

Dextrose Prolotherapy for Recurring Headache and Migraine Pain

This retrospective case series study revealed that Hackett-Hemwall dextrose prolotherapy appears to provide an effective, long-lasting treatment for recurring tension and migraine headache pain and their associated symptoms.



Headaches and migranes are a common occurrence and can be multi-factorial in origin with various triggers. It is thought that weak or loose neck ligaments and/or tendons may act as headache triggers in some people, validating the use of dextrose prolotherapy as a reasonable treatment option. To this end, the authors of this retrospective pilot study analyzed treatment of patients at the Beulah Land charity medical clinic which operated from 1994 to 2005 in Thebes, Illinois. The authors have done an excellent job of collecting and interpreting the data and discussing the issues in this most interesting study.

—Donna Alderman, DO



By Ross A. Hauser, MD and Heather McCullough, MA



Approximately four percent of adults experience headaches nearly every day.¹ Migraine headaches, tension-type headaches, and other recurrent headache pain syndromes remain challenging for clinicians and patients alike in terms of finding the most effective and safest therapies. According to the National Institute of Neurological Disorders and Stroke (NINDS), the American Council for Headache Education (ACHE), and the National Headache Foundation, over 45 million Americans suffer from chronic, recurring headaches and, of these, 28 million suffer from migraines.^{2,3}

While migraines affect 12% of the adult population in the United States, at least 90% have experienced a tension-type headache.⁴ Despite headache being one of the top 10 reasons cited for an outpatient medical visit, they continue to present a challenging and difficult problem for both medical professionals and patients.^{5,6} Debilitating headache pain presents a tremendous economic impact on society—not only with direct costs, but also on indirect costs such as a loss of productivity.⁷ Unfortunately, a reported 49% of headache sufferers do not seek medical care and of those who do, only 28% are very satisfied with the treatment they receive.⁸

While medicine carries 150 diagnostic headache categories, the vast majority of recurring headaches are classified as either migraine or tension. The most common headache types among adults and adolescents are tension headaches, chronic daily

headaches or chronic non-progressive headaches. These muscle contraction headaches cause mild to moderate pain and come and go over a prolonged period of time. Migraine headache pain is often moderate to severe and described as a pounding, throbbing pain lasting from four hours to three days, and usually occurring one to four times per month. Migraines are associated with symptoms such as light sensitivity, noise or odor sensitivity, nausea or vomiting, loss of appetite and stomach upset or abdominal pain. Typical medical treatments for tension or migraine headaches involve the use of medications such as nonsteroidal anti-inflammatory drugs (NSAIDs), triptans or muscle relaxants. Despite the advances in migraine-specific drugs, only 50% of patients with migraine headaches attain more than 50% reduction of headache frequency after three months of treatment.^{9,10}

While some headache sufferers get relief—with avoidance of various foods like chocolate, tyramine-containing cheese and alcoholic beverages, work station ergonomic modification, rest, stress control, and other lifestyle modifications—the bottom line of most of these traditional approaches is that the individual becomes dependent on headache medications and often lives in fear of the next migraine attack or tension headache.^{11,12} Sometimes, the drugs themselves can transform episodic headaches into continuous daily headaches.^{13,14}

Other modalities for treating headaches relate evidence associating headache and migraine pain to vascular changes. Current research suggests that a vascular concept is implausible since vascular changes do not explain the symptoms of attacks and, at the same time, drugs used to treat headaches and migraines do not demonstrate much effect on blood vessels.¹⁵⁻²²

Numerous risk factors, often labeled “triggers,” may result in a migraine-eliciting environment. These include skipped meals,



FIGURE 1. Typical areas injected during cervical Hackett-Hemwall dextrose prolotherapy.

sleep deprivation, hormonal changes, alcohol consumption and acute stress, among others. Individuals may also report pain sensations in areas innervated by the trigeminal system—notably nasal and neck regions, which can then lead to misdiagnosis of sinus or tension headache.²³

Weak or loose ligaments and tendons similarly can become “triggers” for migraine and headache pain. Without treatment, over time, one would begin to see an increase in frequency, duration or intensity of migraine or tension headaches if these loose areas were left untreated.²⁴ Given the limitations of traditional medical therapies for headaches, some headache sufferers are turning to alternative therapies—including prolotherapy which addresses the issue of loose ligaments and tendons in the head and/or neck.^{25,26}

Prolotherapy Modality

Prolotherapy, as defined by *Webster’s Third New International Dictionary*, is “the reha-

bilitation of an incompetent structure, such as a ligament or tendon, by the induced proliferation of cells.” The word “prolo” comes from the word proliferate meaning “to grow.” George S. Hackett, MD, the originator of the technique, coined the term prolotherapy.²⁷ Gustav A. Hemwall, MD was Hackett’s protégé and the main proponent for utilizing and teaching the technique of dextrose prolotherapy from the 1950s through the late 1990s, hence the “Hackett-Hemwall” name. Prolotherapy injections proliferate or stimulate the growth of new, normal ligament and tendon tissue.²⁸ In human prolotherapy studies, biopsies performed after the completion of treatment showed statistically significant increases in collagen fiber and ligament diameter of up to 60% in the treated areas.²⁹ Prolotherapy is based on the theory that the cause of most chronic musculoskeletal pain is ligament and/or tendon weakness (or laxity). Prolotherapy has been shown in one double-blind animal study over a six-week period to increase ligament mass by 44%, ligament thickness by 27%, and the ligament-bone junction strength by 28%.³⁰ Another animal study confirmed that prolotherapy induced the normal healing reaction that occurs when an injured tissue is healing itself. In this study, the prolotherapy treatment caused the circumference of tendons to increase by approximately 25% after six weeks.³¹

This retrospective pilot study was undertaken to evaluate the effectiveness of Hackett-Hemwall dextrose prolotherapy on tension and migraine headache pain and its associated symptoms. Prolothera-

py, by strengthening cervical ligaments and tendons, treats very common trigger and pain locations of the posterior neck. Effective for any age group, we postulate that prolotherapy will likely become an increasingly useful treatment modality in the physician’s armamentarium as the patient population ages and experiences an increase in cervical pain as a trigger for tension and migraine headache pain.

**Patients and Methods
Framework and Setting**

In October 1994, the physician author started a Christian charity medical clinic called Beulah Land Natural Medicine Clinic in an impoverished area of southern Illinois. The primary treatment modality offered was Hackett-Hemwall dextrose prolotherapy for pain. Dextrose was selected as the proliferant used in the prolotherapy solution as it is readily available, is inexpensive when compared to other proliferants, and has a high safety profile. The clinic met every three months until it ended in July 2005. All treatments were provided free of charge.

Patient Criteria

General inclusion criteria included being at least 18 years old, a willingness to undergo at least four prolotherapy sessions (unless the pain remitted with fewer sessions), a reported history of neck pain associated with headaches, or noted tenderness or positive “jump signs” relating to trigger points in the neck upon physical exam.

Interventions

Each patient received bilateral prolotherapy injections with a 15% dextrose, 0.2% lidocaine solution at their bony attachments including the lamina, facet joints, transverse processes of cervical vertebrae C2 to C7, the mastoid process, superior and inferior nuchal ridges on the occiput, posterolateral clavicle and superior angle of the scapula; suboccipital and erector spinae muscles, including longissimus capitis, iliocostalis cervicis, longissimus cervicis, scalene posterior, splenius capitis, splenius cervicis, semispinalis cervicis, and semispinalis capitis; sternocleidomastoid, trapezius, levator scapula, and serratus anterior muscles; as well as the C2-C7 facet joints, including these joints’ articular capsules and the intertransverse ligaments (see Figure 1). No other therapies were used. The patients were asked

TABLE 1. Patient Characteristics Prior to Prolotherapy

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|--|-----------|
| Headache and Migraine Patients | 15 |
| Percentage of Female Patients | 73% |
| Percentage of Male Patients | 27% |
| Average age of Headache and Migraine Patients | 53.2 |
| Percentage of Tension Headache Patients | 54% |
| Percentage of Migraine Patients | 46% |
| Reported daily headaches | 34% |
| Reported weekly headaches | 80% |
| Reported headache or migraine pain of 8 or higher on pain scale of 1 to 10 | 100% |

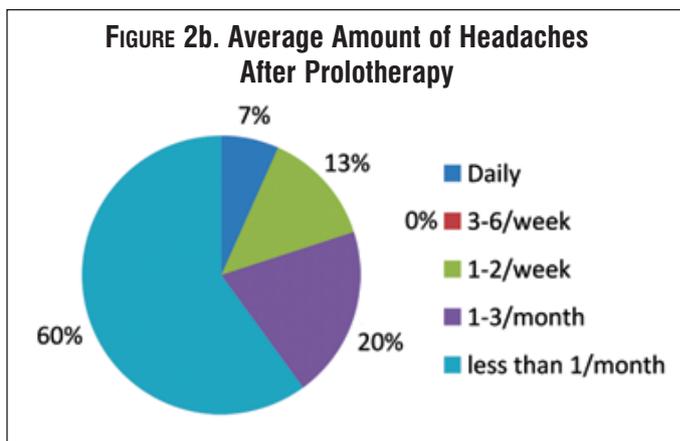
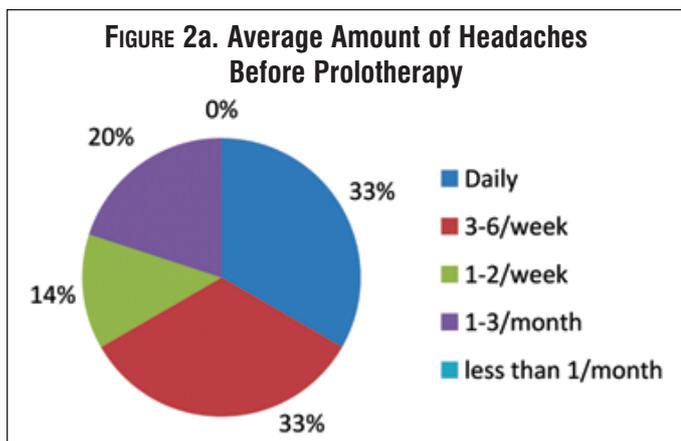


FIGURE 2a, 2b. Starting and ending average amount of headaches before and after receiving Hackett-Hemwall dextrose prolotherapy in 15 patients with headache and migraine pain.

to reduce or stop other pain medications and therapies they were using as much as the pain would allow.

Data Collection

Patients seen in the clinic from 2001 through 2005 who met the inclusion criteria were called by telephone and interviewed by an independent data collector who had no prior knowledge of prolotherapy and was the sole data collector gathering patient information during the telephone interviews. The data was collected an average of 22 months after the patients' last prolotherapy treatment. The patients were asked a series of detailed questions regarding their pain and previous treatments before starting prolotherapy. Their response to prolotherapy treatments was documented in detail with an emphasis on the effect the treatments had on their need for subsequent pain treatments, as well as their quality of life and whether the post-treatment benefits continued substantially after the treatments concluded.

Statistical Analysis

The results of the patient responses were calculated by an independent data analyzer who had no prior knowledge of prolotherapy.

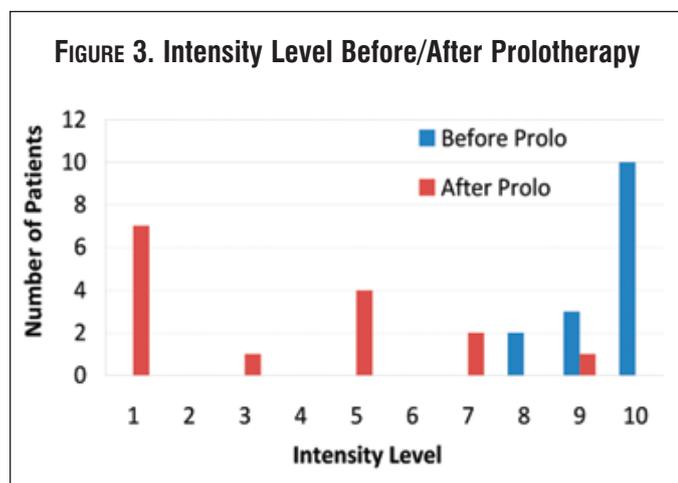


FIGURE 3. Starting and ending intensity level of headaches on a scale of 1-10 before and after receiving Hackett-Hemwall dextrose prolotherapy in 15 patients with headache and migraine pain.

Patient Characteristics

A total of 15 patients met the inclusion criterion with 73% female and 27% male with an average age of 53.2 years. Fifty-four percent of patients reported experiencing tension headaches and 46% reported migraine headache symptoms. Prior to prolotherapy treatment, 34% reported daily headaches and 80% experienced headaches at least once per week. All of the patients reported that the headache or migraine pain reached at least an 8 or higher on a pain scale of 1 to 10 prior to treatment with prolotherapy (see Table 1).

Treatment Outcomes

Headache Type and Frequency

Fifty-four percent reported tension headache symptoms and 46% reported migraine headaches. Of the 15 patients, five reported daily tension or migraine headaches. Another five participants experienced three to six tension or migraine headaches per week. Taken together, 66% of study participants had tension or migraine headaches multiple times each week. All study participants experienced headaches at least monthly prior to treatment with prolotherapy (see Figure 2a). After prolotherapy treatments, 60% reported the frequency of their headaches as less than once per month (see Figure 2b). Only one patient continued to have daily headaches, although all respondents reported a decrease in level of pain overall.

Intensity Level and Length of Headaches

Patients were asked to rate the intensity level of their headaches prior to receiving prolotherapy and after their last prolotherapy treatment, using a scale of 1 to 10 (1 being non-noticeable and 10 being severe). Prior to treatment, 67% reported a pain level of 10 out of 10. The remaining 33% of study participants rated their pain between 8 and 9 out of 10. All of the participants reported that their pain was at least 8 out of 10 on the pain scale prior to prolotherapy treatment. Following treatment, significant decreases in intensity level were noted for 100% of the patients. Forty-seven percent were able to state that the intensity level following treatment was at level 1 (i.e., non-noticeable; see Figure 3).

In this study, participants were also interviewed regarding the average length of time they had headache or migraine pain both prior to prolotherapy and following their last treatment

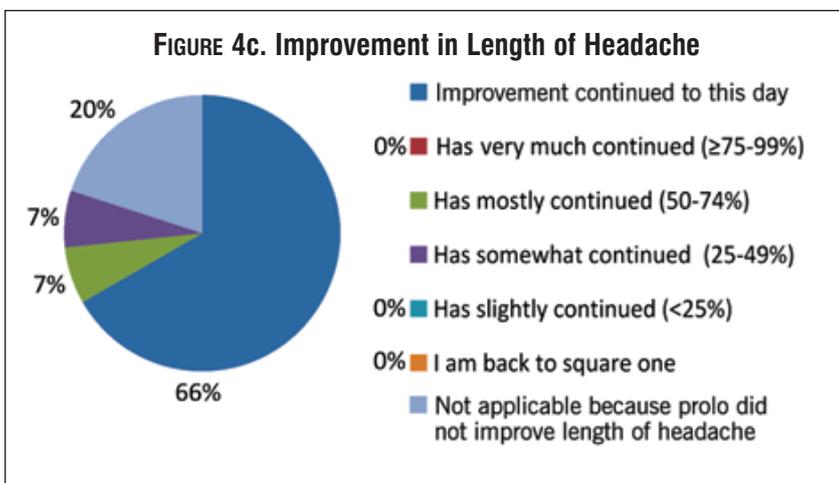
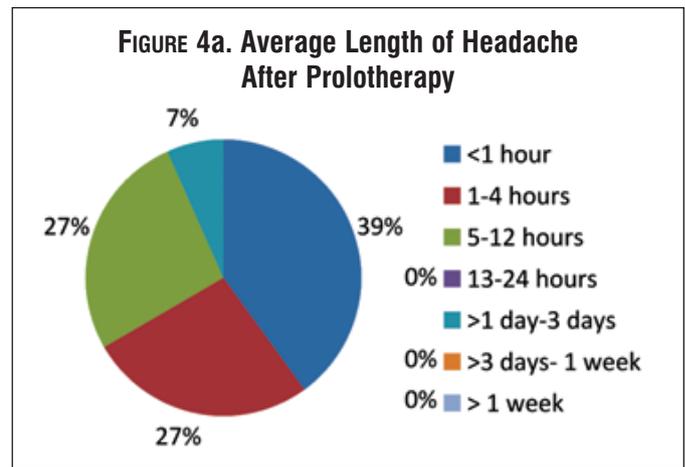
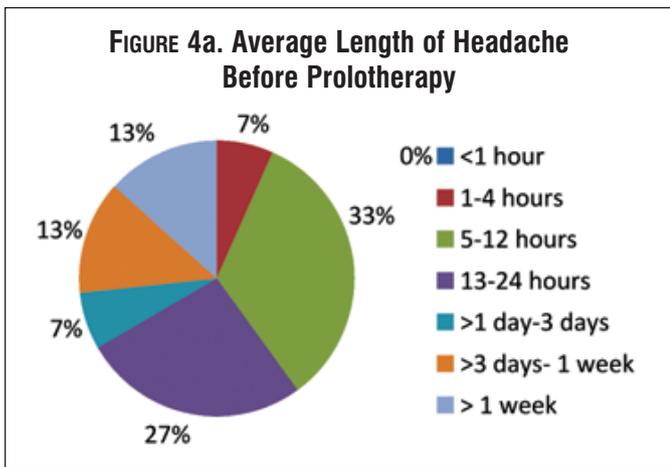


FIGURE 4a, 4b, 4c. Starting and ending average length of headaches before and after receiving Hackett-Hemwall dextrose prolotherapy in 15 patients with tension headache and migraine pain.

of prolotherapy. Thirty-three percent reported that the tension or migraine headache pain lasted between five and 12 hours. Twenty-seven percent experienced pain lasting between 13 to 24 hours. Thirty-three percent experienced tension or migraine headache pain lasting longer than 24 hours, ranging from one day to greater than one week. Following prolotherapy treatments, 39% experienced pain that lasted one hour or less. Fifty-three percent reported pain that lasted under 12 hours following the completion of their prolotherapy treatments (see Figure 4). Sixty-six percent reported improvement that continued an average of 22 months after the completion of prolotherapy treatments.

Associated Symptom Level Before and After Prolotherapy

Patients were asked to rate associated symptoms that generally accompany their headaches, such as nausea and vomiting, on a scale of 1 to 10—both before prolotherapy, as well as at the conclusion of the treatments. Twenty-seven percent rated the associated symptoms at a level of 10 prior to treatment. Following completion of prolotherapy treatments, 67% rated them at a level of one (see Figure 5, page 62).

Patients were also asked if the associated symptom relief was sustained following the completion of prolotherapy treatments.

Sixty-seven percent reported that the improvement continued. Only one patient (7%) reported that prolotherapy had not reduced the level of associated symptoms.

Sensitivity to Light

Sensitivity to light is a common complaint associated with tension or migraine headaches. Study participants reported on light sensitivity both prior to and following completion of the prolotherapy treatments, rating them on a scale of 1 to 10 (with 10 being the most severe). Sixty-seven percent reported a 10 out of 10 light sensitivity prior to treatment. After prolotherapy, 67% reported sensitivity levels of 1, indicating very little sensitivity to light during a headache. Improvement continued for most patients, with 73% reporting reduced sensitivity that had at least somewhat continued to the present (see Figure 6, page 62).

Overall Change in Tension Headache or Migraine Pain

Finally, study participants were asked to place themselves in one of six categories. Patients could choose one of the following answers:

1. I feel totally normal now.
2. It is radically better, but not totally normal.
3. I am very much better due to prolotherapy.
4. I am somewhat better due to prolotherapy.
5. I am not better from prolotherapy.
6. I am worse due to prolotherapy.

Thirty-nine percent experienced a complete resolution in their headache or migraine pain, stating that they “totally normal now.” All of the patients reported that they felt at least “somewhat better” due to their treatment with prolotherapy (see Figure 7, page 64).

Discussion

Principle Findings

The results of this retrospective pilot study strongly suggest that Hackett-Hemwall dextrose prolotherapy can play a role in decreasing intensity level, frequency, duration, number of associated symptoms and light sensitivity in patients with headache

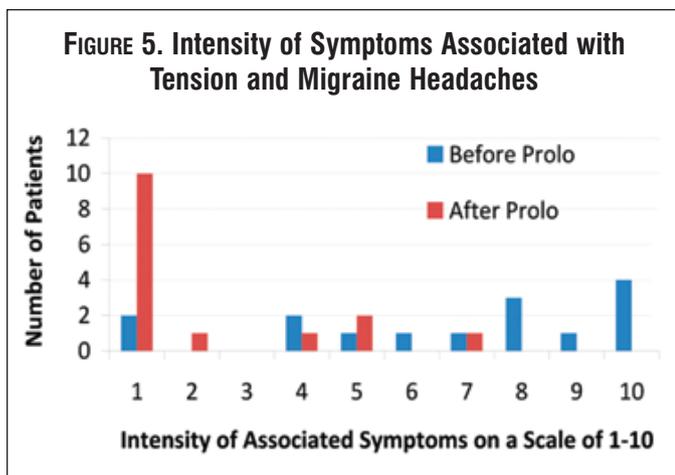


FIGURE 5. Starting and ending intensity of associated symptom level of headaches, on a scale of 1-10, before and after receiving Hackett-Hemwall dextrose prolotherapy in 15 patients with tension headache and migraine pain.

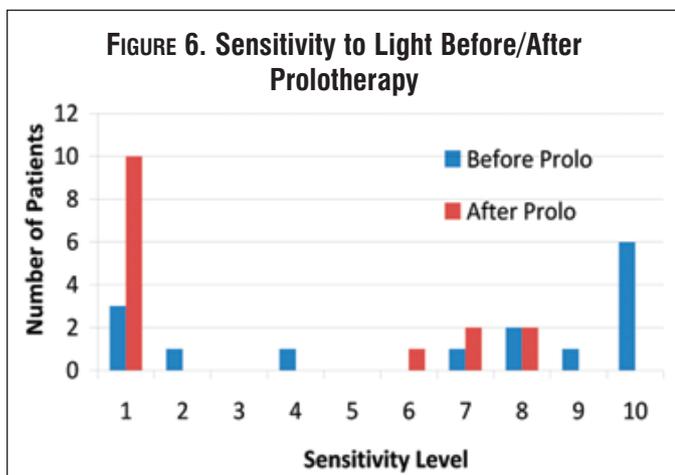


FIGURE 6. Starting and ending sensitivity to light before and after receiving Hackett-Hemwall dextrose prolotherapy in 15 patients with headache and migraine pain.

and migraine pain. One-hundred percent of patients reported they were at least somewhat better after receiving Hackett-Hemwall dextrose prolotherapy, with 39% of these patients reporting 100% improvement. Forty-seven percent of patients stated the intensity of their pain was almost not noticeable after receiving treatment. Notable improvements in the duration of time they suffered from headache pain was also experienced after treatment. Seventy-three percent of patients reported a decreased sensitivity to light during a headache. Symptoms associated with tension and migraine headaches decreased in 80% of the patients in this study.

Study Strengths and Limitations

By virtue of its design, this retrospective pilot study cannot be compared to randomized placebo-controlled clinical trials. Instead, its aim was to document the response of patients with headache and migraine pain to the Hackett-Hemwall technique of dextrose prolotherapy at a charity medical clinic.

Strengths of the study were that numerous parameters effecting tension headache and migraine headache sufferers were studied. Though the sample in this study was small (n=15), the quality of the cases treated is notable. 67% of the cases experienced at least three headaches or migraines a week, and 5 of the 15 participants reported headache or migraine pain occurring daily prior to treatment with prolotherapy.

As this was a charity medical clinic with limited resources and personnel, the only therapy offered was prolotherapy treatments given every three months. In private practice, by contrast, the Hackett-Hemwall technique of dextrose prolotherapy is typically given every four to six weeks. If a client is not improving or has poor healing ability, the prolotherapy solutions may be changed or strengthened or the client is advised about additional measures to improve their overall health. This can include advice on diet, supplements, exercise, changes in medications, additional blood tests, physiotherapy and/or other medical care. Often clients are immediately weaned off any anti-inflammatory and opioid medications that inhibit the inflammatory response that is needed to achieve a healing effect from prolotherapy. Since none of these were done, the results of this study are expected to represent the least optimum level of success achievable with Hackett-Hemwall dextrose prolotherapy.

Another shortcoming of this study was the subjective nature of some of the evaluated parameters including intensity, duration and frequency since the results relied on answers to questions by the patients. In addition to a lack of documentation of the patients' extensive history and physical examination, there was also a lack of X-ray or MRI correlation for diagnosis and response to treatment. Further, any additional pain management care that the patients may have been receiving was not controlled.

Interpretation of Findings

Hemwall-Hackett dextrose prolotherapy was shown to be effective in eliminating the frequency, intensity and length of tension and migraine headaches. In addition, there was a noted decrease of symptoms associated with these headaches after treatment, thus promoting an improved quality of life in patients receiving treatment. For the vast majority of the patients, this improvement continued to the time of this data collection (an average of 22 months after their last prolotherapy treatment).

The utilization of dextrose prolotherapy for relieving headaches was documented back in the early 1960s with research performed by Drs Hackett and Kayfetz. Good to excellent results were reported by Dr. Hackett in 90% of 82 consecutive patients he treated with neck and/or headache pain.^{32,33} Remarkable results were also reported by Dr. Kayfetz and associates who treated 206 patients for headaches due to a trauma. His results showed that in 79% of patients, prolotherapy completely relieved their headaches.³⁴

Could there be a pathophysiological relationship to headache and migraine pain? In a study reported in 2005, *Migraine Pain Location: A Tertiary Care Study of 1283 Migraineurs*, 39.8% of patients experienced pain located occipitally and another 39.7% reported neck pain. Headache location was not correlated with lifetime duration of migraine, intensity, or response to treatment. This study also noted a trend of occipital, neck and vertex trigger areas occurring with chronic migraine. In contrast, episodic migraine locations were more commonly found with or-

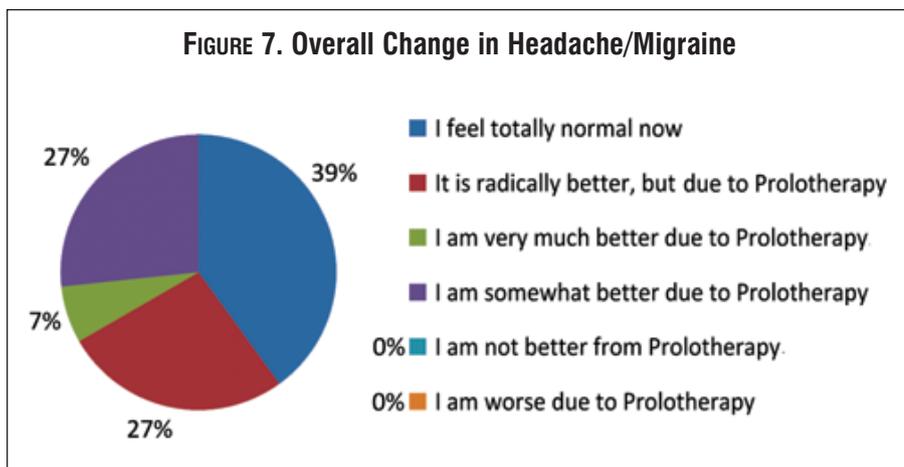


FIGURE 7. Overall changes in tension headache or migraine pain since last treatment of Hackett-Hemwall dextrose prolotherapy.

bital, frontal, and temporal pain. Age also was found to have a significant effect on headache trigger location. After age 50, the frequency of neck pain trigger sharply increased from approximately 40% at age 50 to over 50% by the age of 60.³⁵

The coexistence of headache and neck pain is common and so closely related that treatment of the neck is often necessary to reduce the frequency, intensity, and duration of the headaches.³⁶⁻⁴⁴ In a retrospective study done in one emergency room of patients treated for headaches, intramuscular injections of bupivacaine to the lower cervical muscles provided complete relief from headache pain in 65% of patients and partial relief was reported by an additional 20%.⁴⁵ The injections used in this pilot study were administered into areas of the cervical spine and posterior headache pain and/or tenderness.

In clinical experience, many people state their headache begins at the base of the neck and travels up the back of the head. The most important prognostic tool in such situations is found to be joint pain on palpation.⁴⁶ This is one of the main diagnostic tool used by physicians who perform Hackett-Hemwall prolotherapy. This is a significant clue that the etiology of the headache is in the neck and is producing referred pain, as described in the referral patterns of ligaments of the neck by George S. Hackett, MD, the father of prolotherapy.⁴⁷ This diagnosis may then also be verified immediately after prolotherapy injections containing an anesthetic are administered because it can bring about immediate pain relief to the treated structure or referral pain area, including headaches.⁴⁸

Comparison of pre- and post-study data in this pilot study demonstrated significant improvements across all indicators after patients received Hackett-Hemwall dextrose prolotherapy. This therapy has unique physiological effects that promote long-term repair of these soft tissue structures causing pain—including tension and migraine headache and neck pain:

- Pain is immediately alleviated due to the effect of the anesthetic in the prolotherapy solution and confirms the diagnosis of weak ligaments and tendons in the treated area.⁴⁹
- The proliferant in the prolotherapy solution, dextrose, stimulates localized inflammation which is necessary for the first stage of healing.^{50,51}
- Cells promptly respond to the inflammation by producing growth factors, or facilitators, causing fibroblastic proliferation (cells through which collagen is made and by which ligaments and tendons repair).^{52,53}
- Ligaments and tendons tighten and increase in mass, strength, and thickness due to the collagen tissue production following prolotherapy treatment^{54,55} Upon the final stage of healing, pain will typically subside because the ligament and tendon tissue has matured and strengthened.

The mechanism by which dextrose prolotherapy in this study effectively treated the tension and migraine headaches in these fifteen patients is presumed to be by stimulating cervical ligament repair. As of yet, there is no definite reliable clinical methodology to determine mild to moderate cervical ligament laxity and repair.

The current study followed patients, on average, 22 months after their last prolotherapy treatment and all 100% still had benefit from the prolotherapy they received. While this doesn't prove that ligament repair occurred, it does give credence to the notion that prolotherapy affected cervical structure and function in a positive manner in these patients. Whether dextrose prolotherapy can effectively treat all the headache-types equally is a question further research will have to answer.

Conclusions

In this retrospective pilot study the authors investigated the Hackett-Hemwall technique of dextrose prolotherapy (also known as regenerative injection therapy) on 15 patients with recurring tension or migraine headaches who were followed, on average, 22 months after their last prolotherapy treatment. The study objective was to determine the effectiveness of dextrose prolotherapy on alleviating recurring tension and migraine headache pain and associated symptoms. Phone interviews were conducted to gauge variations in frequency and duration of headaches, levels of pain, change in light sensitivity, and other quality of life measures before and after receiving dextrose prolotherapy.

Clinically significant improvements across all indicators were reported on completion of prolotherapy treatments including decreased intensity level, frequency, duration, number of associated symptoms and light sensitivity in patients with tension and migraine headache pain. One-hundred percent of patients reported they were at least somewhat better after receiving Hackett-Hemwall dextrose prolotherapy with 39% of these patients reporting 100% improvement. Forty-seven percent of patients stated the intensity of their pain was not noticeable after receiving treatment. Notable improvements in the duration of time they suffered from headache pain was also observed. Seventy-three percent of patients reported a decreased sensitivity to light during a headache. Symptoms associated with tension and migraine headaches decreased in 80% of the patients. Eighty percent of study participants reported that the reduction in tension or migraine headache pain as a result of prolotherapy mostly continued (with greater than 75% reduction in pain) since their last treatment. Seventy-three percent of participants re-

ported the improvement of the intensity of their tension or migraine headache pain since receiving their last prolotherapy treatment has continued to this day.

Since this pilot study found such significant improvement from these painful and debilitating conditions, further studies under more controlled circumstances and with larger patient numbers should be done. ■

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References

1. Silberstein SD et al. Classification of daily and near-daily headaches: field trial of revised HIS criteria. *Neurology*. 1996. 47:871-875.
2. Smith TR. Epidemiology and impact of headache: an overview. *Primary Care; Clinics in Office Practice*. 2004. 31:237-241.
3. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders, 2nd Ed. *Cephalgia*. 2004. 24(suppl 1):8-160.
4. Lipton RB et al. Medical consultation for migraines: results from the American migraine study. *Headache*. 1998. 38:87-96.
5. Rothrock JF et al. The impact of intensive patient education on clinical outcome in a clinic-based migraine population. *Headache*. 2006. 46:725-731.
6. Barrett EJ. Primary care for women: assessment and management of headache. *Nurse Midwifery*. 1996. 41:117-127.
7. Raak R et al. Work attendance despite headache and its economic impact: a comparison between two workplaces. *Headache*. 2003. 43:1097-1101.
8. Lipton RB et al. Medical consultation for migraines: results from the American migraine study. *Headache*. 1998. 38:87-96.
9. Wenzel RG et al. Over-the-counter drugs for acute migraine attacks: literature review and recommendations. *Pharmacotherapy*. 2003. 23:494-505.

10. Rothrock JF et al. The impact of intensive patient education on clinical outcome in a clinic-based migraine population. *Headache*. 2006. 46:725-731.
11. Zwart JA, et al. Analgesic use: a predictor of chronic pain and medication overuse headache. The Head-HUNT Study. *Neurology*. 2003. 61:160-164.
12. Katsarava Z et al. Incidence and predictors for chronicity of headache in patients with episodic migraine. *Neurology*. 2004. 62:788-790.
13. Limmroth V et al. Medication overuse headache. *Curr Opin Neurol*. 2004. 17:301-306.
14. Tepper SJ. Debate: Analgesic overuse is a cause, not consequence, of chronic daily headache. *Headache*. 2002. 42:543-547.
15. Goadsby PJ. Pathophysiology of headache. In: Silberstein SD, Limpton RB, Dalessio DJ, Eds. *Wolff's Headache and Other Head Pain, 7th ed.* Oxford University Press. Oxford, England. 2001. pp 57-72.
16. Bolay H et al. Intrinsic brain activity triggers trigeminal meningeal afferents in a migraine model. *Nat Med*. 2002. 8:136-142.
17. Spierings ELH. Mechanisms of migraine headache: the human evidence. *Headache & Pain*. 2003. 14:11-16.
18. Bahra A et al. Brain-stem activation specific to migraine headache. *Lancet*. 2001. 357:1016-1017.
19. Goadsby PJ et al. Migraine: current understanding and treatment. *N Engl J Med*. 2002. 346:257-270.
20. Pietrobon D et al. Neurobiology of migraine. *Nature*. 2003. 43:386-398.
21. Moskowitz MA et al. Neurovascular and molecular mechanisms in migraine headaches. *Cerebrovasc Brain Metab Rev*. 1993. 5:157-77.
22. Knight YE et al. The periaqueductal grey matter modulates trigeminovascular input: a role in migraine? *Neuroscience*. 2001. 106:793-800.
23. Wenzel R et al. Migraine headache misconceptions: barriers to effective care. *Pharmacotherapy*. 2004. 24(5):638-648.
24. Kelman L. Migraine Pain Location: A Tertiary Care Study of 1283 Migraineurs. *Headache*. 2005. 45(8):1038-1047.
25. Coeytaux RR et al. A randomized, controlled trial of acupuncture for chronic daily headaches. *Headache*. 2005. 45:1113-1123.
26. Sheeler R. Alternative treatments: Dealing with chronic pain. *Mayo Clinic Health Newsletter*. April 2005.
27. Hackett G. Referral pain and sciatica in diagnosis of low back disability. *JAMA*. 1957. 163:183-185.
28. Dorman T. Treatment for spinal pain arising in ligaments using Prolotherapy: A retrospective study. *Journal of Orthopaedic Medicine*. 1991. 13(1):13-19.
29. Klein R. Proliferant injections for low back pain: histologic changes of injected ligaments and objective measures of lumbar spine mobility before and after treatment. *Journal of Neurology, Orthopedic Medicine and Surgery*. 1989. 10:141-144.
30. Liu Y. An in situ study of the influence of a sclerosing solution in rabbit medial collateral ligaments and its junction strength. *Connective Tissue Research*. 1983. 2:95-102.
31. Maynard J. Morphological and biomechanical effects of sodium morrhuate on tendons. *Journal of Orthopaedic Research*. 1985. 3:236-248.
32. Hackett G. Prolotherapy in whiplash and low back pain. *Postgraduate Medicine*. 1960. pp 214-219.
33. Hackett G. Prolotherapy for headache. *Headache*. 1962. 1:3-11.
34. Kayfetz D. Whiplash injury and other ligamentous headache-its management with Prolotherapy. *Headache*. 1963. 3:1-8.
35. Kelman L. Migraine Pain Location: A Tertiary Care Study of 1283 Migraineurs. *Headache*. 2005. 45(8):1038-1047.
36. De Hertogh W et al. Management of headache disorders: design of a randomized clinical trial screening for prognostic patient characteristics. *BMC Musculoskeletal Disorders*. 2007. 8:38.
37. Jull G et al. A randomized controlled trial of exercise and manipulative therapy for cervicogenic headache. *Spine*. 2002. 27(17):1835-1843; discussion 1843.
38. Biondi DM. Physical treatments for headache: a structured review. *Headache*. 2005. 45:738-746.
39. Astin AJ et al. The effectiveness of spinal manipulation for the treatment of headache disorders: a systematic review of randomized clinical trials. *Cephalgia*. 2002. 22(8):617-623.
40. Nilsson N et al. The effect of spinal manipulation in the treatment of cervicogenic headache. *J Manipulative Physio Ther*. 1997. 20(5):326-330.
41. Van Etteken H et al. Efficacy of physiotherapy including a craniocervical training programme for tension-type headache: a randomized clinical trial. *Cephalgia*. 2006. 26:983-991.
42. Detar DT et al. Physiotherapy plus a craniocervical training programme was better than physiotherapy alone in tension type headache. Evidence-based medicine. 2007. 12(1):14.
43. Bronfort G et al. Non-invasive physical treatments for chronic/recurrent headache. *Cochrane database of systematic reviews (Online)*. 2007.
44. Lawler SP et al. A randomized, controlled trial of massage therapy as a treatment for migraine. *Annals Behav Med*. 2006. 32(1):50-59.
45. Mellick L et al. Treatment of headaches in the ED with lower cervical intramuscular bupivacaine injections: a 1-year retrospective review of 417 patients. *Headache*. 2006. 46(9):1441-1449.
46. Jull GA et al. Predictors of responsiveness to physiotherapy management of cervicogenic headache. *Cephalgia*. 2005. 25(2):101-108.
47. Hackett G. *Ligament and Tendon Relaxation Treated by Prolotherapy*. Charles C. Thomas. Springfield, Illinois. 1958.
48. Hauser R et al. *Prolo Your Pain Away!* Beulah Land Press. Oak Park, Illinois. 2007.
49. Hackett G. *Ligament and Tendon Relaxation Treated by Prolotherapy*. Charles C. Thomas. Springfield, Illinois. 1958.
50. Robbins S. *Pathologic Basis of Disease. Third Edition*. W.B. Saunders. Philadelphia, PA. 1984. pp 40.
51. Hauser R. *Prolotherapy: An Alternative to Knee Surgery*. Beulah Land Press. Oak Park, Illinois. 2004. pp 38-41.
52. Ibid.
53. Reeves KD. Prolotherapy: Basic science, clinical studies, and technique. In: Lennard, ed. *Pain Procedures in Clinical Practice*. Philadelphia, PA: Hanley & Belfus. 2000. pp 172-190.
54. Maynard J. Morphological and biomechanical effects of sodium morrhuate on tendons. *Journal of Orthopaedic Research*. 1985. 3:236-248.
55. Reeves KD, et al. Randomized prospective double-blind, placebo-controlled study of dextrose Prolotherapy for knee osteoarthritis with or without ACL laxity. *Alt Ther*. 2000. 6:68-80.