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Chapter 59, Prolotherapy

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INTRODUCTION

- Regenerative Injection Therapy (RIT), also known as prolotherapy or sclerotherapy, is an interventional technique for the treatment of chronic musculoskeletal pain due to connective tissue diathesis.[1-4]
- This technique originated in the United States in the mid-1840s for treatment of hernias. [5]
- RIT transitioned to musculoskeletal pathology in the 1930s.[1,3,4,5]
- Since then, the scope of applications has expanded gradually.[1-12]
- It has been proposed recently that pain reduction after RIT is due to chemomodulation or temporary neurolytic action of the injectate. Literature suggests that dextrose/lidocaine or dextrose/glycerin/phenol/lidocaine solutions have a more prolonged pain-relieving action compared to lidocaine alone.[2-4]

CLINICAL ANATOMY

- According to Willard, the connective tissue complex in the cervical, thoracic and lumbar areas incorporates various ligaments and paravertebral fasciae to form a continuous connective tissue stocking surrounding, interconnecting and supporting various soft tissue, vertebral, neurovascular and osseous structures. This arrangement provides bracing and hydraulic amplification effect to the musculature enhancing its strength by up to 30%.[13,14]
- The anterior compartment contains the paravertebral fascia muscles, vertebral bodies, intervertebral disc, anterior and posterior longitudinal ligaments. The middle compartment includes the contents of the spinal canal. The posterior compartment begins medially at the ventral aspect of z-joint capsules and laterally at the posteriolateral aspects of the transverse processes and converges at the apices of the spinous processes.[14]
- Movements of the cranium and spine are accomplished through various types of joints.[14] These include:
    - Syndesmoses, that is, anterior longitudinal ligament, posterior longitudinal ligament, anterior atlanto-

occipital membrane, posterior atlanto-occipital membrane, ligamenta flava, interspinous ligaments, and supraspinous ligaments.[14]
    - Synovial, that is, atlanto-axial, atlanto-occipital, zygapophyseal, costotransverse, costovertebral joints.[14]
        - Symphysis, for example, intervertebral discs. [14]
    - Combined, for example, sacroiliac joint, which is a synovial/syndesmotic articulation.[13,14]
- Connective tissues receive segmental innervation from the respective ventral and dorsal rami.[3,4,13,14]
    - Dorsal rami usually divide into medial and lateral branches (except the first cervical, fifth lumbar that forms only a medial branch, fourth and fifth sacral and coccygeal). [14]
    - Medial branches of the dorsal rami (MBDR) innervate z-joints, multifidus muscles, and intraspinous muscles and ligaments, and supraspinous ligaments.[13,14]
        - Free nerve endings and Pacini and Ruffini corpuscles have been identified in superficial layers of all ligaments, including supraspinous and interspinous, with a sharp increase in their quantity at the attachment to the spinous processes (enthesis) rendering them a source of nociception equal to that of z-joint capsules.[15]
    - Comparatively, the vascular supply is much less abundant. Such a relationship is essential for proper homeostasis.[16-18]
- Pain arising from affected connective tissue such as ligaments and tendons may mimic any referral pain patterns known.
    - Original patterns of referral pain from interspinous syndesmotic joints, that is, intraspinous ligaments, were published by Kellgren in 1939 and were subsequently confirmed in the 1950s by Feinstein and Hackett.[1]
        - Pain patterns from cervical synovial articulations were brought to light by Aprill, Dwyer and Bogduk in 1990 [19]; these were expanded to include upper cervical and thoracic articulations by Dreyfus in 1994.[20]
    - Also in 1994, Dussault described z-joint pain patterns in the cervical and lumbar areas, and Fortin described pain patterns from the sacroiliac joints.[21]
    - The size of this chapter precludes reproduction of the pain maps. There is a significant overlap between pain patterns from synovial and syndesmotic joints, as well as those from symphyseal joints.

PATHOPHYSIOLOGY

- Connective tissues are bradytrophic; their regenerative capabilities are much slower than that of any other tissue.[16,17]
- The natural healing process consists of three over-lapping phases: inflammation, granulation with fibroplasia, followed by contraction with remodeling.[1]
- Connective tissue response to trauma varies with the degree of injury.[16-18]
    - In the presence of cellular damage, regenerative response takes place.
    - In the presence of damage to the extracellular matrix, a combined regenerative, reparative pathway takes place.[3,4]
- Cell replication in combined regenerative reparative process is controlled by chemical and growth factors.[22]
- Natural healing, under best circumstances, may restore connective tissue to its pre-injury length but only to 50-75% pre-injury tensile strength.[16,18]
- The most frequent degenerative changes in ligaments and tendons are hypoxic, followed by lipoid, mucoid and calcific degeneration. A combination of all of these has been observed.[17]
- Modulation of regenerative and degenerative pathways remains a therapeutic challenge, and application of NSAIDs and steroids are of limited value.[18]
- Experimental studies demonstrated that repeated injections of 5% sodium morrhuate at the fibro-osseous attachments (entheses) increased the strength of the bone ligament junction by 28%, ligament mass by 44%, and thickness by 27% in comparison to the saline controls.[10]

MECHANISM OF ACTION

- The RIT mechanism of action is complex and multifaceted. The three most important components are:
  - Chemomodulation of collagen through inflammatory proliferative, regenerative/reparative responses is induced by the chemical properties of the proliferants and mediated by cytokines and multiple growth factors.[2-4]
  - Chemoneuromodulation of peripheral nociceptors provides stabilization of antidromic, orthodromic, sympathetic and axon reflex transmissions. Literature suggests that a dextrose/lidocaine or dextrose/glycerin/phenol/lidocaine combination have a much more prolonged action than lidocaine alone.[2-4]
  - Modulation of local hemodynamics with changes in intraosseous pressure leads to reduction of pain.[2-4]

INDICATIONS FOR RIT

- Discogenic low back pain.[7,8]
- Enthesopathy: A painful degenerative pathological process that results in deposition of poorly organized tissue, degeneration and tendinosis at the fibro-osseous interface and transition towards loss of function. (Note: Enthesis is the zone of insertion of ligament, tendon or articular capsule to bone. The outer layers of the annulus represent a typical enthesis.)[2-4]
- Tendinosis/ligamentosis: A focal area of degenerative changes due to failure of the cell matrix adaptation to excessive load and tissue hypoxia with a strong tendency toward chronic pain and dysfunction.[2-4,12]
- Pathologic ligament softening and laxity: a post-traumatic or congenital condition leading to painful hypermobility of the axial and peripheral joints.[1-4,11,12]
- Chronic pain from ligaments or tendons secondary to repetitive or occupational sprains or strains, e.g., "repetitive motion disorder."[1-4, 11,12]
- Chronic postural cervical, thoracic, lumbar and lumbosacral pain.[1-4,11,12]
- Lumbar and thoracic vertebral compression fractures with a wedge deformity that exerts additional stress on the posterior ligamento-tendinous complex.[1-4, 11,12]
- Recurrent painful subluxations of the ribs at costotransverse, costovertebral and/or costosternal articulations.[2-4,12]
- Osteoarthritis, spondylosis, spondylolysis and spondylolisthesis.[2-4,12]
- Painful cervical, thoracic, lumbar, lumbosacral and sacroiliac instability.[2-4, 12]

SYNDROMES AND DIAGNOSTIC ENTITIES TREATED WITH RIT[1-4,6-8,11, 23]

1. Cervicocranial syndrome: cervicogenic headaches, secondary to ligament sprain and laxity, atlanto-axial and atlanto-occipital joint sprains, mid cervical zygapophyseal sprains
2. Temporomandibular pain and muscle dysfunction syndrome
3. Barre-Lieou syndrome
4. Torticollis
5. Cervical disc syndrome without myelopathy
6. Cervicobrachial syndrome (shoulder/neck pain)
7. Hyperextension/hyperflexion injury syndromes
8. Cervical, thoracic and lumbar zygapophyseal syndromes
9. Cervical, thoracic and lumbar sprain/strain syndrome
10. Costotransverse joint pain
11. Costovertebral arthrosis/dysfunction
12. Slipping rib syndrome
13. Sternoclavicular arthrosis and repetitive sprain
14. Tietze's Syndrome/costochondritis/chondrosis
15. Costosternal arthrosis
16. Xiphoidalgia syndrome
17. Acromioclavicular sprain/arthrosis
18. Scapulothoracic crepitus
19. Iliocostalis friction syndrome
20. Iliac crest syndrome
21. Iliolumbar syndrome
22. Painful lumbar disc syndrome
23. Interspinous pseudoarthrosis (Baastrup's Disease)
24. Lumbar instability
25. Lumbar ligament sprain
26. Spondylolysis
27. Sacroiliac joint pain, subluxation, instability and arthrosis
28. Sacrococcygeal joint pain; coccygodynia

29. Gluteal tendinosis with or without concomitant bursitis
30. Myofascial pain syndromes
31. Ehlers-Danlos syndrome
32. Ankylosing spondylitis (Marie-Strumpell disease)
33. Failed back syndrome
34. Fibromyalgia syndrome
35. Laxity of ligaments

CONTRAINDICATION TO RIT[1-4,12]

- Allergy to proliferant or anesthetic solutions or their components, e.g., phenol, dextrose, or sodium morrhuate
- Acute non-reduced subluxations or dislocations, arthritis, bursitis or tendinitis (septic, gouty, rheumatoid or post-traumatic)
- Recent onset of a progressive neurologic deficit involving the segment to be injected, including but not limited to (severe intractable cephalgia, unilaterally dilated pupil, bladder dysfunction, bowel incontinence)
- Request for a large quantity of narcotics before and after treatment
- Neoplastic and inflammatory lesions involving vertebral and paravertebral structures
- Lack of improvement after infiltration of the putative nociceptive structure with a local anesthetic or severe exacerbation of pain
- Febrile disorder or acute medical/surgical conditions that render a patient's status unstable

COMMONLY UTILIZED SOLUTIONS[1-4,6-8,11,12]

- The most common solution is commercially available 50% dextrose, which is diluted with a local anesthetic. For example, 1 ml of 50% dextrose mixed with 3 ml of 1% lidocaine produces a 12.5% solution. Gradual progressions to 25% dextrose solution have also been used.
- 5% sodium morrhuate is a mixture of sodium salts of saturated and unsaturated fatty acids of cod liver oil and 2% benzyl alcohol. Note that the benzyl alcohol chemically is very similar to phenol and acts as a local anesthetic and preservative.
- Dextrose/phenol/glycerin (DPG or P2G) solution consists of 25% dextrose, 2.5% phenol and 25% glycerin. In reference publications, DPG was diluted with a local anesthetic prior to injection. Dilution ratios are 1:1, 1:2 and 2:3. A 6% phenol in glycerin solution was utilized at donor harvest sites of the iliac crests for neurolytic and proliferative responses.
- Other solutions utilized include pumice suspension, tetracycline, a mixture of chondroitin sulfate, glucosamine sulfate and dextrose.

TECHNICAL CONSIDERATIONS[3,4]

- Any structure that receives innervation is a potential pain generator. To confirm that the structure is a pain generator, the structure proper or its nerve supply has to be injected with a local anesthetic, resulting in abolition of pain.[3, 4]
- For RIT purposes, tissue pain generators are identified by reproducible local tenderness and are confirmed by needling and local anesthetic blocks of the tissue bed, taking its 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 without fluoroscopic guidance: spinous process, supraspinous and intraspinous ligaments, lamina, posterior zygapophyseal joint capsule, transverse process, cervicodorsal fascia, as well as posterior sacroiliac, sacrotuberous and sacrospinous ligaments, as well as posterior sacrococcygeal ligaments.
- The dextrose/lidocaine solution is an effective diagnostic and therapeutic tool for pain arising from posterior column elements when utilized in increments of 0.2-1.0 ml injected at each bone contact in the following sequence:
    - In the presence of midline pain and tenderness, the interspinous ligaments are blocked initially in the midline.
    - If tenderness remains at the lateral aspects of the spinous processes, injections are carried out to the lateral aspects of the apices of the spinous processes,

thus blocking off the terminal filaments of the MBDRs of the dorsal rami.
    - Persistence of paramedial pain dictates blocks of the facet joint capsules, costotransverse joints, sacroiliac ligaments, apices of transverse processes on the lumbar, posterior tubercle of the transverse processes in the cervical region with their respective tendon insertions.
    - Perseverance of lateral tenderness dictates investigation of the structures innervated by the lateral branches of the dorsal rami, that is, iliocostalis tendon insertions to the ribs.
- In this fashion, all potential nociceptors on the course of MBDRs are investigated from the periphery to the center. Utilizing the above-described sequence, the practitioner is able to make a differential diagnosis of pain arising from vertebral and paravertebral structures innervated by MBDRs and lateral branches of the dorsal rami. **(See Figures 59-1 and 59-2)**
- Pain from pathology of the upper cervical synovial joints presents a diagnostic and, more so, a therapeutic challenge. Because of the previously mentioned overlaps of pain patterns, it is usually a diagnosis of exclusion.
- Regarding therapeutic intervention, radiofrequency (RF) lesions and corticosteroid injections do not always produce desired therapeutic value in upper cervical synovial joint pain.
    - It has recently been brought to light that intra-articular atlanto-axial and atlanto-occipital joint injections of 6% phenol have secured a long-lasting therapeutic effect in selected patients.[23]
    - Intra-articular injections of 25% dextrose into the above-mentioned joints, as well as into mid-cervical synovial joints, were reported to relieve persistent pain after RF and capsular injection failure.
- Painful lumbar disc syndrome also remains a therapeutic challenge.
    - Original studies in the 1950s advocated injection of irritating solutions to the lumbar intervertebral disc. Chemonucleoannuloplasty was revived in the last decade by the enthusiastic work of Klein, Eek and Derby.
    - They reported significant pain improvement and return-to-work ratio after intradiscal injections of 25% dextrose mixed with chondroitin sulfate and glucosamine. The pilot group consisted of 30 patients with up to two years follow-up. These patients have failed previous conservative care, laminectomies, and fusions at adjacent levels or IDET.[7,9]
    - Pennsylvania researchers received and reported good results with lumbar intradiscal injections of 25% dextrose for treatment of painful mechanical and chemical discopathy, suggesting that 25% dextrose may provide an immediate and long lasting neurolytic action.

CONCLUSIONS

- RIT/prolotherapy is a valuable method of treatment for correctly diagnosed chronic painful conditions of the musculoskeletal systems.
- Thorough familiarity of the physician with clinical anatomy and pathophysiology, as well as anatomical variations, is necessary to utilize this technique effectively.
- Manipulation under local joint anesthesia and a series of local anesthetic blocks for diagnosis of somatic pain is another commonly utilized option in conjunction with RIT.
- RIT in an ambulatory setting is an acceptable standard of care in the community.
- Recent literature reports that NSAIDs and steroid preparations have limited usage in degenerative painful conditions of ligaments and tendons or chronic painful overuse injuries. Microinterventional regenerative techniques and proper rehabilitation up to six months or a year supported with acetaminophen and opioid analgesics may be more appropriate.

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