 points on the VAS, compared to about a 4-point reduction for the treated group, with similar changes in the ODI. This finding persisted and grew over time. Placebo/nocebo research shows that the placebo effect is greater with devices (97). Gerdesmeyer et al (83) confirm that finding as the placement of a catheter around the sacral hiatus, a device, created a placebo effect whereas providing physical therapy, no device, did not. By extension, this finding confirms the belief that procedural studies which do not show a placebo effect are flawed and should be discounted. However, this study also lacks one aspect of randomized trials (i.e., no treatment group). The study also demonstrates appropriate follow-up of 12 months.

Gerdesmeyer et al (83) did something unusual. Instead of studying the patients with post lumbar surgery syndrome or central spinal stenosis in which there is fair evidence for percutaneous adhesiolysis, they have used intractable radiculopathy which failed to respond to epidural injections for the study population, drawing the study participants from their patient population. Gerdesmeyer et al (83) must be commended for this placebo control trial, which is not feasible in the United States, which clearly shows the effectiveness of interventional techniques, specifically percutaneous adhesiolysis, with an exemplary design of a placebo. Thus, it should prove to all nihilists the efficacy of percutaneous adhesiolysis.

Another interesting finding is that the study was not performed by Racz and colleagues or Manchikanti and colleagues who have been criticized for their development and interest in this procedure.

One issue with percutaneous adhesiolysis is how the procedure differs from epidural injections with a non-spring-wired catheter. We do not know with certainty which of the factors involved in adhesiolysis is necessary for its success: the spring-wired catheter;

whether the saline is hypertonic or normal; the use of hyaluronidase; whether the procedure is done on a one- or three-day basis; or the volume injected.

Hyaluronidase does have evidence supporting its use, although that evidence did not reach statistical significance. Gerdesmeyer et al (83) correctly point out that hyaluronidase promotes increased spread by opening up tight junctions between tissue planes, not by lysing dense surgical scar. Given that the goal of the procedure is to break up adhesions so that nerves can move freely and that medications can reach the nerves, hyaluronidase should be a part of the adhesiolysis procedure.

At this point, we do not have enough evidence to recommend normal saline over hypertonic saline.

The procedure must be done with a spring-wired catheter.

Percutaneous adhesiolysis is a safe and effective procedure to treat patients with low back and/or leg pain due to disc herniations, post lumbar surgery syndrome and spinal stenosis. With Gerdesmeyer et al's study (83), the final criterion to acceptance of this procedure, the need for a large scale, high-quality, multi-center study with long-term follow-up, has been met. We now have six high quality randomized controlled trials showing its efficacy and safety. With this level of data supporting its use, percutaneous adhesiolysis should be made widely available to these patients.

Practically, most American centers cannot do a three-day procedure because of cost concerns, meaning that the one-day procedure will continue. About 95% of adhesiolysis procedures done in the United States are done on a one-day basis.

The next issue of crucial importance for interventional pain management is cost utility. Allegedly, the effectiveness of multiple interventions for managing chronic pain is questionable. A cost utility analysis continues to be a cornerstone of evidence-based medicine, clinical practice, and health care policy making. Consequently, multiple cost effectiveness analyses\studies have been performed related to managing spinal pain (98-109). The cost effectiveness analysis in numerous studies has shown highly variable results, with cost effectiveness ranging from $304 to $579,527, with a median of $13,015 for quality of life year (QALY) gain. Specifically, for the recently performed SPORT study of surgical interventions (107,108), the costs for QALY gained from surgery relative to nonoperative care in lumbar disc herniation was either $69,403 or $34,355 based on the insurer; for spinal stenosis, the cost was $77,600 per QALY gained, whereas for degenerative spondylolisthesis surgery, the QALY was $115,600. The reviews of epidural injections have been highly variable, with some illustrating ineffectiveness for epidural injections. However, Manchikanti et al (84), in an analysis of 4 pathologies, with chronic low back and lower extremity pain with a 2 year follow-up for caudal epidural injections with or without steroids, using actual reimbursement data, showed a cost utility for one year of QALY of $2,206 for disc herniation, $2,136 for axial or discogenic pain without disc herniation, $2,155 for central spinal stenosis, and $2,191 for post surgery syndrome. The average cost utility analysis per year was $2,172.50 for all patients and $1,966.03 for patients who were judged to be successful with at least 3 weeks of improvement noted with the first 2 epidural injections.

More importantly, in this cost utility assessment, the authors have not utilized the benefits of return to employment. When return to employment was considered among these chronic patients, only a small proportion of them were eligible for employment. This evaluation shows that at the baseline, 82 out of 124 patients were employed, whereas at the end of the study, 117 out of 124 were employed, increasing employment from 66.1% to 94.3%. Thus, calculating the number of individuals employed with an average salary of $34,000 in McCracken County or $40,000 in Kentucky, the salary benefits alone in these patients would exceed $1 million equivalent, or higher than the total expenditures for all the procedures in these patients. Thus, cost utility is achieved even without considering improvement in all other patients who have not returned to work.

Thus, this issue of Pain Physician inaugurates a new era in interventional pain management with an outstanding placebo controlled trial, an excellent cost utility analysis involving 4 randomized trials with a large proportion of patients derived from randomized controlled trials with a 2 year follow-up and robust outcome measures.

Regardless, this may not be the end of criticism even though multiple acquisitions of interventional techniques has been dispelled. It will be interesting to see how the criticism by methodologists, nihilists, or clinicians opposed to interventional techniques about deficiencies that are non-existent in these analysis, will have to be reinvented based on new issues.

Conflict of Interest

Dr. Helm is a clinical investigator with Epimed and receives research support from Cephalon/Teva, AstraZeneca, and Purdue Pharma, LP. He has attended an advisory group meeting for Activas.

Dr. Benyamin is a consultant with Bioness and Nevro; serves on the advisory boards of Vertos Medical and Nuvo Pharma; teaches/lectures for Vertos Medical, Boston Scientific, Neurotherm, and Bioness; and receives research/grants from Alfred Mann Foundation, Teknon Foundation, Spinal Restoration, Inc., Bioness, Boston Scientific, Vertos Medical, Medtronic, Kimberly Clarke, Epimed, BioDelivery Sciences International, Inc., Theravance, Mundipharma Research, Cephalon/Teva, AstraZeneca, and Purdue Pharma, LP.

Dr. Falco is a consultant for St. Jude Medical Inc. and Joimax Inc.

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