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Regenerative injection therapy for axial pain

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Chronic pain is considered epidemic coupled with claims of inadequate treatment. While the understanding of pain, including diagnosis and treatment, is in its infancy, significant progress has been made with diagnostic and therapeutic interventional techniques during the past two decades. Though the structural basis of spinal pain is well established, some patients continue to present a diagnostic and therapeutic challenge. In addition to target-specific fluoroscopically guided techniques, Regenerative Injection Therapy (RIT), also known as prolotherapy, is a viable treatment in managing chronic spinal pain. Proponents suggest effectiveness of RIT in treating musculoskeletal pain, while opponents suggest otherwise. Multiple published studies show (RIT) is effective despite continued controversy. This review will describe various aspects of regenerative injection therapy, technical aspects and clinical effectiveness.

Chronic spinal pain is highly prevalent in the United States, placing an enormous burden on society in terms of patient suffering and cost. A search for effective treatments is a priority.[1]

Interventional pain management is defined as the discipline of medicine devoted to the diagnosis and treatment of pain by application of interventional techniques independently or in conjunction with other modalities of treatment.[2] Interventional technique is defined as a minimally invasive procedure for precise percutaneous delivery of therapeutic/diagnostic modalities to targeted areas in managing chronic, persistent or intractable pain.[3] Based on these definitions, regenerative injection therapy (RIT) is the oldest interventional technique in current use. RIT triggers influx of macrophages, fibroblasts, release of growth factors and ultimately, new collagen formation. RIT leads to strengthening of connective tissues, reduction of pain and disability. A variety of agents including phenol, dextrose, and glycerin, alone or in various combinations, mixed with local anesthetics have been used in RIT.

Nonradicular axial or somatic pain may be felt in the extremities. Kuslich and coworkers[4] identified intervertebral discs, facet joints, dura of the nerve root, ligaments, fascia and muscles as tissues capable of transmitting pain in the low back. The same philosophy is applicable to thoracic and cervical areas. Pain due to nerve root irritation, facet joint, discogenic and sacroiliac joint pain are proven to be common causes of pain by appropriate diagnostic techniques.[2] However, vertebrae, muscles, and ligaments are not "proven" to be common sources of spinal pain due to lack of adequate, reliable and valid diagnostic technology.[5] Utilizing advanced imaging, neurophysiologic and precision diagnostic techniques, spinal pain can be identified in approximately 50% to 80% of patients.[2] Nonetheless, there continues to be 20% to 50% of patients without appropriate diagnosis.[2,5–9] Further, axial and periaxial pain patterns from ligaments, muscles, intervertebral discs and facet joints overlap significantly. Therefore, patients continue to present with a diagnostic dilemma and a therapeutic challenge.[2,4–14]

A short definition of RIT, also known as prolotherapy, is an interventional technique for chronic pain caused by connective tissue diathesis.[15–26]

Terminology

Before the 1930s, all injections were under one umbrella of "Injection Treatment" with the addition of a pathological

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descriptor, for examples: "Injection Treatment of Hernia"[16] or "Injection Treatment of Varicose Veins." The term "sclerotherapy" was coined by Biegeleisen in 1936.[17]

In 1956, Hackett concluded that sclerotherapy implied scar formation, and introduced the term "prolotherapy" as "the rehabilitation of an incompetent structure by generation of new cellular tissue."[12] Current understanding of the basic science is such that regenerative/reparative healing process consists of three overlapping phases: inflammatory, proliferative with granulation, and remodeling with contraction. The regeneration and repair extend beyond the proliferative stage.[27-29] RIT was coined to reflect currently prevailing anatomic and pathophysiologic trends in nomenclature.[18-20]

RIT stimulates chemomodulation of collagen by repetitive induction of inflammatory and proliferative stages leading to tissue regeneration and repair, thus increasing tensile strength, elasticity, mass and load-bearing capacity of collagenous connective tissues. The process is mediated by hormones and numerous growth factors. This makes RIT a viable treatment for painful chronic enthesopathies, tendinosis, ligamentosis and ligament laxity, which in turn are a common histopathologic component of the following entities: disc, facet, dorsal rami and iliac crest syndromes.[18–20]

Local anesthetics in diagnosis of musculoskeletal pain

It was understood in the 1930s that posterior primary rami provide motor and sensory supply to muscles, tendons, thoracolumbar fascia, ligaments, aponeuroses, their origins and insertions, and NO definite diagnosis could be made based on clinical presentation alone. To facilitate the differential diagnosis of musculoskeletal pain infiltration of procaine at the nociceptive tissue beds, specifically at the fibro-osseous junctions, was introduced by Leriche, Haldeman and Soto-Hall, Steindler and Luck.[20,30,31] The following criteria were established to prove a causal relationship between the structure and pain symptoms: (1) reproduction of local and referral pain by needle contact and (2) suppression of local tenderness and referral/radiation pain by procaine infiltration.[30]

The same basic principles have been advocated since the inception of RIT as well as other currently employed injection procedures, to objectively confirm the source(s) of pain and augment clinical diagnosis by local anesthetic blocks.[8,9,30–46]

Pathophysiologic considerations

Ligaments and tendons are fibrous collagenous tissue with a crimped, wave-like appearance under a light microscope. This crimped pattern unfolds during initial collagen loading.[20,47,48] Elongated beyond 4% of the original length, ligaments and tendons lose elasticity and recoil capability to the original crimp wave appearance. They become permanently laxed leading to joint hypermobility. Sub failure was reported at earlier stages of elongation in degenerated ligaments. Natural healing, at best, may restore connective tissue to its preinjury length but only 50% to 75% of its preinjury tensile strength.[15,18,20,47–49]

Collagenous tissues are deleteriously affected by steroid administrations, NSAIDs, inactivity and denervation.[27–29,48–50] In the presence of repetitive microtrauma with insufficient time for recovery, use of steroids and NSAIDs, tissue hypoxia, metabolic and hormonal abnormalities as well as other less defined causes, connective tissue divert toward a degenerative pathway.[27–29,49] Therefore, "a judicious utilization of antiinflammatory therapy remains useful, albeit adjunctive, therapy."[27,28,49,51]

Connective tissue response to trauma is inflammatory/regenerative/reparative and varies with the degree of injury. In the presence of cellular damage, regenerative pathway takes place; in case of extracellular matrix damage, a combined regenerative/reparative pathway takes place. Both are controlled by hormones, chemical and growth factors.[27,28,48,49] Central denervation such as in quadriplegia leads to a statistically high, accelerated degeneration.[28] Corticosteroids do not arrest or slow the course of degenerative process.[27,28]

Neoneurogenesis and neovasculogenesis are integral components of both regenerative/reparative and degenerative processes. Nerve and vascular tissue in-growth into degenerated intervertebral discs, posterior spinal ligaments, hard niduses of fibromyalgia, together with neuropeptides in the facet joint capsules, sacroiliac ligaments have been documented.[29,52–55]

Rationale

Rationale for RIT in chronic painful pathology of fibrous connective tissue such as ligaments and tendons evolved mainly from clinical, experimental and histological research performed for injection treatment of hernia. In hernias, inflammatory response to injectate induced proliferation and subsequent regenerative/reparative healing phases lead to a fibrotic closure of the defect. This process actually reproduced the healing by second intention. Of specific interest is the intense neovasculogenesis and neoneurogenesis accompanying the inflammatory phase and regressing during the contraction phase. It is the regression of neoneurogenesis that probably explains the pain reduction.[16–20] Ability to induce proliferative regenerative repetitive response in ligaments and tendons was demonstrated in experimental and clinical studies with up to a 65% increased diameter of collagen fibers.[17,23–25,56]

Clinical anatomy in relation to RIT

Irregularly tubular shape of a human body is maintained by continuous compartmentalized fascial stocking. This stocking, cross-sectionally and longitudinally, incorporates, interconnects and supports various ligaments, tendons, muscles, neurovascular and osseous structures. Collagenous connective tissues, despite slightly different biochemical content, blend at their boundaries and at the osseous structures functioning as a single unit.[15,20,47,57] This arrangement provides bracing and hydraulic amplification effect to lumbar muscles, increasing contraction strength up to 30%.[58]

Movements of the spine and cranium are accomplished through various well innervated joints, which are located in the anterior, middle and posterior columns. These joints are syndesmotic, synovial and symphyseal. Syndesmotic joints are anterior and posterior longitudinal ligaments (ALL, PLL), anterior and posterior atlanto-occipital membranes (AAOM, PAOM), supraspinous and interspinous ligaments (SSL, ISL), and ligamentum flavum (LF). Symphyseal joints are intervertebral discs (IVD). Synovial joints are atlanto-axial (AA), atlanto-occipital (AO), zygapophyseal (ZJ), costotransverse (CT) and costovertebral (CVJ) sacroiliac (SI) joint is a combined synovial–syndesmotic one.[47,57,58] Differential diagnosis is based on understanding of the regional and segmental anatomy, pathology, as well as segmental, multisegmental, and intersegmental communications in innervation of the compartments and their contents around the spine. This is provided by ventral rami (VR), dorsal rami (DR), gray rami communicants (GRC), sinuvertebral nerves (SVN) and sympathetic chain (SC).[20,31,47,57,58]

Lumbar interspinous ligaments receive innervation from the medial branches of the dorsal rami. Three types of nerve terminals in posterior spinal ligaments have been confirmed microscopically. They are the free nerve endings, the Pacini and the Ruffini corpuscles. A sharp increase in free nerve endings quantity at the spinous processes attachments (enthesis) were documented rendering them putatively nociceptive.[50] Experimental and empiric observations suggest that similar arrangement may exist at the cervical and thoracic spinous processes also rendering them putatively nociceptive.[10,11]

Based on the IASP criteria[59] utilizing controlled local anesthetic blocks, in patients without radiologic or neurophysiologic evidence of nerve root compression, cervical facet joints have been shown to be responsible for pain in 54% to 67% of the patients, thoracic facet joints have been responsible 42% to 48% in chronic thoracic pain, lumbar facet joints have been responsible for 15% to 45% pain in chronic low back pain, and sacroiliac joints have been responsible for 10% to 19% pain in low back pain. Utilizing IASP criteria, discogenic pain has been established in 26% to 39% of the patients.[9,42] There are no studies evaluating the prevalence of the pain secondary to atlantooccipital or atlantoaxial joints. Overall, strong evidence was shown for diagnostic facet joint blocks for the diagnosis of facet joint pain, and lumbar provocative discography for discogenic pain.[32] Moderate evidence was shown for sacroiliac joint pain, and for transforaminal epidural injections in the preoperative evaluation of patients with negative or inconclusive imaging studies, but with clinical findings of nerve root irritation, the evidence was shown to be limited.[2] The effectiveness of multiple interventional techniques also varies substantially based on the evaluators. Moderate to strong evidence was shown for multiple therapeutic interventional techniques including medial branch blocks and medial branch neurotomies; caudal epidural steroid injections and transforaminal epidural steroid injections; lumbar percutaneous adhesiolysis and implantable therapies.[2,60,61] Based on the extensive review of precision diagnostic blocks, and therapeutic interventional techniques in managing spinal pain, it appears that multiple hidden or unproven pain generators continue to persist.

Table 1 The proposed RIT mechanism of action is complex and multifaceted as follows[20,22,25,58,63,64]:

- Cellular and extracellular matrix damage induced by mechanical transection with the needle stimulates inflammatory cascade, governing release of growth factors.
- Compression of cells by relatively large extracellular volume as well as cell expansion or constriction due to osmotic properties of injectate stimulates the release of intracellular growth factors.
- Chemomodulation of collagen through inflammatory, proliferative, regenerative/reparative response is induced by the chemical properties of the injectates and mediated by cytokines and multiple growth factors.
- Chemoneuromodulation of peripheral nociceptors provides stabilization of antidromic, orthodromic, sympathetic and axon reflex transmissions.
- Modulation of local hemodynamics with changes in intraosseous pressure leads to reduction of pain. Empirical observations suggest that a dextrose/lidocaine combination has a much more prolonged action than lidocaine alone.
- Temporary repetitive stabilization of the painful hypermobile joints, induced by inflammatory response to the injectates, provides a better environment for regeneration and repair of the affected ligaments and tendons.
- Additional possible mechanisms of action include the disruption of adhesions by that have been created by the original inflammatory attempts to heal the injury by the large volume of injectate the relatively large volume of chemically non-irritating injectate assumes the role of a space occupying lesion in a relatively tight and slowly equilibrating extracellular compartment of the connective tissue.

Spondyloarthropathies with enthesopathies are rarely, if ever, included in the differential diagnosis or therapeutic plan by the interventional pain community. The reason why the other pain generators are not included in differential diagnosis can be explained by *the spinal uncertainty principle, in a simple example of two motion segments, where disc, facets and musculotendinous compartments, each considered as one putative nociceptive unit, and the total number of clinically indistinguishable combinations rises to 63 possibilities. It is practically impossible to address such a magnitude of possibilities under fluoroscopic guidance*.[62]

The primary target for RIT is the tissue bed pathology and pain, taking innervation into account. Therefore, RIT may afford evaluation of many putative pain generators from the variety of pain presentations of the axial spinal pain and, when correctly implemented, can offer an attractive, practical alternative that can be accomplished at the same office visit (Table 1).

Indications

Multiple indications for RIT are described in Table 2.

Seronegative spondyloarthropathies accompanied by enthesopathies comprise the list of syndromes and conditions

Table 2 Multiple indications described in the literature for RIT include the following[18–20,25,58,65–68]:

1. Painful enthesopathies, tendinosis or ligamentosis from overuse, occupational and postural conditions known as Repetitive Motion Disorders
2. Painful enthesopathies, tendinosis or ligamentosis secondary to sprains or strains
3. Painful hypermobility, instability and subluxation of the axial joints secondary to ligament laxity accompanied by restricted range of motion at reciprocal segment(s) that improve temporarily with manipulation
4. Vertebral compression fractures with a wedge deformity that exert additional stress on the posterior ligamento-tendinous complex
5. Recurrent painful rib subluxations at the costotransverse, costovertebral, sternochondral, articulations
6. Osteoarthritis, spondylolysis and spondylolisthesis
7. Post surgical cervical, thoracic, and low back pain (with or without instrumentation)
8. Posterior column sources of nociception refractory to steroid injections, nonsteroidal anti-inflammatory therapy (NSAID) and radiofrequency procedures
9. Enhancement of manipulative treatment and physiotherapy
10. Internal disc derangement

representing a multi-etiological connective tissue diathesis with common pathogenesis treated with RIT as described in Table 3.[15,17–20,49,58,64–70]

Contraindications to RIT include general contraindications that are applicable to all injection techniques such as:

1. Allergy to anesthetic solutions;
2. Bacterial infection, systemic or localized to the region to be injected;
3. Bleeding diathesis secondary to disease or anticoagulants;
4. Fear of the procedure or needle phobia;
5. Paraspinal neoplastic lesions involving the musculature and osseous structures;
6. Recent onset of a progressive neurologic deficit including but not limited to severe intractable cephalgia, unilaterally dilated pupil, bladder dysfunction, bowel incontinence, etc.;
7. Requests for large quantity of sedation and/or narcotics before and after treatment; and
8. Severe exacerbation of pain or lack of improvement after local anesthetic blocks.

Specific contraindications are:

1. Acute arthritis (septic, gout, rheumatoid or posttraumatic with hemarthrosis);
2. Acute bursitis or tendonitis;
3. Acute nonreduced subluxations, dislocations or fractures; and
4. Allergy to injectable solutions or their ingredients such as dextrose, sodium morrhuate or phenol.

Clinical effectiveness

There have been multiple publications including systematic reviews,[21,71] randomized controlled trials (RCTs),[22,72–75] numerous nonrandomized reports including prospective and retrospective clinical studies.[76–80] Prolotherapy is most effective when it is practiced in conjunction with manipulation. Consequently, the first RCT evaluated prolotherapy in conjunction with manipulation.[73] Thirty-five patients out of 40 in the treatment group and 16 of 41 in the control group achieved >50% improvement in pain and disability, sustained at 6 months. The treating solution was dextrose/phenol/glycerin (DPG) and the control solution was normal saline. These findings have been misconstrued as evidence of manipulation efficacy rather than prolotherapy.[81]

The second RCT[72] also evaluated DPG solution but with 0.25% lidocaine/normal saline control. This study reported that 30 of 39 patients in the treatment group and 21 of 40 in the control group achieved a 50% or greater improvement in pain or disability at 6 months. Overall, both treatment groups improved markedly.

A third RCT[74] using a lidocaine control group provided three injection treatments with much lower volumes of injectate than in the other trials and without manipulation or exercises. No changes in mean pain or disability scores in either group were reported over 6 months; therefore, it was concluded that prolotherapy was ineffective.

Most recent RCT[22] had 110 participants with nonspecific low-back pain back, average duration of 14 years. Study was conceived with a null hypothesis that prolotherapy would be no more effective than control. It compared 20% dextrose solution with normal saline injections and either flexion/extension exercises or normal activity. At 2 years both groups reported a sustained 50% reduction in pain and disability. It was concluded that in chronic nonspecific low-back pain, significant and sustained reductions in pain and disability occur with ligament injections irrespective of the solution injected or the concurrent use of exercises. Such success rates were as good as those reported for surgery, spinal cord stimulation[82,83] or multidisciplinary treatment[84] or for patients with low-back pain of shorter duration. This

Table 3 Conditions treated with RIT

- Cervico-cranial syndrome, cervicogenic headaches (atlanto-axial, atlanto-occipital joint and mid-cervical facet joint sprains)
- Barré Lieou Syndrome
- Torticollis
- Cervical, thoracic and lumbar midline spinal pain "of unknown origin"
- Cervicobrachial syndrome (shoulder/neck pain)
- Hyperextension/hyperflexion injury syndromes
- Cervical, thoracic and lumbar sprain/strain syndrome
- Costovertebral and costotransverse arthrosis, ligament strain/strain and joint pain
- Sacroiliac joint instability, hypermobility, repetitive sprain/strain, pain
- Myofacial pain syndromes
- Marie-Strumpell disease
- Ligament laxity with hypermobility and pain, Ehler's-Danlos syndrome
- Iliac crest syndromes, iliocostalicis friction syndrome, iliolumbar syndrome
- Piriformis syndromes
- Ankylosing spondylitis

longitudinal study demonstrated that: (1) pain and tenderness at the enthesis is a significant clinical finding treatable by injection in "nonspecific" low back pain, and (2) serendipitously chosen combination of volume and concentration of injectates combined with needle placement into ligaments, produced equally beneficial results in both arms of the experiment and is highly unlikely to present a placebo effect.[85-87]

A systematic review by Yelland and coworkers[21] echoed trends observed in the earlier RCTs and uncontrolled studies. It found that repeated ligament injections, regardless of injectate, provide long-lasting relief of pain and disability and that prolotherapy is more effective when combined with manipulation. There is substantial evidence of prolotherapy effectiveness from nonrandomized prospective and retrospective studies as well as case reports[75–79] and testimonials including one from the former Surgeon General of the United States, C. Everett Koop, MD.[88] Because of technicalities and heterogeneity, present literature offers moderate evidence of prolotherapy effectiveness in select patients utilizing appropriate technique and cointerventions. They concluded that more research is needed to compare prolotherapy with noninjection therapies and its effectiveness for discogenic pain.

Clinical presentation and evaluation

As is obvious from the list of syndromes, there is a wide variety of presenting pain complaints from headaches (occipital and suboccipital), neck, cervicothoracic, between the shoulder blades, scapular and shoulder regions, thoracolumbar, low back, buttocks, sacroiliac, trochanteric area and any combination of the above.[13,15,17–20,49,58,63,64-70,72,75,76,89] The intensity, duration and quality of pain are variable, as well as the onset, which may be sudden or gradual. The evaluation may reveal postural abnormalities, functional asymmetries, combinations of kyphoscoliosis, flattening of cervical and lumbar lordosis, arm and/or leg length discrepancies. Variable combinations of flexion/extension, rotation and lateral bending combined with contractions against resistance provoke pain.

The pertinent subjective clinical finding is exquisite tenderness at the fibro-osseous junctions (enthesis). The area(s) of such tenderness are identified and marked to become the subject of needle probing, "needling," and infiltration with local anesthetic. Initial needle placement at the fibro-osseous junction usually reproduces the pain that becomes worse on infiltration of local anesthetic, typically to subside within 15 seconds after infiltration. Abolishment or persistence of tenderness, local or referred pain objectifies the finding of tenderness, concludes the clinical examination and becomes the basis for clinical diagnosis and further injections with RIT.

Radiologic evaluation

Plain radiographs are of limited diagnostic value in painful pathology of the connective tissue but may detect structural or positional osseous abnormalities such as anterior or posterior listhesis on flexion/extension lateral views and degenerative changes in general with deformity of z-joints.[1,90]

MRI may detect pathology of intervertebral disc, ligamentous injury, interspinous bursitis, enthesopathy, z-joint disease, sacroiliac joint pathology, neural foraminal pathology, bone contusion, infection, fracture or neoplasia. MRI may exclude or confirm spinal cord disease and pathology related to extramedullary, intradural and epidural spaces.[90,91] CT scans may detect small avulsion fractures of facets, laminar fracture, fracture of vertebral bodies and pedicles, neoplasia, or degenerative changes.[90] Bone scans are useful in assessment of the entire skeleton to rule out metabolically active disease process.[90] However, medical literature continues to report back pain cannot be diagnosed in up to 85% of cases.[92] Thus pivotal to the proper management of chronic spinal pain is the ability to pinpoint an anatomical diagnosis. For this purpose physical examination is neither reliable nor valid.[93] Medical imaging provides little sound information.[94] No technique of physical examination has sufficient reliability and validity to allow a patho-anatomic diagnosis to be made.[93,94] Radiographic investigations, including magnetic resonance imaging, reveal only some conditions with certainty.[93]

Technical considerations

Any structure that receives innervation is a potential pain generator. Because pain maps overlap significantly, the question is, "How to navigate in this sea of unknown?" For the purpose of RIT, the following step by step approach is recommended. Patients' "pain and tenderness" is accepted for face value without dismissal or allocation to a distant "proven" source. It is the *knowledge of clinical anatomy, pain patterns and pathology that guides the clinical investigation,* based on clinical experiments of many clinicians and researchers over the years.

Initially, pain generators are identified by reproducible tenderness and movements that provoke pain; the areas are marked. Tenderness over posterior column structures is considered an objective finding until proven otherwise, especially in the midline.[20,58,64,89,95] Confirmation is obtained by needling and local anesthetic blocks of the tissue at the enthesis taking the nerve supply into account.

In experienced hands, using palpable landmarks for guidance, the following posterior column elements innervated by the dorsal rami may be safely injected with or without fluoroscopic guidance: tendons and ligaments enthesis at the spinous process, lamina, posterior ZJ capsule, transverse process and thoracolumbar fascia insertions.

The 0.5% lidocaine solution is an effective, initial diagnostic option for pain arising from posterior column elements when utilized in increments of 0.5 to 1.0 mL injected after each bone contact initially blocking the structures innervated by terminal filaments of the MBDRs with the sequence as follows:

1) (a) In the presence of midline pain and tenderness, enthesis of various structures inserting to the spinous process are blocked initially in the midline at the previously marked level(s). (b) The area(s) reexamined about one minute after each injection for tenderness and movements that provoked pain.

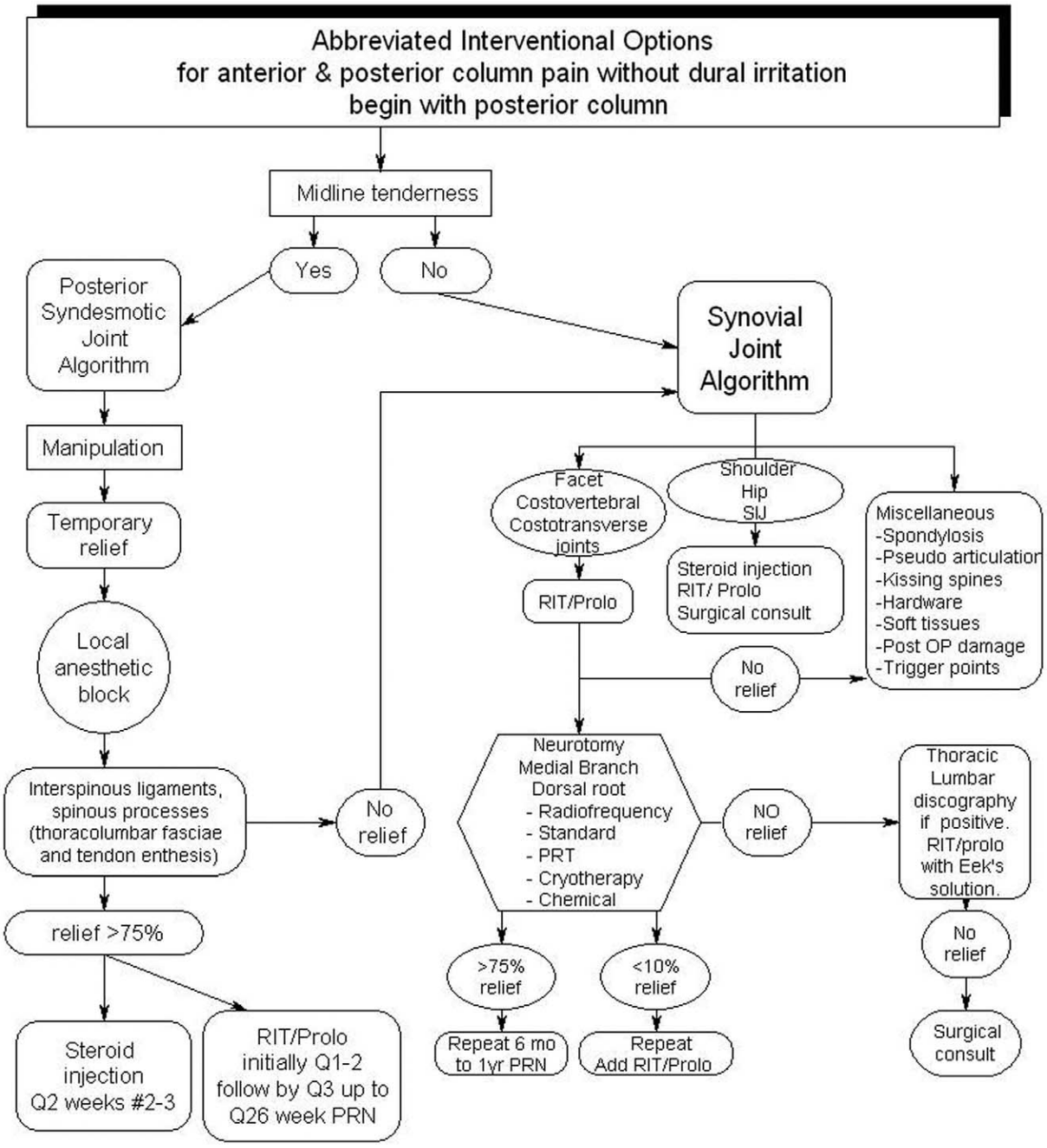

Figure 1 Abbreviated interventional options for anterior and posterior column pain without dural irritation—begin with posterior column. Modified excerpt from Percutaneous Management Options for Spinal Pain by Richard Derby and Felix Linetsky.

2) If tenderness remains at the lateral aspects of the spinous processes, injections are performed to the lateral aspects of their apices thus continuing on the course of medial branches or dorsal ramus. Step (b) is repeated.

3) Persistence of paramedial pain dictates blocks of ZJ capsules (cervical, thoracic and lumbar), costotransverse joints or posterior tubercle of the transverse processes in the cervical region with their respective tendon insertions. Step (b) is repeated.

4) Perseverance of lateral tenderness dictates investigation of the structures innervated by the lateral branches of the dorsal rami, ie, enthesis of iliocostalis at the ribs, ventral sheath of thoracolumbar fascia at the lateral aspects of the lumbar transverse processes, iliac crests insertions. Step (b) is repeated.

In this fashion, all potential nociceptors on the course of medial branches or dorsal ramus and lateral branches are investigated from its periphery to the origin. Consequently, a differential diagnosis of pain arising from vertebral and paravertebral structures innervated by medial branches or dorsal ramus and lateral branches can be made (Figures 1 and 2).

Manipulation under local anesthesia may be performed at any stage after local anesthesia has taken effect and the musculature sufficiently relaxed.[96]

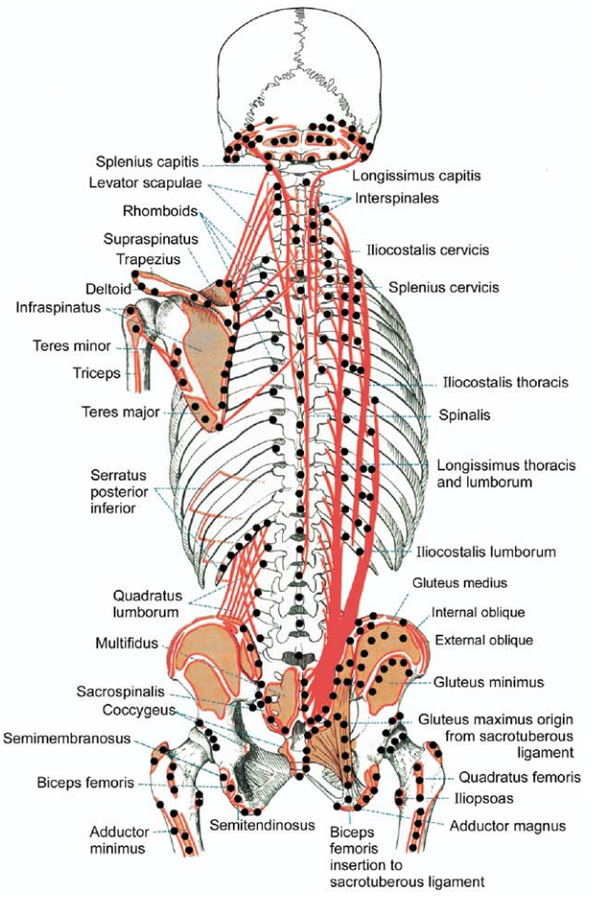

Figure 2 Schematic drawing demonstrating sites of origins and tendon insertions (enthesis) of the vertebral and paravertebral and peripheral musculature in the cervical, thoracic and lumbar regions and partly upper and lower extremities. Clinically significant painful enthesopathies are common at these locations defined by dots. Dots also represent most common locations of needle insertions and infiltration during RIT (please note: not all of the locations must be treated in each patient). Modified from Sinelnicov's Atlas of Anatomy (vol 1), Meiditsina Moskow, 1972. Modified and prepared for publication by Tracey Slaughter. (Color version of figure is available online.)

Pain from the upper cervical synovial joints presents a diagnostic and a therapeutic challenge. Because pain patterns overlap, it is usually a diagnosis of exclusion. Intraarticular atlanto-axial and atlanto-occipital joint injections of 3% phenol have secured a long-lasting therapeutic effect in selected patients.[70] Also a good therapeutic effect with intraarticular injections of 25% dextrose to the same joints and mid-cervical synovial joints, were reported to relieve persistent pain after RF and capsular injection failure.[65] *Because of the possible serious complications, all intraarticular injections of the axial Synovial joints including AA, AO, ZJ, costovertebral, and intervertebral discs should be performed only under fluoroscopic guidance by an experienced practitioner.*

Painful connective tissue proximal to enthesis are commonly injected at the following sites: spinous processes, occipital bone at inferior and superior nuchal lines, mastoid processes, posterior tubercles of transverse processes, posterior tubercles and angles of the ribs, proximal and distal portions of the clavicle, superomedial margin and spine of the scapula, sternum and xyphoid, capsular ligaments of cervical, thoracic and lumbar ZJs, and costotransverse joints, posterior sacroiliac, interosseous and sacrotuberous ligaments and occasionally SI joint. Tendon insertions to the medial and lateral aspects of the iliac crests.

Complications

Complications do occur with RIT but statistically, they are rare. The most recent statistical data are from a survey of 450 physicians performing prolotherapy. A hundred twenty respondents revealed that 495,000 patients received injections. Twenty-nine instances of pneumothorax have been reported, 2 of them requiring chest tube placement. Twenty-four nonlife threatening allergic reactions were also reported. Stipulating that each patient had at least 3 visits and during each visit receives at least 10 injections; the occurrence of pneumothorax requiring chest tube is 1 per 247,500 injections. Self-limited pneumothoraces is 1 per 18,333 and allergic reaction is 1 per 20,625 injections.[97]

In the 1960s, five cases of postinjectional arachnoiditis were reported.[98] Two of them were fatal.[99,100] One was a direct sequence of arachnoiditis; another was a sequence of incompetent shunt and persistent hydrocephalus with increased intracranial pressure.[99] Of the three other cases, the first, with mild paraparesis, recovered after a ventriculojugular shunt. The second recovered spontaneously with a mild neurological deficit.[100] The third case remained paraplegic.[98] Three cases of intrathecal injections have not been reported in the literature because of medico-legal issues. Two of them resulted in paraplegia. The first occurred after injection at the thoracic level, the second after a lumbar injection. A third case was performed by an untrained person who injected zinc sulfate solution at the cranio-cervical level resulting in immediate onset of severe neurologic deficit, quadriplegia and subsequent hydrocephalus.

One case of self-limiting sterile meningitis after lumbosacral sclerosing injections was reported in 1994.[101] Adjacent endplate fractures associated with intradiscal dextrose injections was recently reported.[102] Postspinal puncture headaches have been reported after lumbosacral injections.[22] Two such cases occurred in the first authors practice during the past 14 years. Patients recovered after 1 week with bed rest and fluids. Overall, pneumothorax is the most common reported complication. Injections of anterior synovial joints, such as sternoclavicular, costosternal and interchondral, may also result in pneumothorax in the same subset of patients.

Solutions for injections

The most common solutions are dextrose-based. To achieve a 12.5% concentration, dilution is made with local anesthetic in 1:3 proportions, ie, 1 mL of 50% dextrose mixed with 3 mL of 1% lidocaine. A 1:2 proportion, ie,1 mL of 50% dextrose with 2 mL of 1% lidocaine, will equal 16.5%

dextrose. Further, a 1:1 dilution makes a 25% dextrose solution.

For intraarticular injections, a 25% dextrose solution is commonly utilized though a recent double-blind study suggests that 10% dextrose solution may be equally effective.[103]

If dextrose proves ineffective, progression to a stronger solution such as sodium morrhuate up to full strength has been described. A 5% sodium morrhuate is a mixture of sodium salts of saturated and unsaturated fatty acids of cod liver oil and 2% benzyl alcohol, which acts as a local anesthetic and a preservative. Note that benzyl alcohol chemically is very similar to phenol.

Dextrose/phenol/glycerin solution consists of 25% dextrose, 2.5% phenol and 25% glycerin and is referred to as DPG, a.k.a. P2G. It is diluted in concentrations of 1:2; 1:1 or 2:3 with a local anesthetic before injection.

Diluted 6% phenol in glycerin solution is advocated by Wilkinson for injections at donor harvest sites of iliac crests for neurolytic and proliferative responses.[67]

Conclusion

Chronic spinal pain is common and an expensive problem in the United States. Prolotherapy is one of the interventional techniques utilized in managing spinal pain. Present evidence with inclusion of systematic reviews, randomized and nonrandomized evidence indicates effectiveness of RIT in painful spinal conditions with enthesopathies.

References

1. Luo X, Pietrobon R, Liu GG, et al: Estimates and patterns of direct health care expenditures among individuals with back pain in the United States. Spine 29:79-86, 2004
2. Manchikanti L, Staats PS, Singh V, et al: Evidence-based practice guidelines for interventional techniques in the management of chronic spinal pain. Pain Physician 6:3-80, 2003
3. Medicare Payment Advisory Commission Report to the Congress. Paying for Interventional Pain Services in Ambulatory Settings, 2001
4. Kuslich SD, Ulstrom CL, Michael CJ: The tissue origin of low back pain and sciatica: a report of pain response to tissue stimulation during operation on the lumbar spine using local anesthesia. Orthop Clin North Am 22:181-187, 1991
5. Bogduk N: Low back pain, in Clinical Anatomy of the Lumbar Spine and Sacrum (ed 3). New York, NY, Churchill Livingstone, 1997, pp 187-214
6. Manchikanti L, Singh V, Fellows B: Structural basis of chronic low back pain, in Manchikanti L, Slipman CW, Fellows B (eds): Interventional Pain Management: Low Back Pain: Diagnosis and Treatment. Paducah, KY, ASIPP Publishing, 2002, pp 77-96
7. Cavanaugh JM, Ozaktay AC, Yamashita T, et al: Mechanisms of low back pain: a neurophysiologic and neuroanatomic study. Clin Orthop 335:166-180, 1997
8. Pang WW, Mok MS, Lin ML, et al: Application of spinal pain mapping in the diagnosis of low back pain: analysis of 104 cases. Acta Anaesthesiol Sin 36:71-74, 1998
9. Manchikanti L, Singh V, Pampati V, et al: Evaluation of the relative contributions of various structures in chronic low back pain. Pain Physician 4:308-316, 2001
10. Kellgren J: On the distribution of pain arising from deep somatic structures with charts of segmental pain areas. Somatic Pain 35-46, 1939
11. Feinstein B, Langton JN, Jameson RM, et al: Experiments on pain referred from deep somatic tissues. J Bone Joint Surg 36A:281-996, 1954
12. Hackett G: Ligament and Tendon Relaxation (Skeletal Disability) Treated by Prolotherapy (Fibro-Osseous Proliferation) (ed 3). Springfield, IL, Charles C. Thomas, 1958
13. Travell JG, Simmons, DG: Myofacial Pain and Dysfunction-Triggered Point Manual (vol 1). Baltimore, MD, Williams and Wilkins, 1991
14. Bonica J, Loeser J, Chapman C et al: The Management of Pain (vol II, ed 2). Philadelphia, PA, Lea and Febiger, 1990
15. Linetsky F, Willard F: Use of regenerative injection therapy: injecting sclerosing solutions into painful areas can relieve low back pain. Pain Clin 1:19-23, 1999
16. Linetsky F: Sclerotherapy: clinical applications in the treatment of hernias. Pain Clin 2:20-24, 2000
17. Biegeleisen H: Varicose Veins, Related Diseases and Sclerotherapy: A Guide for Practitioners. Montreal, Canada, Eden Press, 1984
18. Linetsky F, Mikulinsky A, Gorfine L: Regenerative injection therapy: history of application in pain management, part I 1930s–1950s. Pain Clin 2:8-13, 2000
19. Linetsky F, Botwin K, Gorfine L, et al: Position paper of the Florida Academy of Pain Medicine on Regenerative Injection Therapy: effectiveness and appropriate usage. Pain Clin 4:38-45, 2002
20. Linetsky F, Miguel R, Saberski L: Pain management with regenerative injection therapy (RIT), in Weiner RS (ed): Pain Management: A Practical Guide for Clinicians. Washington DC, American Academy of Pain Management, 2002, pp 381-401
21. Yelland MJ, Del Mar C, Pirozzo S, et al: Prolotherapy injections for chronic low back pain: a systematic review. Spine 19:2126-2133, 2004
22. Yelland MJ, Glasziou PP, Bogduk N, et al: Prolotherapy injections, saline injections, and exercises for chronic low-back pain: a randomized trial. Spine 29:9-16, 2004
23. Hackett GS, Hemwall GA, Montgomery GA: Ligament and Tendon Relaxation Treated by Prolotherapy. G.A. Hackett Oak Park, Illinois: Hemwall, GA, 1991, pp 94-100
24. Liu YK, Tipton CM, Matthes RD, et al: An in situ study of the influence of a sclerosing solution in rabbit medial collateral ligaments and its junction strength. Connect Tissue Res 11:95-102, 1983
25. Klein RG, Dorman TA, Johnson CE: Proliferant injections for low back pain: histologic changes of injected ligaments and objective measurements of lumbar spine mobility before and after treatment. J Neurol Orthop Med Surg 10:123-126, 1989
26. Ongley MJ, Dorman TA, Eek BC, et al: Ligament instability of knees: a new approach to treatment. Man Med 3:152-154, 1988
27. Leadbetter W: Anti-inflammatory therapy in sports injury: the role of nonsteroidal drugs and corticosteroid injection. Clin Sports Med 14:353-410, 1995
28. Jozsa L, Kannus P: Human Tendons, Anatomy, Physiology and Pathology. Human Kinetics. Champaign, IL, 1997
29. Cotran R, Kumar V, Collins T: Robbins Pathologic Basis of Disease. Philadelphia, PA, WB Saunders, 1999
30. Steindler A, Luck J: Differential diagnosis of pain low in the back; Allocation of the source of pain by the procaine hydrochloride method. JAMA 110:106-113, 1938
31. Haldeman K, Soto-Hall R: The diagnosis and treatment of sacro-iliac conditions by the injection of procaine (novocain). J Bone Joint Surg 20, 1938
32. Boswell M, Singh V, Staats P, et al: Accuracy of precision diagnostic blocks in the diagnosis of chronic spinal pain of facet or zygapophyseal joint origin: a systematic review. Pain Physician 6:449-456, 2003
33. Lord SM, Barnsley L, Wallis BJ, et al: Chronic cervical zygapophyseal joint pain after whiplash: a placebo-controlled prevalence study. Spine 21:1737-1745, 1996
34. Barnsley L, Lord SM, Wallis BJ, et al: Lack of effect of intraarticular corticosteroids for chronic pain in the cervical zygapophyseal joints. N Engl J Med 330:1047-1050, 1994
35. Manchikanti L, Singh V, Pampati V, et al: Evaluation of the prevalence of facet joint pain in chronic thoracic pain. Pain Physician 5:354-359, 2002

36. Manchikanti L, Boswell MV, Singh V, et al: Prevalence of facet joint pain in chronic spinal pain of cervical, thoracic, and lumbar regions. BMC Musculoskelet Disord 5:15, 2004
37. Manchikanti L, Hirsch JA, Pampati V: Chronic low back pain of facet (zygapophysial) joint origin: is there a difference based on involvement of single or multiple spinal regions? Pain Physician 6:399-405, 2003
38. Manchikanti L, Singh V, Pampati V, et al: Is there correlation of facet joint pain in lumbar and cervical spine? An evaluation of prevalence in combined chronic low back and neck pain. Pain Physician 5:365-371, 2002
39. Schwarzer AC, Aprill CN, Derby R, et al: Clinical features of patients with pain stemming from the lumbar zygapophysial joints. Is the lumbar facet syndrome a clinical entity? Spine 19:1132-1137, 1994
40. Schwarzer AC, Aprill CN, Derby R, et al: The relative contributions of the disc and zygapophyseal joint in chronic low back pain. Spine 19:801-806, 1994
41. Schwarzer AC, Wang SC, Bogduk N, et al: Prevalence and clinical features of lumbar zygapophysial joint pain: a study in an Australian population with chronic low back pain. Am Rheum Dis 54:100-106, 1995
42. Schwarzer AC, Aprill CN, Derby R, et al: The prevalence and clinical features of internal disc disruption in patients with chronic low back pain. Spine 20:1878-1883, 1995
43. Fortin JD, Dwyer AP, West S, et al: Sacroiliac joint: pain referral maps upon applying a new injection/arthrography technique. Part I: asymptomatic volunteers. Spine 19:1475-1482, 1994
44. Fortin JD, Aprill CN, Ponthieux B, et al: Sacroiliac joint pain referral patterns upon application of a new injection/arthrography technique. Part II: clinical evaluation. Spine 19:1483-1489, 1994
45. Schwarzer AC, Aprill CN, Bogduk N: The sacroiliac joint in chronic low back pain. Spine 20:31-37, 1995
46. Maigne JY, Aivakiklis A, Pfefer F: Results of sacroiliac joint double block and value of sacroiliac pain provocation test in 54 patients with low back pain. Spine 21:1889-1892, 1996
47. Gray H: Gray's Anatomy (British ed 38). London, Churchill Livingstone, 1995
48. Best T: Basic science of soft tissue, in Delee J, Drez D (eds): Orthopedic Sports Medicine Principles and Practice (vol 1). Philadelphia, PA, WB Saunders, 1994, pp 7-53
49. Reeves K: Prolotherapy: present and future applications in soft-tissue pain and disability. Phys Med Rehabil Clin N Am 6:917-926, 1995
50. Yahia H, Newman N: A light and electron microscopic study of spinal ligament innervation. Z Mikrosk Anat Forsch 103:664-674, 1989
51. Leadbetter W: Cell-matrix response in tendon injury. Clin Sports Med 11:533-578, 1992
52. Freemont A: Nerve ingrowth into diseased intervertebral disc in chronic back pain. Lancet 178-181, 1997
53. Ashton IK, Ashton BA, Gibson SJ, et al: Morphological basis for back pain: the demonstration of nerve fibers and neuropeptides in the lumbar facet joint capsule but not in ligamentum flavum. J Orthop Res 10:72-78, 1992
54. Tuzlukov P, Scuba N, Gorbatovskaya A: The morphological characteristics of fibromyalgia syndrome. Arkh-Pathol, 55:47-50, 1993
55. Fortin J, Vilensky J, Merkel G: Can the sacroiliac joint cause sciatica? Pain Physician 6:269-271, 2003
56. Maynard JA, Pedrini VA, Pedrini-Mille A, et al: Morphological and biochemical effects of sodium morrhuate on tendons. J Orthop Res 3:234-248, 1985
57. Willard F: Gross anatomy of the cervical and thoracic regions: understanding connective tissue stockings and their contents. In 20th AAOM Annual Conference and Scientific Seminar. Orlando, FL, 2003
58. Linetsky F, Eek B, Derby R, et al: Regenerative injection therapy, in Manchikanti, Slipman, Fellows (eds): Low Back Pain Diagnosis and Treatment. Paducah, KY, American Society of Interventional Pain Physicians, 2002, pp 519-540
59. Merskey H, Bogduk N: Classification of chronic pain, in Merskey H, Bogduk N (eds): Descriptions of Chronic Pain Syndromes and Definition of Pain Terms (ed 2). Seattle, WA, IASP Press, 1994, pp 180-181
60. Manchikanti L, Singh V, Vilims BD, et al: Medial branch neurotomy in management of chronic spinal pain: systematic review of the evidence. Pain Physician 5:405-418, 2002
61. Boswell MV, Hansen HC, Trescot AM, et al: Epidural steroids in the management of chronic spinal pain and radiculopathy. Pain Physician 6:319-334, 2003
62. Dickey S: The spinal uncertainty principle. Pain Clin 3:42-47, 2001
63. Linetsky F, Miguel R, Torres F: Treatment of cervicogenic pain and cervicogenic headaches with regenerative injection therapy. Curr Pain Headache Rep 8:41-48, 2004
64. Reeves K: Prolotherapy: basic science, clinical studies, and technique, in Lennard T (ed): Pain Procedures in Clinical Practice. Philadelphia, PA, Hanley and Belfus Inc, 2000, pp 172-189
65. O'Neill C: Intra-articular dextrose/glucosamine injections for cervical facet syndrome, atlanto-occipital and atlanto-axial joint pain, combined ISIS AAOM approach in 20th American Association of Orthopaedic Medicine Annual Conference and Scientific Seminar; A common sense approach to "hidden" pain generators. Orlando, FL, 2003
66. Klein R, Eek B: Prolotherapy: an alternative approach to managing low back pain. J Musculoskel Med May:45-59, 1997
67. Wilkinson H: The Failed Back Syndrome, Etiology and Therapy (ed 2). Berlin, Springer-Verlag, 1992
68. Derby R, Eek B, Lee S, et al: Comparison of intradiscal restorative injections and intradiscal electrothermal treatment (IDET) in the treatment of low back pain. Pain Physician 7:63-66, 2004
69. Linetsky F: History of sclerotherapy in urology. Pain Clin 2:41-43, 2000
70. Stanton-Hicks M: Cervicocranial syndrome: Treatment of atlanto-occipital and atlanto-axial joint pain with phenol/glycerine injections. In 20th American Association of Orthopaedic Medicine Annual Conference and Scientific Seminar; A common sense approach to "hidden" pain generators. Orlando, FL, 2003
71. Nelemans PJ, deBie RA, deVet HCW, et al: Injection therapy for subacute and chronic benign low back pain. Spine 26:501-515, 2001
72. Klein RG, Eek BC, DeLong WB, et al: A randomized double-blind trial of dextrose-glycerine-phenol injections for chronic, low back pain. J Spinal Disord 6:23-33, 1993
73. Ongley MJ, Klein RG, Dorman TA, et al: A new approach to the treatment of chronic low back pain. Lancet 2:143-146, 1987
74. Dechow E, Davies RK, Carr AJ, et al: A randomized, double-blind, placebo controlled trial of sclerosing injections in patients with chronic low back pain. Rheumatology 38:1255-1259, 1999
75. Wilkinson HA: A single-blinded randomized and crossover study of phenolic prolotherapy for periosteal trigger points causing axial spinal pain. Unpublished.
76. Yelland M, Yeo M, Schluter P: Prolotherapy injections for chronic low back pain: results of a pilot comparative study. Australasian Musculoskeletal Med 5:20-23, 2000
77. Klein R, Eek B, O'Neill C, et al: Biochemical injection treatment for discogenic low back pain. Spine J 3:220-226, 2003
78. Derby R, Eek B, Lee S, et al: Comparison of intradiscal restorative injections and intradiscal electrothermal treatment (IDET) in the treatment of low back pain. Pain Physician 7:63-66, 2004
79. Mathews R, Miller M, Bree S: Treatment of mechanical and chemical lumbar discopathy by dextrose 25%. J Min Invas Spinal Tech 1:58-61, 2001
80. Reeves K, Hassanein: Randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity. Alt Ther Health Med 6:68-74,77-80, 2000
81. van Tulder MW, Koes BW, Bouter LM: Conservative treatment of acute and chronic nonspecific low back pain. A systematic review of randomized controlled trials of the most common interventions. Spine 22:2128-2156, 1997
82. Turner JA, Loeser JD, Bell KG: Spinal cord stimulation for chronic low back pain: a systematic literature synthesis. Neurosurgery 37: 1088-1095, 1995
83. Fritzell P, Hagg O, Wessberg P, et al: Swedish Lumbar Spine Study Group. Volvo Award Winner in Clinical Studies: Lumbar fusion versus nonsurgical treatment for chronic low back pain: a multicenter randomized controlled trial from the Swedish Lumbar Spine Study Group. Spine 26:2521-2532, 2001

84. Guzman J, Esmail R, Karjalainen K, et al: Multidisciplinary rehabilitation for chronic low back pain: systematic review. BMJ 322:1511-1516, 2001
85. Linetsky F, Saberski L, Dubin J, et al: Letter to the Editor in response to Yelland et al. Spine 29:1840-1841, 2004
86. Kidd R: Letter to the Editor in response to Yelland et al. Spine 29:1841-1842, 2004
87. Yelland M: Letter to the Editor in response to Yelland et al. Spine 29:1842-1843, 2004
88. Koop CE: Prolotherapy articles. American Association of Orthopaedic Medicine. Available at: http://www.kalindra.com/prolotherapy.htm.
89. Kayfetz DO, Blumenthal LS, Hackett GS, et al: Whiplash injury and other ligamentous headache: its management with prolotherapy. Headache 3:1-8, 1963
90. Resnick D: Diagnosis of Bone and Joint Disorders (ed 3). Philadelphia, PA, WB Saunders, 1995
91. Stark D, Bradley W: Magnetic Resonance Imaging (vol 1 and 2). St. Louis, MO, Mosby, 1999
92. Bogduk N, McGuirk B: Precision Diagnosis, in Bogduk N, McGuirk B (eds): Medical Management of Acute and Chronic Low Back Pain. An Evidence-Based Approach: Pain Research and Clinical Management (vol 13). Amsterdam, Elsevier Science BV, 2002, pp 169-176
93. Bogduk N, McGuirk B: Assessment in Bogduk N, McGuirk B (eds): Medical Pain Management of Acute and Chronic Low Back Pain. An Evidence-Based Approach: Pain Research and Clinical Management (vol 13). Amsterdam, Elsevier Science BV, 2002, pp 127-138
94. Bogduk N, McGuirk B: Causes and sources of chronic low back pain, in Bogduk N, McGuirk B (eds): Medical Management of Acute and Chronic Low Back Pain. An Evidence-Based Approach: Pain Research and Clinical Management (vol 13). Amsterdam, Elsevier Science BV, 2002, pp 115-126
95. Broadhurst N, Wilk VJ: Vertebral mid-line pain: pain arising from the interspinous spaces. J Orthopaed Med 18:2-4, 1996
96. Dreyfuss P, Michaelsen M, Horne M: MUJA: manipulation under joint anesthesia/analgesia: a treatment approach for recalcitrant low back pain of synovial joint origin. J Manipulative Physiol Ther 18:537-546, 1995
97. Dorman T: Prolotherapy: a survey. J Orthopaed Med 15:49-50, 1993
98. Keplinger J, Bucy P: Paraplegia from treatment with sclerosing agents. JAMA 173:1333-1335, 1960
99. Schneider R: Fatality after injection of sclerosing agent to precipitate fibro-osseous proliferations. JAMA 170:1768-1772, 1959
100. Hunt W, Baird W: Complications following injections of sclerosing agent to precipitate fibro-osseous proliferation. J Neurosurg 18:461-465, 1961
101. Grayson M: Sterile meningitis after lumbosacral ligament sclerosing injections. Journal Orthopaed Med 16:98-99, 1994
102. Whitworth M: Endplate fracture associated with intradiscal dextrose injection. Pain Physician 5:379-384, 2002
103. Reeves K, Hassanein K: Randomized prospective double-blind placebo-controlled study of dextrose prolotherapy for knee osteoarthritis with or without ACL laxity. Alternative Ther Health Med 6:68-74,77-80, 2000