Regenerative Injection Therapy

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Regenerative injection therapy (RIT), also known as prolotherapy or sclerotherapy, provides a mild neurolytic effect followed by a complex restorative process with biochemically induced collagen regeneration.[1]

Prior to the 1930s, all injections were listed under the umbrella of "Injection Treatment" with the addition of a pathological descriptor (i.e., "Injection Treatment of Hernia"[1] or "Injection Treatment of Varicose Veins"). The term "sclerotherapy" was coined by Biegeleisen in 1936.[2]

In 1956, Hackett[3] introduced the term "prolotherapy," as "the rehabilitation of an incompetent structure by generation of new cellular tissue," because sclerotherapy implied scar formation. In the same text he published pain maps from ligaments and tendons which have remained largely unknown to the medical community (Figs. 1-6). Contemporary understanding of the basic science is that the regenerative/reparative healing process consists of 3 overlapping phases: inflammatory, proliferative with granulation, and remodeling with contraction. The regenerative and reparative stages extend beyond the proliferative stage.[4-6] The term "regenerative injection therapy" was coined to reflect currently prevailing anatomic and pathophysiologic trends in nomenclature.[7]

RIT stimulates chemo-modulation of collagen by repetitive induction of inflammatory and proliferative stages which leads to tissue regeneration and repair. As a result, the tensile strength, elasticity, mass, and load-bearing capacity of collagenous connective tissues increases. This complex process is mediated by hormones and multiple growth factors.

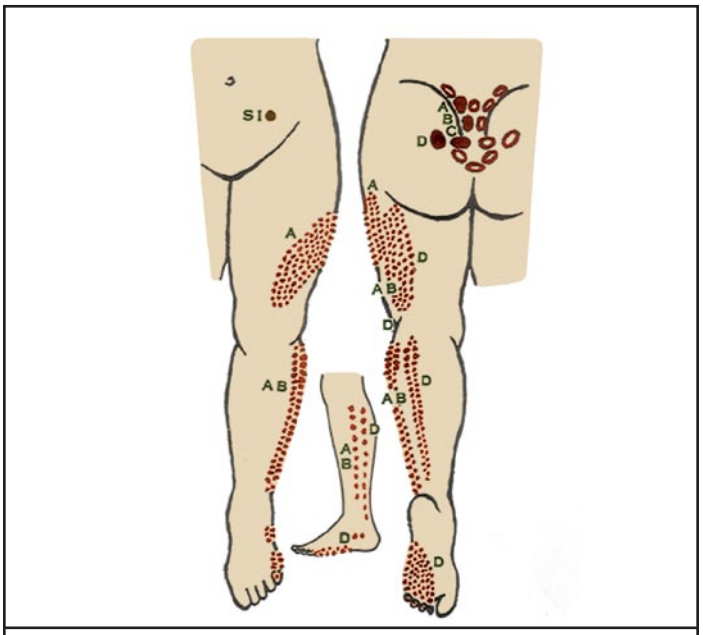

Fig. 1. *Referred pain from posterior sacroiliac ligament (sacroiliac joint instability). Referred pain areas from the upper fibers (AB); from the lower fibers (D)*

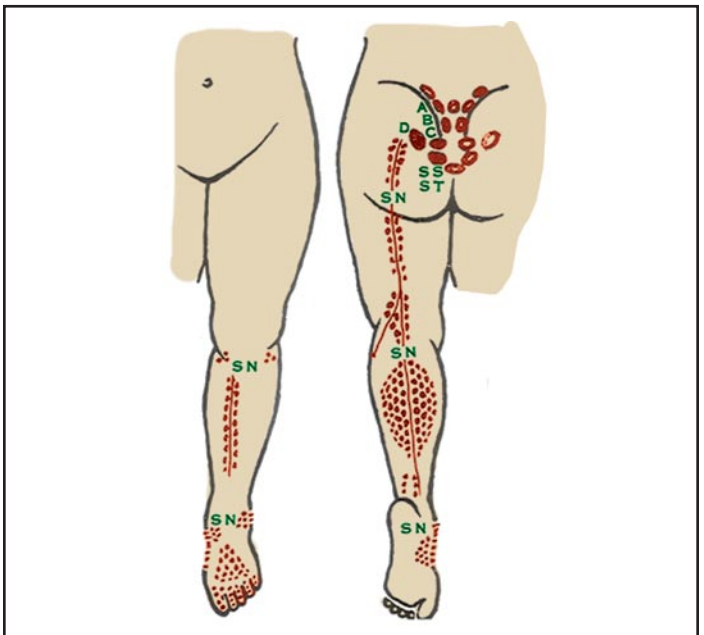

Fig. 2. *Sciatica type of pain from posterior sacroiliac, sacrospinous, and sacrotuberous ligaments (sacroiliac joint instability). Pain = SN.*

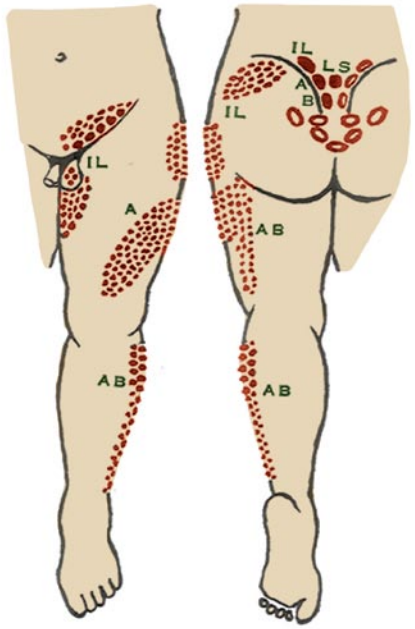

Fig. 3. *Referred pain from iliolumbar and posterior sacroiliac (upper) ligaments (lumbosacral and sacroiliac joint instability).*

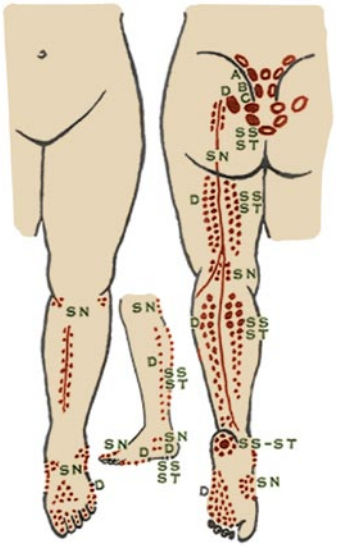

Fig. 4. *Referred pain and sciatica type of pain from posterior sacroiliac (lower) sacrospinous and sacrotuberous ligaments (sacroiliac joint instability). The conducted pain of sciatica (SN) is illustrated in one dermatome with the referred pain of the sacral ligaments (D-SS-ST).*

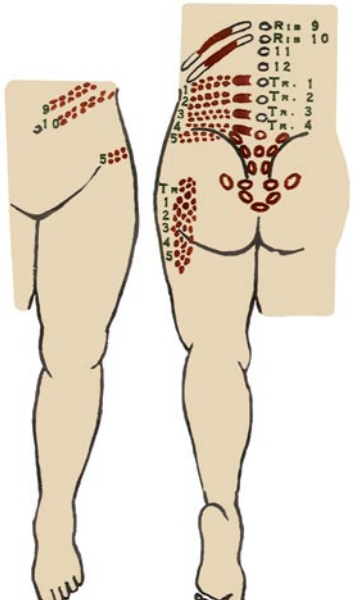

Fig. 5. *Trigger points and referred pain from sacrospinalis and iliocostalis tendons – lumbar vertebrae (transverse process) and ribs. Referred pain areas (1-2-3-4-5) (9-10) and trigger points of pain (Tr. 1-2-3-4-5) Rib (9-10).*

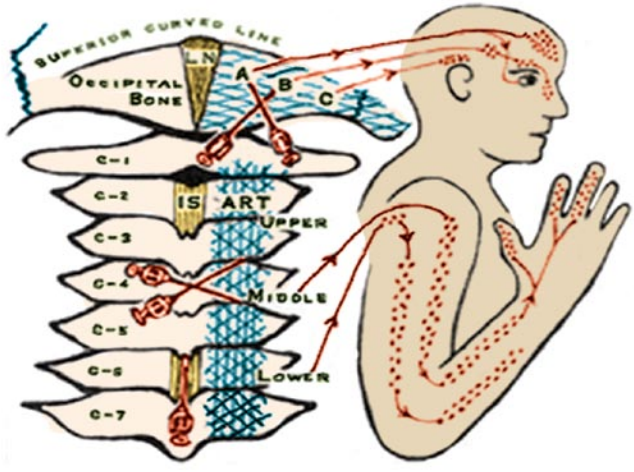

Fig. 6. *Trigger points and referred pain areas. Position of needles for diagnosis and treatment. Needles for Diagnosis and Treatment. Occipital Tendons: Referred Pain, Headache, Dizziness. A: Forehead, Eye. B. Temple, Eyebrow, Nose. C. Above Ear. Cervical Ligaments. IS Interspinous Ligaments. ART Articular Ligaments. Referred Pain - Upper: Neck; Middle: Arm, Forearm, Thumb, 1 and 2 fingers; Lowe: Acromium Process, Arm, Forearm.*

Indications

- Indications for regenerative injection therapy are listed in Table 1.[7-13]
  - As described in Table 2, seronegative spondyloarthropathies, accompanied by enthesopathies, comprise the list of syndromes and conditions representing a multi-etiological connective tissue diathesis with common pathogenesis treated with RIT.[2,3,7,9,13-16]
- Contraindications to RIT include general contraindications that are applicable to all injection techniques; specific contraindications for RIT are listed in Table 3.

Table 1. *Indications for regenerative injection therapy.*

- Painful enthesopathies, tendinosis or ligamentosis from overuse, occupational and postural conditions known as Repetitive Motion Disorders
- Painful enthesopathies, tendinosis or ligamentosis secondary to sprains or strains
- 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
- Vertebral compression fractures with a wedge deformity that exert additional stress on the posterior ligamento-tendinous complex
- Recurrent painful rib subluxations at the costotransverse, costovertebral, and sternochondral articulations
- Osteoarthritis, spondylolysis, and spondylolisthesis
- Postsurgical cervical, thoracic, and low back pain (with or without instrumentation)
- Posterior column sources of nociception refractory to steroid injections, nonsteroidal anti-inflammatory therapy (NSAID), and radiofrequency procedures
- Enhancement of manipulative treatment and physiotherapy
- Internal disc derangement

Table 2. *Conditions treated with regenerative injection therapy.*

- Cervico-cranial syndrome, cervicogenic headaches (atlanto-axial, atlanto-occipital joint and mid-cervical facet joint derangements, C2-3 thru C5-6 internal disc derangements)
- Barré Liéou 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 sprain/strain and joint pain
- Sacroiliac joint instability, hypermobility, repetitive sprain/strain, pain
- Myofascial pain syndromes
- Marie-Strümpell disease
- Ligament laxity with hypermobility and pain, Ehler's-Danlos syndrome
- Iliac crest syndromes, iliocostalis friction syndrome, iliolumbar syndrome
- Piriformis syndromes
- Ankylosing spondylitis

Table 3. *Contraindications for regenerative injection therapy.*

General Contraindications

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

Specific Contraindications

- Acute arthritis (septic, gout, rheumatoid, or post-traumatic with hemarthrosis)
- Acute bursitis or tendonitis
- Acute nonreduced subluxations, dislocations, or fractures
- Allergy to injectable solutions or their ingredients such as dextrose (corn), sodium morrhuate (fish), or phenol

Clinical Applications

- Regenerative injection therapy has been the subject of multiple published articles, including systematic reviews,[17,18] randomized trials,[19-23] and numerous nonrandomized publications which include prospective and retrospective clinical studies as well as case reports.[24,25]
- In the systematic review of prolotherapy injections for chronic low back pain,[16] the authors included 4 randomized trials[19-23] which were considered as high quality with a total of 344 patients. Among the 4 studies, the authors reported that 2 studies[20,21] showed significant differences between the treatment and control groups for those reporting over 50% reduction in pain or disability; however, their results could not be pooled.
  - In addition, in one study, co-interventions confounded independent evaluation of results; in the other, there was no significant difference in mean pain and disability scores between the groups.[20,21]
  - In the third study there was little or no difference between the groups in regard to the number of individuals who reported over 50% improvement in pain and disability.[22]
  - Reporting only mean pain and disability scores, the fourth study[19] showed no difference between groups.
  - The authors of this systematic review concluded that there was conflicting evidence regarding the efficacy of prolotherapy injections in reducing pain and disability in patients with chronic low back pain.
  - They also concluded that in the presence of co-interventions, prolotherapy injections were more effective than controlled injections, more so when both injections and co-interventions were controlled concurrently.

Clinical Presentation and Evaluation

- A wide variety of presenting complaints include occipital and suboccipital headaches, posterior midline and paramedial cervical, cervicothoracic, thoracic, thoracolumbar, lumbar, and lumbosacral pain as well as scapular and shoulder regions, between the shoulder blades, low back, buttocks, sacroiliac, trochanteric areas pain, and any combination of the above (Table 2).[2,9-16,20,23,24,26-29]
- The onset may be sudden or gradual; the intensity, duration, and quality of pain are variable but usually associated with a traumatic event.
  - Physical exam may reveal postural abnormalities, functional asymmetries, combinations of kyphoscoliosis, flattening of cervical and lumbar lordosis, and arm and/or leg length discrepancies.
  - Pain is provoked by variable combinations of flexion/extension, rotation, lateral bending, and/or contractions under load.
- The exquisite tenderness at the fibro-osseous junction (enthesis) is the pertinent subjective clinical finding.
  - These areas of 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 which becomes worse upon infiltration of the local anesthetic and typically subsides within 15 seconds after infiltration.
- Determination of abolishment or persistence of tenderness (local or referred pain objectifies the finding of tenderness) concludes the clinical exam and becomes the basis for clinical diagnosis and further RIT procedures.

Pathophysiology

- Ligaments and tendons are fibrous collagenous tissue that has a crimped, wave-like appearance under a light microscopy.
  - The crimped pattern unfolds during initial collagen loading.[1,30-32]
  - When elongated beyond 4% of their original length, ligaments and tendons lose their elasticity and ability to recoil to the original crimped, wave-like appearance.
    - They become permanently laxed, leading to joint hypermobility.
- Subfailure was reported at earlier stages of elongation in degenerated ligaments.
  - Natural healing, at best, may restore connective tissue to its pre-injury length but only 50 – 75% of its pre-injury tensile strength.[1,16, 30-32]
- Collagenous tissues are deleteriously affected by steroid administrations, NSAIDs, inactivity, and denervation.[4-6,15,32-34]
- Connective tissue response to trauma varies with the degree of injury and is always inflammatory/regenerative/reparative in nature.
  - In the presence of cellular damage, a regenerative pathway takes place; in the case of extracellular matrix damage, a combined regenerative/reparative pathway takes place. These pathways are modulated by hormones, and chemical and growth factors.[4,5,15,32]
  - Central denervation such as in quadriplegic patients leads to a statistically high accelerated degeneration.[5] Corticosteroids do not alter the course of this degenerative process.[4,5]
- Neoneurogenesis and neovasculogenesis are integral components of both regenerative/reparative and degenerative processes.[6,35-38]
- Rationale for RIT in the chronic painful pathology of fibrous connective tissue evolved from clinical, experimental, and histological research of the injection treatment of hernia.
  - In hernias, inflammatory response to injectate induced proliferation and subsequent regenerative/reparative healing phases that have led 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 initial phases that is regressing during the contraction phase.
- Pain reduction is in part explained by the regression of neoneurogenesis.[2,7]
- Experimental and clinical studies demonstrated up to a 65% increased diameter of collagen fibers in ligaments and tendons due to induced proliferative regenerative repetitive responses.[2,4,8,39,40]

Table 4. *The proposed mechanism of action of regenerative injection therapy.*

- Temporary neurolysis with chemoneuromodulation of peripheral nociceptors is achieved by chemical properties of the injectates and provides stabilization of antidromic, orthodromic, sympathetic, and axon reflex transmissions.
  - Temporary neurolysis is achieved via mechanical transsections of some small myelinated and unmyelinated C fibers by the needle or hydraulic pressure of the injected volume.
- Modulation of local haemodynamics with changes in intra-ligamentous, intra-tendinous, and intra-osseous pressure leads to reduction of pain. Empirical observations suggest that dextrose/lidocaine action is much more prolonged than that of lidocaine alone.
- Mechanical transsections of cells and extracellular matrix by the needle causes cellular damage, and stimulates inflammatory cascade and 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.
- Chemo modulation 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.
  - 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.
  - The large volume of injectate disrupts adhesions that were created by the original inflammatory attempts to heal the injury, akin to epidural or intra-abdominal lyses of adhesions.
- A relatively large volume of osmotically inert injectate assumes the role of a space occupying lesion in a tight and slowly equilibrating extracellular compartment of the connective tissue. It initiates inflammatory cascade and also irrigates catabolic interleukins.

Anatomy

- The 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, and neurovascular and osseous structures.
  - Collagenous connective tissues, in spite of their slightly different biochemical content, blend at their boundaries and at the osseous structures, functioning as a single unit.[1,32,41]
    - This arrangement provides a bracing and hydraulic amplification effect to the lumbar muscles, increasing contraction strength up to 30%.[9]
- Various well innervated joints allow movements of the extremities, spine, and cranium.
  - These joints are syndesmotic, synovial, and symphyseal.
  - Spinal joints are located in the anterior, middle, and posterior columns.
  - Syndesmotic joints are anterior and posterior longitudinal ligaments, anterior and posterior atlanto-occipital membranes, supraspinous and interspinous ligaments, and ligamentum flavum.
  - Symphyseal joints are intervertebral discs.
  - Synovial joints are atlanto-axial, atlanto-occipital, zygapophyseal, costotransverse, and costovertebral; the sacroiliac joint is a combined synovial-syndesmotic one.[1,8,31,41-43]
- Differential diagnosis is based on an understanding of the regional and segmental anatomy and pathology, as well as the segmental, multisegmental, and intersegmental communications in innervation of the compartments and their contents around the spine.
  - This is provided by ventral rami, dorsal rami, gray rami communicants, sinuvertebral nerves, and the sympathetic chain.
- 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 pacinian and Ruffini corpuscles. These nerve endings arise from lumbar medial branches.
  - A sharp increase in the quantity of free nerve endings at the spinous processes attachments (enthesis) were documented, rendering them putatively nociceptive.[33]
  - Experimental and empiric observations suggest that a similar arrangement exists at the cervical and thoracic spinous processes, therefore rendering them putatively nociceptive.[39,44] Willard[41] demonstrated that cervical MBs on the distal course innervate the multifidus and interspinales muscles.
  - A formal anatomic study reconfirmed these observations.[45]
- Spondyloarthropathies with enthesopathies are rarely, if ever, included in the differential diagnosis or therapeutic plan by the interventional physicians.
  - Tissue bed pathology, pain, and tenderness are the primary targets for RIT, taking innervation into account.
  - Therefore RIT may afford evaluation of many putative nociceptors from the variety of pain presentations and when correctly administered, offers a practical advantage that can be accomplished in one office visit (Fig. 7).

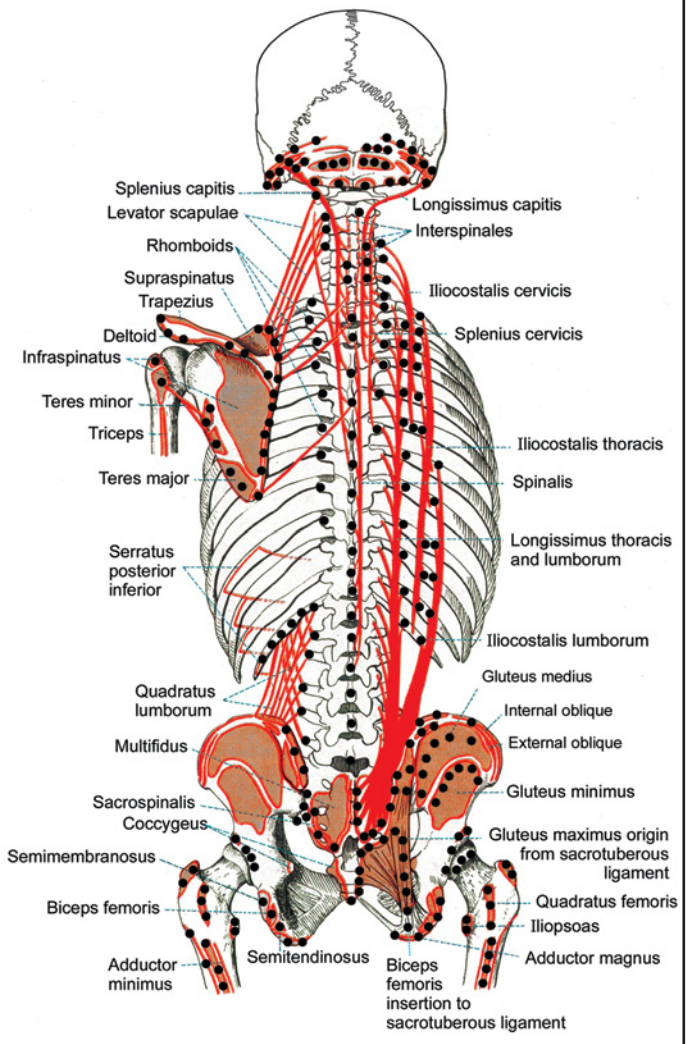

Fig. 7. *Schematic drawing demonstrating sites of origins and tendon insertions (enthesis) of the vertebral and paravertebral and peripheral musculature in the cervical, thoracic, and lumbar regions and partly upper and lower extremities. Clinically significant painful enthesopathies are common at the locations defined by dots. Dots also represent most common locations of needle insertions and infiltration during RIT.*
Modified from Sinelnicov. *Atlas of Anatomy*, Vol. 1, Meiditsina Moskow, 1972.
Modified and prepared for publication by Tracey Slaughter.

Mechanism of Action

The proposed mechanism of action for regenerative injection therapy is complex and multifaceted as is listed in Table 4.[8,9,19,28-30,47-57]

Solutions for Injections

- Four groups of solutions are used for RIT; and simply by virtue of being injected into connective tissue, all of them become irritants. By the chemical properties, hypertonic dextrose, phenol, and glycerin are neurolytic. The 4 groups are:
  - Osmotic shock agents, such as hypertonic dextrose and glycerin
  - Chemical irritants such as phenol
  - Chemo tactic agents such as sodium morrhuate
  - Particulates such as pumice suspension
- Injectates always contain a mixture of local anesthetic with other ingredients.
  - The most common solutions contain lidocaine/dextrose mixtures in various concentrations. Lidocaine is available in 0.5-2% concentration, dextrose in a 50% concentration.
    - To achieve a 10% dextrose concentration, dilution is made with lidocaine in 4:1 proportions (i.e., 4 mL of 0.5-1% lidocaine is mixed with 1 mL of 50% dextrose), osmolality 555 mOsm/L.
    - To achieve a 12.5% dextrose concentration, dilution is made with lidocaine in 3:1 proportions (i.e., 3 mL of 0.5-1% lidocaine mixed with 1 mL of 50% dextrose), 694 mOsm/L.
    - A 2:1 proportion (i.e., 2 mL of 0.5-1% lidocaine with 1 mL of 50% dextrose) will equal 16.5% dextrose, 916 mOsm/L.
    - A 3:2 proportion makes a 20% dextrose solution, 1110 mOsm/L.
    - A 1:1 dilution makes a 25% dextrose solution, 1,388 mOsm/L.
- A 25% dextrose solution is used for intraarticular and intradiscal injections.
  - Based on a recent double-blind study, proponents of noninflammatory RIT/prolotherapy suggest that a 10% dextrose solution may be equally effective for intraarticular use.[46]
  - Any solution with osmolality greater than a 1,000 mOsm/L is neurolytic because the myelin lamellae separate and unmyelinated fibers may show total destruction, after soaking for 1 hour in distilled water or solutions with osmolality greater than 1,000 mOsm/L.[47]
- When dextrose is ineffective, progression to a stronger irritant such as sodium morrhuate has been described in various dilutions up to a full strength.
  - Five percent sodium morrhuate is a mixture of sodium salts of saturated and unsaturated fatty acids of cod liver oil and 2% benzyl alcohol (chemically very similar to phenol), which acts as both a local anesthetic and preservative.
- Dextrose/phenol/glycerin (DPG) solution contains dextrose and glycerin in equal 25% amounts, 2.5% phenol and water.
  - It is referred to as DPG or P2G and prior to injection is diluted in concentrations of 1:2=1368 mOsm/L; 1:1=2052 mOsm/L or 2:3=1641 mOsm/L, with a local anesthetic.
- Diluted 5% phenol in 50% glycerin solution is used for the treatment of spinal enthesopathies and injections at donor harvest sites of the iliac crest for neurolytic and regenerative/reparative responses. Prior to injection 1 mL of this solution is mixed with 4 mL of local anesthetic 1,086 mOsm/L.[11,23]
  - Neurolytic intraarticular injections of a 10% aqueous phenol, diluted to 5% with omnipaque or omniscan contrast and local anesthetic, are used in the pain management department of Mayo Clinic, to facilitate nursing care in severely debilitated patients.[48]
  - Various concentrations of water and glycerine based phenol solutions have been described. The literature suggests that perineural phenol glycerine combinations produce a better regenerative/reparative response.[49-57]

Technique

- Using palpable landmarks for guidance, experienced practitioners may safely inject with or without fluoroscopic guidance, the posterior column elements innervated by the dorsal rami: tendons and ligaments enthesis at the spinous process, lamina, posterior zygapophyseal 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 medial branches with the sequence as follows:
- Step 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).
- Step B: The area(s) is re-examined about 1 minute after each injection for tenderness and movements that provoked pain.
  - If tenderness remains at the lateral aspects of the spinous processes, injections are carried out to the lateral aspects of their apices, thus continuing on the course of medial branches or dorsal ramus. Step B is repeated.
  - Persistence of paramedial pain dictates blocks of zygapophyseal capsules (cervical, thoracic, and lumbar),

costotransverse joints, or the posterior tubercle of the transverse processes in the cervical region with their respective tendon insertions. Step B is repeated.
  - Perseverance of lateral tenderness dictates investigation of the structures innervated by the lateral branches of the dorsal rami, such as the enthesis of iliocostalis or serratus posterior superior/inferior at the ribs, the ventral sheath of thoracolumbar fascia at the lateral aspects of the lumbar transverse processes, or the iliac crests insertions. Step B is repeated.
- In this fashion, all potential nociceptors on the course of medial branches and LB are investigated from their periphery to the origin.
  - Thus the differential diagnosis of pain arising from vertebral and paravertebral structures innervated by medial branches and LB is made based on the results of the blocks (Figs. 7 and 8).
- Manipulation under local anesthesia can be performed after anesthetic has taken effect and the musculature is sufficiently relaxed.[58]
- Pain from the upper cervical synovial joints presents a diagnostic and a therapeutic challenge because of the pain patterns overlap.
  - Therefore it is usually a diagnosis of exclusion.
  - A 3% phenol solution has secured a long-lasting therapeutic effect in selected patients after intra-articular, atlanto-axial, and atlanto-occipital joint injections.[16] A 25% dextrose intra-articular injection in these joints and midcervical synovial joints, was reported to relieve persistent pain after radiofrequency and capsular injection failure.[10]
  - The possibility of serious complications dictates that all intra-articular injections of the axial synovial joints; specifically atlanto-axial and atlanto-occipital, zygapophysial, costovertebral, and intervertebral discs, should be performed only under fluoroscopic guidance by an experienced practitioner.
- Most commonly injected sites of painful spinal enthesopa-

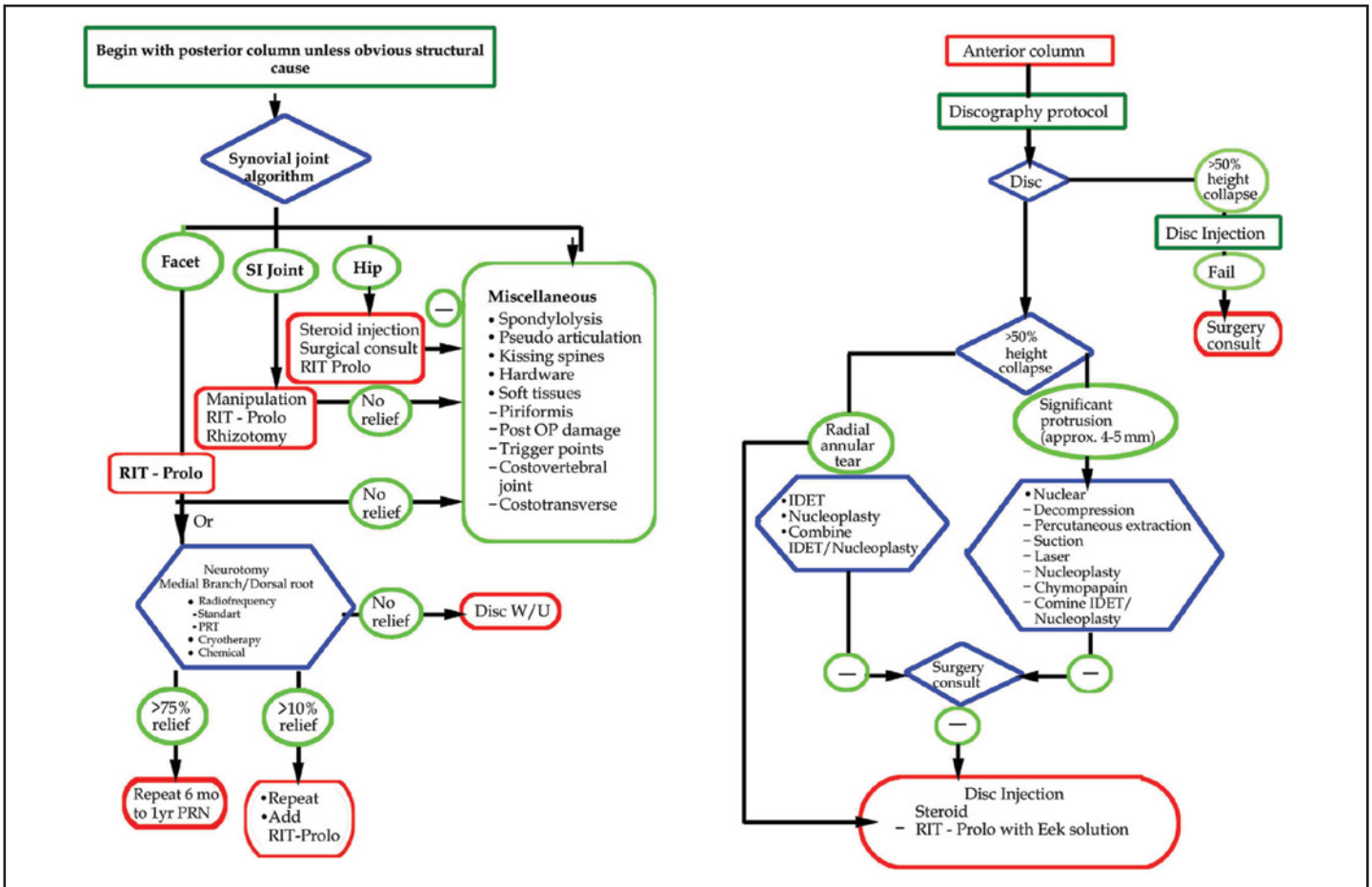

Fig. 8. *Percutaneous management options for spinal pain.*

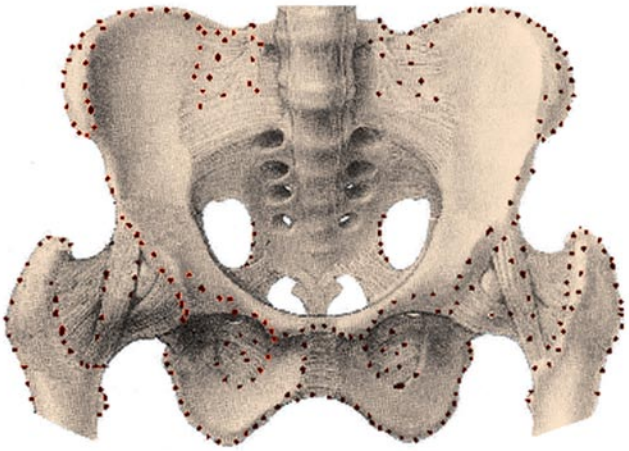

Fig. 9. *Illustration of the most common locations (dots) of pelvic enthesopathies and position of the needle tip during injection.*

thies of the posterior column are innervated by the medial (MB) and lateral (LB) branches of the dorsal rami:

- Spinous processes (superior, inferior, and lateral surfaces especially at the apex), terminal filaments
- Occipital bone at inferior and superior nuchal lines
- Posterior tubercles of cervical transverse processes (when palpable)
- Thoracic and lumbar transverse processes
- Capsular ligaments of cervical, thoracic, and lumbar zygapophysial joints
- Costotransverse joints and capsules
- Tendons and ligaments at the postero-medial, superior, inferior, and lateral surfaces of the iliac crests and spines
- Posterior tubercles and angles of the ribs

♦ Multiple other peripheral sites innervated by their respective nerves are depicted in Figs. 1-9.

- Proximal and distal portions of the clavicle
- Mastoid processes
- Greater and lesser humeral tuberocities, medial and lateral epicondiles
- Superomedial, medial, lateral margins, inferior and superior angles, spine, coracoids, and acromions of the scapulas
- Sternum, xiphoid, and anterior ribs
- Pubic tubercles, superior and inferior rami; ischial spines, tuberocities and rami
- Greater and lesser femoral trochanters, medial and lateral epicondiles

Side Effects and Complications

Complications do occur with regenerative injection therapy but statistically, they are rare.

♦ The most recent statistical data on complications are from a survey in 2006 of 171 physicians providing RIT injection treatment.[59]

- These respondents had been providing this treatment for a median of 10 years, and described treating a median of 500 patients each, giving a median of 2,000 injections each.
  - One hundred sixty-four spinal headaches were reported, as were 123 pneumothoraces. There were 73 temporary systemic reactions, and 54 patients with temporary nerve damage.
  - Sixty-nine adverse events required hospitalization, which included 46 of the patients with a pneumothorax and none of the spinal headache patients.
  - There were 5 cases of permanent nerve damage. Only 3 surveys included information on the specific injury:
    - One case of mild to moderate leg pain, 1 case of persistent numbness in a small area of the gluteal region, and 1 case of persistent numbness in the quadriceps region.

♦ These findings are similar to a survey by Dorman of 450 physicians performing RIT/prolotherapy.[60]

- One hundred-twenty respondents revealed that 495,000 patients received injections.
- Twenty-nine instances of pneumothorax were reported, 2 of them requiring chest tube placement.
- Twenty-four nonlife threatening allergic reactions were also reported.[60]
  - Stipulating that each patient had at least 3 visits and during each visit received at least 10 injections, the occurrence of pneumothorax requiring a chest tube was 1 per 247,500 injections.
  - Self-limited pneumothoraxes were 1 per 18,333 and allergic reactions were 1 per 20,625 injections.[60]

♦ In the 1960s, 5 cases of postinjectional arachnoiditis were reported.[61]

- Two of them were fatal.
- One was a direct sequence of arachnoiditis; another was a sequence of incompetent shunt and persistent hydrocephalus with increased intracranial pressure.
- Of the 3 other cases, the first, with mild paraparesis, recovered after a ventriculo-jugular shunt.
- The second recovered spontaneously with a mild neurological deficit.
- The third case remained paraplegic.

♦ 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.
- Adjacent endplate fractures associated with intradiscal dextrose injections were recently reported.[62]
- Postspinal puncture headaches have been reported after lumbosacral injections.[19] Two such cases occurred in the first author's practice during the past 14 years. Both patients recovered after 1 week with bed rest and fluids.

♦ Overall, pneumothorax is the most commonly reported complication.
- Injections of anterior synovial joints, such as sternoclavicular, costosternal, and interchondral, may also result in pneumothorax in the same subset of patients.

Key Points

1. Regenerative injection therapy/prolotherapy is 1 of the interventional techniques for treatment of chronic pain arising from multi-etiologic connective tissue diathesis with common pathogenesis.

2. Utilizing advanced imaging, neurophysiologic and precision diagnostic techniques, spinal pain can be identified in approximately 50% to 80% of patients, which leaves 20% to 50% of patients without appropriate diagnosis.

3. Axial and periaxial pain patterns from ligaments, tendons, muscles, intervertebral discs, and facet joints overlap significantly.

4. Rationale for RIT in the 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.

5. There are 4 groups of solutions used for RIT; simply by the virtue of being injected into connective tissue, all of them become irritants. By the chemical properties, hypertonic dextrose, phenol, and glycerin are neurolytic.

6. The same basic principles that have been advocated in all currently employed diagnostic blocks have been used in RIT since its inception to objectively confirm the source(s) of pain and to augment clinical diagnosis by local anesthetic.

7. Heterogeneity issues make it difficult to perform a comprehensive review and statistical analysis of the large volume of existing literature on the subject.

8. Publications questioning the validity of perivertebral enthesopathies, perivertebral ligaments, and tendons as pain generators are misleading.

9. The literature presented in this chapter, including randomized, nonrandomized, and systematic reviews, offers moderate evidence of RIT/prolotherapy effectiveness in select patients utilizing appropriate technique and manipulation.

10. Rare, but serious complications have been reported.

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PART TWO

NON-SPINAL INTERVENTIONAL TECHNIQUES