ORIGINAL ARTICLE

Side Effects and Adverse Events Related to Intraligamentous Injection of Sclerosing Solutions (Prolotherapy) for Back and Neck Pain: A Survey of Practitioners

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ABSTRACT. Dagenais S, Ogunseitan O, Haldeman S, Wooley JR, Newcomb RL. Side effects and adverse events related to intraligamentous injection of sclerosing solutions (prolotherapy) for back and neck pain: a survey of practitioners. Arch Phys Med Rehabil 2006;87:909-13.

Objective: To study the side effects and adverse events related to intraligamentous injection of sclerosing solutions (prolotherapy) for back and neck pain.

Design: Practitioner postal survey.

Setting: Postal survey of practitioners of prolotherapy for back and neck pain in the United States and Canada.

Participants: A sample of prolotherapy practitioners from 2 professional organizations were surveyed about their training and experience, use of specific treatment procedures, estimated prevalence of side effects, and adverse events related to prolotherapy for back and neck pain.

Interventions: Not applicable.

Main Outcome Measures: Prevalence of side effects and adverse events.

Results: Surveys were completed by 171 practitioners (response rate, 50%). Ninety-eight percent held medical degrees, and 83% were board certified in various disciplines. Respondents had a median of 10 years of experience, during which they had treated a median of 500 patients and given a median of 2000 treatments. Side effects with the highest median estimated prevalence were pain (70%), stiffness (25%), and bruising (5%). There were 472 reports of adverse events, including 69 that required hospitalization and 5 that resulted in permanent injury secondary to nerve injury. The vast majority (80%) were related to needle injuries such as spinal headache (n=164), pneumothorax (n=123), temporary systemic reactions (n=73), nerve damage (n=54), hemorrhage (n=27), nonsevere spinal cord insult (ie, meningitis, paralysis, spinal cord injury) (n=9), and disk injury (n=2).

Conclusions: Side effects related to prolotherapy for back and neck pain, such as temporary postinjection pain, stiffness, and bruising, are common and benign. Adverse events related to prolotherapy for back and neck pain are similar in nature to other widely used spinal injection procedures. Further study is needed to fully describe the adverse event profile of prolotherapy for back and neck pain.

Key Words: Adverse effects; Back pain; Neck pain; Rehabilitation; Sclerosing solutions; Spinal injections.

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PATIENTS WITH CHRONIC BACK and neck pain face a variety of treatment options. Without compelling evidence regarding the long-term efficacy of most conventional therapies, patients often turn to complementary and alternative medicine (CAM) for spinal care.[1] Lack of knowledge about the safety of particular CAM therapies may hinder their acceptance. This is especially true of the more invasive CAM therapies that have a greater potential for serious adverse events, such as injection of solutions into soft tissue (ie, ligament and/or tendon) to promote their growth and/or repair (prolotherapy).

Prolotherapy has been used for back and neck pain for more than 60 years for a variety of chronic musculoskeletal conditions.[2] This treatment approach was adapted from sclerosing injections used for soft-tissue disorders such as hernia and varicose veins. Prolotherapy involves repeated injection of various drug solutions commonly consisting of chemical irritants into ligaments and tendons. One of the proposed mechanisms is that prolotherapy induces the acute inflammatory cascade resulting in fibroblastic proliferation and collagen growth in chronically injured connective tissue.[3] This mechanism may partially explain the pain relief achieved with prolotherapy.

The safety of prolotherapy has been questioned openly in the literature by medical authorities and privately by a number of physicians.[4] Thus, its safety needs to be investigated. Dozens of clinical efficacy studies reporting on thousands of patients have not reported any serious adverse events (defined as life threatening, resulting in death, hospitalization, disability, or congenital anomaly, or requiring intervention to prevent permanent impairment or damage) related to prolotherapy for back and neck pain.[2,5] It is likely, however, that the incidence of serious adverse events is too low to be detected with these methods or is underreported in these studies. Research aimed at improving our understanding of adverse events related to prolotherapy must therefore use other methods of study (eg, surveys) capable of capturing a much larger population of patients exposed to this treatment. A questionnaire for practitioners of prolotherapy was recently developed to address this issue.

The primary objective of this study was to record the number, nature, and sequelae of adverse events related to prolotherapy for back and neck pain. Secondary objectives were to describe the training and experience of practitioners offering this treatment, determine the use of specific treatment procedures, and estimate the prevalence of common side effects.

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METHODS

Target Population

Postal surveys were mailed to members of the American Academy of Orthopaedic Medicine (AAOM) and the American College of Osteopathic Pain Management and Sclerotherapy (ACOPMS), 2 associations closely affiliated with prolotherapy conference. Surveys were also distributed to nonmembers attending the 2004 AAOM annual conference in La Jolla, CA. Excluded from the survey were association members and conference attendees identified by their credentials as being unable to practice spinal care (ie, podiatrists, dentists), whose postal address was invalid (eg, moved with no forwarding address, retired), or those living outside the United States or Canada. No compensation was provided for participating in the study. This study was determined to be exempt from full review by the Western Institutional Review Board (Olympia, WA).

Questionnaire Design and Distribution

The survey instrument contained 20 questions related to practitioner training and experience, use of specific treatment procedures, estimated prevalence of side effects, number of adverse events, and detailed adverse event reports regarding prolotherapy for back and neck pain (original survey instrument is available on request). To maintain anonymity, surveys were sent by postal mail, and participants were tabulated from numbers on the outside of the return envelopes, which were discarded before data entry. Nonresponders were sent 2 reminders by postal mail at 6-week intervals. Completed surveys were returned between April and September 2004. Survey results were recorded at the University of California at Irvine Statistical Consulting Center and independently verified by an investigator (SD).

Statistical Analysis

Descriptive statistical analysis was conducted by using statistical application software.[a] After observing skewed distribution curves for numeric data, median and interquartile (ie, 25th and 75th percentiles) values were reported along with the mean, standard deviation, and range. Median and interquartile values help minimize the potential effects of statistical outliers on a small dataset of this nature. Given the study design, no inferential statistical analysis was conducted.

RESULTS

Response Rate

Of the 314 AAOM members identified in the directory as practicing prolotherapy, 72 were excluded (9 could not practice spinal care, 51 had invalid addresses, 9 lived overseas, 3 did not practice prolotherapy). Of the 74 ACOPMS members in the directory, 8 were excluded (1 could not practice spinal care, 1 was deceased, 6 had invalid addresses). A total of 153 surveys were received from this population of 308 eligible members, a 50% response rate. An additional 18 surveys were completed by nonmembers attending the 2004 AAOM conference; the total number of responses was therefore 171.

Training and Experience

The most common degree reported was doctor of medicine (MD) (n=104), followed by doctor of osteopathic medicine (DO) (n=60). The most common medical specialties were physical medicine (n=53) and general practice (n=49). One hundred thirty-five of the 153 respondents were board certified in related disciplines. Respondents had learned prolotherapy through continuing medical education courses and by observing colleagues. Respondents had a median of 10 of years of experience with prolotherapy for back and neck pain, during which time they treated a median of 500 patients and provided a median of 2000 treatments. The spinal region treated most often with prolotherapy was lumbosacral (median, 60%) (tables 1, 2).

Table 1: Training of Practitioners Performing Prolotherapy for Back and Neck Pain

Variable	n
Degree	
Doctor of medicine	104
Doctor of osteopathy	60
Doctor of naturopathy	2
Nurse practitioner	2
Medical specialty	
Physical medicine	53
General practice	49
Other	21
Anesthesiology	18
Orthopedics	14
Internal medicine	10
Board certified	
Yes	135
No	28
Board discipline	
General practice	36
Pain management	25
Other	21
Physical medicine	20
Anesthesiology	2
Prolotherapy training	
AAOM course	99
Other	85
Observing a colleague	80
Ravin course	66
Hackett course	60

Use of Specific Treatment Procedures

Prolotherapy solutions typically contained multiple ingredients, primarily anesthetic (ie, lidocaine [n=109], procaine [n=40], marcaine [n=31]) and irritants (ie, dextrose [n=163], phenol [n=72], glycerin [n=64], sodium morrhuate [n=49], zinc [n=3]). Drug solutions were obtained from pharmacies (n=108), prepared by practitioners (n=87), or obtained from other sources (n=12). A minority of respondents administered local anesthetic injections (n=27), intravenous sedation (n=22), or oral sedation (n=12) before the injection procedure. Skin sterilization was performed with alcohol (n=95), alcohol and betadyne (n=40), betadyne (n=25), other (n=7), or none (n=4). The median needle length and gauge used in the lumbosacral region was 7.6cm (3in) by 22 gauge, larger than the median 5.1-cm (2in) by 25-gauge needle used in the cervical and thoracic regions. The median volume of drug solution injected during each treatment was higher in the lumbosacral region (15.0mL) than in the cervical and thoracic regions (10mL).

Side Effects

The side effect with the highest estimated median prevalence was pain (70%), followed by stiffness (25%), bruising (5%), and temporary numbness (1%). Other side effects listed on the

Table 2: Experience of Practitioners Offering Prolotherapy for Back and Neck Pain

Variable	Median	Mean ± SD	Range	Lower Quartile*	Upper Quartile†
Years of experience					
In practice	21	22±12	1–63	14	30
With spinal prolotherapy	10	12±9	1–63	6	15
Total no. of spinal prolotherapy					
Patients	500	2279±9234	1–110,000	100	1625
Treatments	2000	11,042±52,595	3–660,000	400	6000
% of spinal prolotherapy treatments in the					
Cervical region	25	23±15	0–100	10	20
Thoracic region	10	12±9	0–45	5	20
Lumbosacral region	60	65±10	0–100	50	80

Abbreviation: SD, standard deviation.
*Lower quartile is the 25th percentile.
†Upper quartile is the 75th percentile.

questionnaire (ie, headache, nausea and vomiting, skin infection, temporary numbness, temporary weakness) had a median reported prevalence of 0% (table 3).

Adverse Events

There were 472 adverse events related to prolotherapy for back and neck pain reported in this survey. The most commonly reported adverse events were cases of spinal headache (n=164), pneumothorax (n=123), temporary systemic reactions (n=73), and nerve damage (n=54). A total of 69 adverse events required hospitalization with the most common reason being pneumothorax (n=48). A total of 5 adverse events resulted in permanent injury, all secondary to nerve damage (table 4).

After compiling data from respondents, we made 2 revisions to the adverse event categories. The adverse-event categories meningitis/paralysis/spinal cord injury, presented separately in the survey, were combined into "spinal cord insult." This revision was made after reading comments and detailed adverse-event reports indicating that respondents were using these categories interchangeably to describe temporary symptoms such as lost or diminished sensation or strength in the lower limbs and so on. Similarly, the adverse event categories anaphylaxis/cardiopulmonary events/shock/systemic toxicity were combined into "temporary systemic reactions." This revision was made after reading detailed adverse-event reports and comments indicating that respondents were using some of these categories interchangeably to describe various types of rapid-onset, short-lived symptoms such as presyncope, syncope, dizziness, hypotension, and bradycardia. The revised categories better reflect the nature of the adverse events reported.

Detailed Adverse Event Reports

A total of 284 detailed adverse-event reports were received. Reports from 119 cases of spinal headache indicated they most frequently followed treatment in the lumbar region (n=82), had an onset of 1 to 24 hours (n=96), and required no treatment (n=58). Reports from 87 cases of pneumothorax indicated they most frequently followed treatment in the thoracic region (n=73), had an onset of 1 to 24 hours (n=43), and required hospitalization (n=46). Reports from 19 cases of temporary systemic reactions indicated they most frequently followed treatment in the cervical region (n=12), had an onset of 0 to 60 minutes (n=14), and required hospitalization (n=7). Reports from 14 cases of hemorrhage indicated they most frequently followed treatment in the lumbar region (n=12), had an onset of 1 to 24 hours (n=2), and required no treatment (n=3). Reports from 11 cases of infection indicated they most frequently followed treatment in the lumbar region (n=6), had an onset of more than 2 days (n=5), and required medication (n=9). Reports from 9 cases of spinal cord insult indicated they most frequently followed treatment in the cervical (n=4) and lumbar regions (n=4), had an onset of 0 to 60 minutes (n=7), required no treatment (n=4), and were not serious (ie, they did not result in hospitalization, permanent injury, or death).

Reports from 23 cases of nerve damage indicated they most frequently followed treatment in the lumbar region (n=13), had an onset of 0 to 60 minutes (n=12), and required no treatment (n=10). Detailed adverse-event reports were provided for 3 of the 5 cases of nerve damage that resulted in permanent injury. These indicated that the sequelae included 1 case of persistent mild to moderate leg pain, 1 case of persistent

Table 3: Estimated Prevalence (%) of Side Effects Associated With Prolotherapy for Back and Neck Pain

Variable	Median	Mean ± SD	Range	Lower Quartile*	Upper Quartile†
Bruising	5	13.9±20.7	0–100	1	20
Headache	0	1.8±7.9	0–100	0	1
Nausea and vomiting	0	0.8±1.8	0–10	0	1
Pain	70	57.9±36.7	0–100	21	95
Skin infection	0	0.2±1.9	0–25	0	0
Stiffness	25	36.3±36.5	0–100	0	75
Temporary numbness	1	13.4±25.5	0–100	0	10
Temporary weakness	0	1.4±3.8	0–30	0	1

*Lower quartile is the 25th percentile.
†Upper quartile is the 75th percentile.

Table 4: Number of Adverse Events Associated With Prolotherapy for Back and Neck Pain

Variable	Total	Requiring Hospitalization	Resulting in Permanent Injury
Diabetic complications	2	0	0
Spinal disk injury	2	1	0
Hemorrhage	27	2	0
Infection	18	4	0
Nerve damage	54	1	5
Pneumothorax	123	48	0
Spinal headache	164	6	0
Spinal cord insult	9	0	0
Systemic reactions	73	7	0
Total	472	69	5

numbness in a small area in the lower gluteal region, and 1 case of persistent numbness in the quadriceps. Respondents did not indicate how long they had followed up on these cases after the adverse event.

Malpractice Claims

A total of 13 malpractice claims related to prolotherapy for back and neck pain were reported by respondents, although the outcome of these claims was not assessed. The vast majority of respondents (n=157) did not report any malpractice claims related to this treatment.

DISCUSSION

To our knowledge, data from this survey provide the most comprehensive understanding to date of the training and experience of practitioners offering prolotherapy for back and neck pain, their use of specific treatment procedures, the estimated prevalence of side effects, and the nature and sequelae of adverse events related to this treatment approach. With regard to training, almost all (98%) respondents held MD or DO degrees, and many (83%) were board certified in related disciplines such as physical medicine and pain management. This indicates that prolotherapy, commonly considered a CAM treatment, is being practiced by conventionally trained physicians. In fact, some respondents reported learning about prolotherapy through conventional medical education such as a rotation (n=1), residency (n=2), fellowship (n=2), or preceptorship (n=2). Respondents were well-experienced clinicians with a median of 21 years in practice and 10 years administering prolotherapy for back and neck pain. The finding that the respondents provided a median of 2000 prolotherapy treatments to 500 patients agrees with published literature indicating that patients often receive 4 to 6 treatments at weekly to monthly intervals during the course of care.[2] The total number of patients treated by all respondents numbered in the hundreds of thousands, which is suggestive of a strong demand from patients for prolotherapy.

A clear majority of respondents reported injecting drug solutions that contained dextrose, glycerin, phenol, and lidocaine, whereas less than 2% still used zinc, one of the inappropriately strong chemical irritants that was implicated in serious adverse events related to prolotherapy in the 1950s.[6] Although reasons for favoring particular drug ingredients in prolotherapy solutions were not sought from respondents, conversations with practitioners have indicated that, absent compelling efficacy data regarding specific ingredients, those with greater perceived safety (eg, dextrose) are generally favored. Most practitioners obtained these drug solutions from pharmacies, although a sizeable portion reported preparing these themselves, making sterility a potential concern. However, because admixtures for injection (eg, lidocaine, methylprednisolone) are commonly prepared in physician offices without difficulty, it is reasonable to assume that customary vigilance regarding aseptic preparation is also being observed for prolotherapy solutions. Almost all (96%) respondents used common skin sterilization before the injections, thus minimizing the risk of infection.

A majority (87%) of respondents did not administer intravenous sedation before the injection procedure, thus reducing a potential source of complications. The heterogeneity in the use of specific treatment procedures such as the composition and volume of the drug solution injected, for example, may be attributable to a lack of standardization in the treatment approach taught in various continuing medical education courses on the subject.

The nature and estimated prevalence of side effects reported in this survey are consistent with observations from a randomized controlled trial of prolotherapy for chronic low back pain, which reported the following symptoms in its participants at least once during the course of care: increased pain (88%), increased stiffness (76%), headache (59%), nausea and diarrhea (42%), and other symptoms (56%).[7] Discrepancies in these figures and those reported in our survey are likely caused by differences in study methodology. Common side effects such as temporary pain and stiffness are consistent with a commonly proposed mechanism of action for prolotherapy. This theory purports that injection of irritants produces a controlled acute inflammatory response to stimulate fibroblastic proliferation and connective tissue repair.[3] Although these side effects appear benign and short lived, they may present a relative contraindication to this treatment for patients with a low pain threshold who could be adversely impacted by a temporary increase in pain. If practitioner are able to identify such patients a priori, clinical experience suggests that certain modifications (eg, light sedation, injection of smaller volumes, or lower than usual concentration of irritants) may be appropriate to minimize postinjection pain.

The majority (61%) of adverse events reported in this study consisted of spinal headache and pneumothorax. Both of these adverse events were easily treated, and neither resulted in any permanent sequelae. Other adverse events reported in this survey that may also have been caused by injection technique include disk injuries, nerve damage, spinal cord injuries, and hemorrhage. These injuries are similar in nature to those routinely reported after other common spinal injection procedures such as facet joint, epidural, or local injections.[8-12] Many spine clinicians perceive these common injection procedures as safe and prescribe them for their patients on a regular basis, despite lack of compelling evidence for their long-term efficacy.[12] It is also important to note that these injuries can occur irrespective of the drug being injected. Many of the detailed adverse event reports in our survey indicate that needle injuries occurred when probing for the desired injection site with the needle tip, before delivering the intended bolus of drug. Although we are aware that fluoroscopy is occasionally used for needle guidance by certain prolotherapy practitioners, this equipment is not widely available to many practitioners. Moreover, there is currently no evidence that this procedure leads to fewer needle injuries.

The other major group of adverse events reported in this survey consisted of temporary systemic reactions. Several comments from respondents indicated that these reactions were likely attributable to the local anesthetics contained in the solution, some of which are known to have the potential for these effects.[13-15] We were unable to ascertain if any true cases of systemic toxicity confirmed by abnormal laboratory values may have occurred as a result of adverse reactions to various

components of the solution injected. The absence of reported systemic toxicity may indicate that practitioners do not routinely monitor their patients for this possibility. This finding, however, is consistent with a previous randomized clinical trial that found no difference in pre- and posttreatment laboratory testing (ie, complete blood count, sedimentation rate, chemistry panel, thyroid function, urinalysis) between the group assigned to dextrose/glycerin/phenol injections or saline injections.[16]

The nature of adverse events reported in this study was similar to those from a previous survey of prolotherapy practitioners by Dorman[17] in 1993. The 95 respondents in that study had collectively treated 494,845 patients for a variety of conditions, with the most common indication being low back (69%) followed by other areas of the spine (20%). Respondents to that survey reported a total of 65 "complications." The most commonly reported complication was 29 cases of pneumothorax (2 of which required chest tubes), followed by 24 cases of allergic reactions and 12 other cases requiring hospitalization or resulting in transient or permanent nerve damage; few details were provided regarding the complications or their sequelae. That survey also reported that most respondents used a combination of dextrose, glycerin, and phenol in their prolotherapy drug solutions, which concurs with the results of our study.

We are well aware of the limitations and biases inherent to this study design. One of the most likely limitations of the study is recall bias. Given the design of the study (ie, written survey), recall bias may have played a role in the responses. Future researchers should account for potential recall bias in their study design. Considering the response rate of approximately 50%, 1 limitation is a potential participant bias. Given the number of participants who reported and provided details on adverse events, as well as the anonymity provided by our methods, the effect of participant bias was likely minimized. Another limitation is that physicians practicing prolotherapy for back and neck pain who were not members of the AAOM or ACOPMS were not surveyed; differences in the outcomes measured that may exist between members and nonmembers are unknown. There is also possible estimation bias, whereby large numbers such as total treatments may be overstated and small numbers such as adverse events may be understated. We thus declined to provide potentially misleading ratio data. Similarly, we refrained from making direct statements regarding the rate of reported adverse events per injection in this study given the uncertainty and high potential for recall bias in estimating both the numerator (ie, rare and likely underreported adverse events over a long period) as well as the denominator (ie, total number of treatments given and patients treated). Another reason for not emphasizing rates per injection or treatment was that the data reported in this survey were not normally distributed and skewed heavily by outliers, which would have made any reported rates difficult to interpret.

Nevertheless, data on rare adverse events are seldom captured in small clinical trials. Any insight about their nature and estimated occurrence gathered from physician surveys capturing a large patient population is useful to plan additional studies on the topic and provides interim data to both physicians and patients. Despite the limitations of data obtained from practitioner surveys, this study represents the most thorough examination of the nature, number, and severity of adverse events and side effects related to prolotherapy for back and neck pain and overcomes the low statistical power of clinical efficacy studies in estimating the incidence of rare adverse events.

CONCLUSIONS

The most frequently reported adverse events related to prolotherapy are similar to those associated with other commonly used spinal injection treatments and included spinal headache, pneumothorax, and nerve damage. Common side effects included pain, stiffness, and bruising, consistent with the injection procedure and purported mechanism of action of acute inflammation. The majority of practitioners offering prolotherapy for back and neck pain are board-certified physicians who learned this treatment approach through continuing education courses. Although heterogeneity exists in the use of specific treatment procedures, the use of drug solutions containing ingredients previously associated with serious adverse events has been discontinued. To better assess the true risk of adverse events related to prolotherapy for back and neck pain, future studies designed to overcome biases inherent to practitioner surveys should be conducted. Such studies should include (1) confirmation of self-reported survey data through independent audit of patient records for adverse events and (2) prospective, multicenter, longitudinal cohort studies of patients receiving prolotherapy to monitor and record adverse events. Data from these additional studies could then be used to more accurately estimate and evaluate any risks associated with this treatment approach.

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