Position Paper of the Florida Academy of Pain Medicine on Regenerative Injection Therapy: Effectiveness and Appropriate Usage

Voted and accepted by the Florida Academy of Pain Medicine membership at the Annual Conference at the Hyatt Regency Tampa, Florida, on Saturday, June 30, 2001.

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The Florida Academy of Pain Medicine endorses regenerative injection therapy and supports its usage for chronic pain associated with sprained or strained ligaments or tendons, repetitive motion disorders, postural pain, and recurrent somatic dysfunctions resulting from lax ligaments.

Regenerative injection therapy (RIT), also known as prolotherapy, is an interventional technique for the treatment of chronic pain due to connective tissue diathesis by induction of collagen chemomodulation though inflammatory, proliferative, and regenerative/reparative responses mediated by multiple growth factors." The purpose of this position paper is to:

1. Inform the members of the Florida Academy of Pain Medicine (FAPM) and the medical community at large regarding the validity of an under-utilized type-specific treatment for chronic musculoskeletal pain related to connective tissue pathology.

2. Outline common indications and conditions treated with RIT, as well as contraindications thereto.

3. Encourage the use of RIT for the treatment of appropriate painful pathology of the connective tissue.

METHODOLOGY

To determine the validity of RIT, a committee of interventional pain physicians was formed to review pertinent literature. The committee reviewed 78 articles, 9 complete textbooks, and 51 relevant articles and chapters from additional textbooks.

FINDINGS

From 1937 through 2000, more than 40 publications reported case studies and retrospective, prospective, and animal studies evaluating the results of RIT treatment. The studies reported the findings of RIT treatment of more than 530,000 patients. Improvement based on return to work and restoration of functional and occupational activities occurred in 48% to 82% of the patients. Resolution of pain ranged from 0% to 100%. Complications included pneumothorax (28), chest tube placement (2), allergic reaction (24), grand mal seizure (1), and aseptic meningitis (1).

The findings of the FAPM committee substantially contrast with the position of Florida Workmen's Compensation and the Health Care Financing Administration (HCFA) Medicare guidelines, section 35-13, which states that "Prolotherapy, joint sclerotherapy, and ligamentous injections with sclerosing agents—not covered... the effectiveness of these therapies has not been verified by scientifically controlled studies." (For further information, see http://www.hcfa.gov/coverage/8b3.htm.) The committee recommends consideration of RIT as a type-specific treatment for post-traumatic, degenerative, overuse, and painful conditions of the musculoskeletal system related to the pathology of the connective tissue.

For decades, a small group of allopathic and osteopathic physicians has been practicing RIT. Pilot, retrospective, open-face prospective, and double-blind placebo-controlled studies have clearly indicated the effectiveness of RIT in the treatment of chronic musculoskeletal pain arising from post-traumatic and degenerative changes in connective tissue such as ligaments, tendons, fascia, and intervertebral discs.'-101

Clinical and experimental electron microscopic studies have proved that newly formed connective tissue has biomechanical properties similar to those of normal ligaments and tendons .61,11.16,15 Preliminary results of clinical prospective trials for chemonucleo-annuloplasty with proliferation-causing substances show significant promise .14,11.64,14

Conclusions reached in the literature and drawn from extensive clinical experience have found RIT an effective therapy for numerous chronic pain conditions. This position paper reviews the clinical and pathophysiologic aspects of RIT. The Florida Academy of Pain Medicine endorses RIT when used appropriately for the treatment of specific chronic pain entities.

MECHANISM OF ACTION

The RIT mechanism of action is complex and multifaceted. The six currently identified components are:

1. The mechanical transection of cells and matrices induced by the needle causes cellular damage and stimulates an inflammatory cascade. 1,6-1,11,19,102-104
2. Compression of cells by the extracellular volume of the injected solution stimulates intracellular growth factors .6-1.101-101
3. Chemomodulation of collagen through inflammatory proliferative, regenerative/reparative responses induced by the chemical properties of the proliferants and mediated by cytokines and multiple growth factors. 3,6,33,37-39,105-108
4. Chemoneuromodulation of peripheral nociceptors and antidromic, orthodromic, sympathetic, and axon reflex transmissions. 3,6,43-50
5. Modulation of local hemodynamics with changes in intraosseous pressure leading to the reduction of pain. Empirical observations suggest that a dextrose/lidocaine combination has a much more prolonged action than lidocaine' alone. 6,43-50,109-111
6. A temporary repetitive stabilization of the painful hypermobile joints, induced by the inflammatory response to the proliferants, provides a better environment for regeneration and repair of affected ligaments and tendon S. 3,4,6,26,27,37-41,91,92,94-97

PUTATIVE PAIN-GENERATING STRUCTURES AFFECTED BY RIT [5-32,35-69,80-104,112 128]

2. Ligaments: Intra-articular, periarticular, capsular
3. Tendons
4. Fascia
5. Enthesis: The zone of insertion of ligament, tendon, or articular capsule to bone
6. Intervertebral discs: The outer layers of the annulus represent a typical enthesis.

TISSUE PATHOLOGY

1. Sprain: Ligamentous injury at the fibro-osseous junction or intersubstance disruption secondary to sudden or severe twisting of a joint with stretching or tearing of ligaments. [107-128-130]
2. Strain: Muscle/tendon injury at the fibromuscular or fibro-osseous interface. When concerned with peripheral muscles and tendons, sprains and strains are identified as separate injuries and in three stage gradations: first-, second- and third-degree sprain or strain." [28-130]
3. Enthesopathy: A painful degenerative pathologic process that results in deposition of poorly organized tissue, degeneration and tendinosis at the fibro-osseous interface, and transition toward loss of function. [1.6,77,107,128,129]
4. Tendinosis/ligamentosis: A focal area of degenerative changes owing to failure of cell matrix adaptation to excessive load and tissue hypoxia with a strong tendency toward chronic pain and dysfunction .[6.1.11.103,105-107 128]
5. Pathologic ligament laxity: A post-traumatic or congenital condition leading to painful hypermobility of the axial and peripheral joints .[3,1,11,26-32,35-40]

INDICATIONS [1-12,35-70,75-101,112-126,130,131]

Chronic pain from ligaments or tendons secondary to sprains or strains

2. Pain from overuse or occupational conditions known as repetitive motion disorders, ie, neck and wrist pain in typists and computer operators, tennis and golfers' elbow, and chronic supraspinatus tendinosis
3. Chronic postural pain of the cervical, thoracic, lumbar, and lumbosacral regions
4. Painful recurrent somatic dysfunctions secondary to ligament laxity that improves temporarily with manipulation. Painful hypermobility and subluxation at given peripheral or spinal articulation(s) or mobile segment(s) accompanied by a restricted range of motion at reciprocal segment(s)
5. Thoracic and lumbar vertebral compression fractures with a wedge deformity that exerts stress on the posterior ligamento-tendinous complex
6. Recurrent painful subluxations of ribs at the costotransverse, costovertebral and/or costosternal articulations
7. Osteoarthritis of axial and peripheral joints, spondylosis, spondylolysis, and spondylolisthesis
8. Painful cervical, thoracic, lumbar, lumbosacral, and sacroiliac instability secondary to ligament laxity
9. Failed back surgery syndrome
10. Back pain refractory to radiofrequency and intradiscal electrothermal therapy procedures
11. Tendon, ligament, and synovial joint nociceptive sources. Not responding to anti-inflammatory treatment approach
12. Enhanced results of physical therapy and chiropractic/osteopathic manipulations

SYNDROMES AND DIAGNOSTIC ENTITIES SUCCESSFULLY TREATED WITH RIT [2-32,35-70,74-132]

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 segmental dysfunctions
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. Thoracic segmental dysfunction
15. Tietze's syndrome
16. Costochondritis/chondrosis
17. Costosternal arthrosis
18. Xiphoidalgia syndrome
19. Acromioclavicular sprain/ arthrosis
20. Shoulder hand syndrome
21. Recurrent shoulder dislocations
22. Scapulothoracic crepitus
23. Iliocostalis friction syndrome
24. Iliac crest syndrome
25. Iliolumbar syndrome
26. Internal lumbar disc disruption
27. Interspinous pseudoarthrosis (Baastrup's disease)
28. Lumbar instability
29. Lumbar ligament sprain
30. Spondylolysis
31. Sacroiliac joint pain
32. Sacrococcygeal joint pain
33. Gluteal tendinosis
34. Trochanteric tendinosis
35. Myofascial pain syndromes
36. Ehlers-Danlos syndrome
37. Osgood-Schlatter disease
38. Ankylosing spondylitis (Marie-Strumpell disease)
39. Failed back syndrome
40. Fibromyalgia syndrome
41. Baker's cyst
42. Foot and/or ankle
    - Sinus tarsi syndrome
    - Metatarsalgia
    - Chronic ankle sprain
    - Instability
    - Laxity of ligaments

CONTRAINDICATIONS

1. Allergy to anesthetic or proliferant solutions or their ingredients such as dextrose, sodium morrhuate, or phenol
2. Acute non-reduced subluxations or dislocations
3. Acute arthritis (septic or post-traumatic with hemarthrosis)
4. Acute bursitis or tendinitis
5. Capsular pattern shoulder and hip designating acute arthritis accompanied by tendinitis
6. Acute gout or rheumatoid arthritis
7. 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)
8. Requests for a large quantity of sedation and/or narcotics before and after treatment
9. Paraspinal neoplastic lesions involving the musculature and osseous structures
10. Severe exacerbation of pain or lack of improvement after infiltration of the putative nociceptive structure with a local anesthetic

H. Any acute medical or surgical condition that renders the patient's status unstable

12. Infection or neoplasia overlying the area of injection

COMMONLY USED SOLUTIONS

The most common solutions for injection therapy are dextrose based. Dilutions can be made with local anesthetic (eg, I mL 50% dextrose plus 3 mL 1% lidocaine). Gradual progression to 25% dextrose solution can be considered .[4-8,22]

For intra-articular injection of the knee, a 25% dextrose solution had been used for decades .[4] Recently, a 10% dextrose solution has been investigated and has proved effective." The 5% sodium morrhuate contains sodium salts of saturated and unsaturated fatty acids of cod liver oil and 2% benzyl alcohol. Note that the benzyl alcohol is chemically similar to phenol and acts as a local anesthetic and preservative .[4,6,11,77,94]

Dextrose phenol glycerin solution consists of 25% dextrose, 2.5% phenol, and 25% glycerin. In all referenced studies, it was diluted with a local anesthetic of the practitioner's choice before injection. Dilution reported ratios are 1:1, 1:2, and [2:3.'0,19,20,21,118] The 6% phenol in glycerin solution was used at donor harvest sites of the iliac crests for neurolytic and proliferative responses. [72,101] Other solutions include pumice suspension, tetracycline, a mixture of chondroitin sulfate, glucosamine sulfate with dextrose, and Plasmo "Q-U" .[4,15,25.30-32,64.126]

CONCLUSIONS

1. Regenerative injection therapy, also known as prolotherapy, is valuable for the treatment of chronic painful conditions of the

locomotive systems.

2. Thorough familiarity of normal, pathologic, cross-sectional, and clinical anatomy, as well as anatomical variations and functions is necessary to ensure appropriate technique.
3. Current literature supports manipulation under local joint anesthesia and a series of local anesthetic blocks for somatic pain.
4. Use of RIT in an ambulatory setting is an acceptable standard of care in the community.
5. Current literature suggests that NSAIDs and steroid preparations have limited use in chronic painful overuse conditions and in degenerative painful conditions of ligaments and tendons: however, they are occasionally helpful to curb a significant inflammatory reaction to proliferants. Microinterventional regenerative techniques and proper rehabilitation up to 6 months or I year, supported with mild opioid analgesics, may be more appropriate.

SUMMARY

RIT is a safe and effective treatment modality that is very useful in a significant number of pain syndromes arising from ligament and tendon diathesis, as well as other clearly delineated pain problems. Physicians who use RIT must be knowledgeable in clinical anatomy and function and should be properly trained in this technique via a combination of seminars or workshops, apprenticeships, or visiting fellowships to safely and effectively use this treatment. The Florida Academy of Pain Medicine endorses RIT, when administered appropriately for the treatment of specific chronic pain entities.

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