A History of the Applications of Regenerative Injection Therapy in Pain Management, Part II 1960s–1980s

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Over time, regenerative injection therapy/prolotherapy has proved effective in relieving chronic neck, shoulder, knee, and lower back pain. Elimination of pain associated with cervicogenic headaches of traumatic and nontraumatic origin has also been reported.

The history of regenerative injective therapy from 1930s to the 1950s was reviewed in the April 2000 issue of The Pain Clinic *by Drs. Linetsky, Mikulinsky, and Gorfine.*

Through the 1960s, George Hackett, MD continued his clinical and basic science research of regenerative injection therapy (RIT) or prolotherapy. In many publications during that time, Hackett emphasized the common pathogenesis of impaired local circulation in chronic conditions such as neuritis, headaches, whiplash, osteoporosis, bone dystrophy, bronchospasm, and arteriosclerosis. Excess antidromic, sympathetic, and axon reflex stimulation causes local vasodilatation and edema, perpetuating a vicious cycle of tendon relaxation, degenerative changes, enthesopathy, tendinosis, and laxity.[1-10]

Extended subsequent animal experiments with multiple solutions conducted by Hackett revealed that the strongest fibro-osseous proliferations were achieved with Sylnasol, zinc sulfate solutions, and silica oxide suspension. The strongest acute inflammatory reaction was obtained with Sylnasol and zinc sulfate followed by silica oxide. Whole blood moderately stimulated fibro-osseous proliferation. Hydrocortisone used alone or in combination with proliferants inhibited proliferation from 3 to 4 weeks. At the fracture sites proliferants increased callus formation in 3 weeks. When they were used in combination with steroids, callus formation was markedly inhibited.[3]

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Hackett's positive results were initially corroborated by Green, Compere, Neff, and Myers.[11-16] In fact, Myers reported improvement in 82% of his patients.[16] By 1961, Blasche reported the first prospective study of patients treated with RIT for lower back pain. Thirty-two of 42 patients were receiving workmen's compensation: these cases are notoriously the most difficult to treat. The remaining 10 patients had private insurance. Patients were observed for 3 years. Complete recovery was achieved in 20 patients. Thirteen patients reported no change in their condition, and nine patients underwent surgery. Four patients with clinical presentation of acute herniated disc, in whom RIT was used without hope of success, had better outcomes than any other patients in this study. In three patients who underwent surgical intervention, specimens were obtained from the sites of injections and were reported as normal fibrous tissue.[17]

A multicenter study conducted by Kayfetz et al was published in 1963. Sixty percent of patients were followed for 1 year, and 27% were followed for 3 to 5 years. A total of 264 patients received RIT treatments for headache, 78% of which were of traumatic origin, 22% were of nontraumatic origin. Fifty-six percent of patients had symptoms of Barre-Lieou syndrome. Symptoms lasted longer than 1 month in 86% of subjects and longer than 1 year in 46% of patients. Seventy-nine percent of patients in the traumatic group were completely relieved of headache. Forty-seven percent of patients in the nontraumatic group reported complete relief of headaches. There were no infections or other complications after RIT.[18]

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In 1963, Kayfetz reported a 5-year follow-up of 189 patients who had received RIT for whiplash injuries. Of these, 153 (81%) had injuries associated with the thoracic and lumbar areas, and 98 (52%) had Barre-Lieou syndrome. Symptoms had persisted for more than 1 month in 55% of patients and for more than 1 year in 21% of patients. The majority of patients received from 6 to 30 injections in one office visit and were treated on 1 to 10 occasions. The duration of treatment ranged from 1 to 6 months. Pain relief was considered excellent by 113 (60%), good by 15 (8%) and fair by 34 (18%) patients. Seventy-five percent of patients considered themselves cured from pain.[19]

In response to adverse effects resulting from alleged incidental intrathecal injections of zinc sulfate,[20-22] Hackett conducted experiments with intrathecal injections of this solution in rabbits. Clinical doses (4 to 5 drops) did not produce a noticeable effect. Increased doses produced spinal anesthesia from which the rabbits completely recovered after the anesthetic wore off. Higher doses (up to 10 drops) were required to induce temporary paraplegia.[3]

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In 1967, RIT had become an issue for the courts. A California court declared that a physician treating a patient had deviated from the method as described by Hackett. It was concluded that a physician could follow a method or form of treatment propounded by the minority of physicians provided they were reputable and of good standing in the medical community. Variations from a preferred method of treatment would result in a violation and be considered a deviation from the generally accepted method of treatment. The court concluded that "as a matter of law, RIT, as a method of treatment, cannot be said to be inappropriate or to [constitute] malpractice even though it has not been accepted as a common method of treatment by the medical profession generally."[23]

Abroad, positive results with Hackett's method were obtained by Ongley, Barbor, Cyriax, and Coplans.[24-27] Barbor presented a study of 153 patients who suffered back pain for up to 20 years. Of these, 111 (74%) patients reported relief to their satisfaction; 17 (11%) failed to improve; and 31 patients (23%) required periodic booster injection for relief. Twenty-five patients were lost to follow-up.

The solution used for the injections included dextrose, phenol, and a solution of glycerine (DPG) (2 cc) plus a local anesthetic (3 cc).[26]

Cyriax included a detailed description of sclerosant injections to interspinous and facet joint capsular ligaments of the cervical, thoracic, and lumbar regions in his texts.[24,25] He further described a single-blind study of sclerosant therapy conducted by Sanford in 1972. Of 100 patients, only 3 were lost to follow-up. The following three solutions were compared: (1) 2 mL of DPG sclerosant plus 8 mL of saline; (2) 10 mL of 0.5% procaine; and (3) 10 mL of saline. The diluted sclerosant and procaine solutions were nearly equally effective in relieving pain in more than 50% of cases. Procaine and normal saline were equally ineffective in 50% of cases. The saline solution was effective in less than 33% of patients. A 20% solution of DPG was significantly less effective than the full-strength solution.[24,25]

In 1974, Blumenthal reported two cases of migraine headache and one case of cluster headache successfully cured by RIT and a minor modification of Hackett's technique in the treatment of cervicodorsal pain.[28] In 1976, Leedy reported a 70% improvement in low back pain of 50 patients who were treated with sclerosant injections and followed for 6 years. He also published several articles describing the method.[29,30] In a comparison of RIT with acupuncture for the treatment of chronic musculoskeletal pain, a later report by Vanderschot concluded that RIT had a faster onset of action offered pain relief of greater duration.[31,32]

In a comparison of prolotherapy with acupuncture for the treatment of chronic musculoskeletal pain, Vanderschot concluded that prolotherapy had a faster onset of action and offered pain relief of greater duration.

In 1978, Chase reported up to 70% or better improvement in long-standing cases of head, neck/shoulder, and low back pain syndromes.[33,34] Koudele reported findings of Haws and Willman on histologic changes in human tissue treated up to 5 times with sclerosant injections for low back pain. The following changes were observed and documented on slides. The DPG solution produced early coagulation necrosis, followed by early collagen formation. In 6 months, a small zone of residual inflammatory cells was documented in an area of a very dense collagen. In two other specimens treated with DPG, a dense collagen with fibrosis, occluded blood vessels, and a dense whirl of scar was observed. After an injection of pumice suspension, an area of dense collagen and fibrosis surrounding a lake of pumice without foreign body reaction but with a capsule formation was documented.[34]

In 1982, Hirshberg reported a prospective study of 16 patients with the iliolumbar syndrome. Nine patients were treated with infiltration of lidocaine at the insertion of the posterior iliolumbar ligament to the iliac crest; seven were injected with a mixture containing equal amounts of 50% dextrose and 2% Xylocaine, a total of 5 cc. Significant recovery was reported by 10 patients. Six of the seven patients treated with dextrose/Xylocaine recovered; whereas, only four of nine patients treated with Xylocaine recovered.[35]

By 1985, Maynard reported a decrease in collagen fibrils and hydroxyproline content and an overall increased mass of tendons in experimental animals injected with sodium morrhuate.

In a blinded study, rabbits were injected with medial collateral ligaments. Repeated injections of 5% sodium morrhuate at the fibro-osseous attachments (enthesis) significantly increased bone-ligament-bone junction strength of treated rabbits by 28%, ligament mass by 44% and thickness by 27%, compared with saline controls. Morphometric analysis of electron micrographs demonstrated a highly significant increase in the diameter of collagen fibril in the experimental ligaments compared with those of the control animals. These findings confirmed that sodium morrhuate had a significant regenerative influence on dense connective tissue at the insertion sites.[36] By 1985, Maynard reported a decrease in collagen fibrils and hydroxyproline content and an overall increased mass of tendons in experimental animals injected with sodium morrhuate. The average tendon circumference increased up to 25%.[37] The mean value of the injected tendons was 19.2 ± 3.3 mm compared with 15.1 ± 2.0 mm for the controls.

A double-blind, randomized RIT study was conducted by Ongley in 81 subjects with chronic low back pain. Patients were injected either with a DPG solution or saline. Statistically significant improvement greater than 50% was demonstrated in patients who had been injected with the DPG solution. The experimental group demonstrated a greater improvement than the control group in overall disability scores.[38] In a later study, Ongley demonstrated a significant statistical improvement in five patients treated with RIT for painful instability of the knees. Ligament stability data was obtained by a three-dimensional computerized goniometry, integrated with force measurements.[39]

In a 5-year retrospective survey on 17 patients who were treated with RIT for low back pain, 70% of patients reported excellent to very good results.[40] In 1989, Klein documented histologic proliferation and regeneration of ligaments in human subjects in response to injections of DPG solution. Patients acknowledged increased range of motion documented by computerized inclinometry and decreased pain.[41]

SUMMARY

Clinical and basic scientific research of RIT/prolotherapy for relief of chronic pain was performed from 1960s through 1980s. Results supported the research of the pioneers of this form of therapy and have emphasized that RIT is an effective treatment for post-traumatic pain and pain

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associated with overuse of the connective tissue such as ligaments and tendons.

Clinical trials of RIT have continued through the 1990s to the present. Intra-articular injections demonstrated definite improvements. Preliminary reports of intradiscal injections demonstrated promising results. In the next article in this series, the advances of RIT from the 1990s through the present will be reviewed.

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