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ORIGINAL RESEARCH

Approximately Three Years of Prolotherapy Experience of a Traditional and Complementary Medicine Center: An Epidemiologic Study

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Abstract
Objective: Prolotherapy is a regenerative injection-based treatment which is increasingly using in musculoskeletal disorders. There are studies about the usage of prolotherapy in diseases but there is not an epidemiological study in the literature. The aim of this study is to resolve the lack of epidemiological studies about prolotherapy.
Materials-Methods: Ten-thousand-three-hundred-nineteen patients who were applied to our outpatient clinic between January 1, 2017 and 2021 were included in the study.
Results: The number of patients' injured area was 10319 with the mean age of 54.2±13.8. 2886 male (28.0%) and 7433 females (72.0%) were evaluated, and 844 of these patients (8.2%) did not receive the treatment. The reasons for admission / treatment of the patients were 35.3% (3647) low back and hip pain, 33.9% (3503) osteoarthritis of the knee, 13.3% (1369) neck pain. The number of sessions was 3.90±2.0 for completed treatments. Treatment results of the patients showed a significant difference according to gender ($p<0.001$). There was a statistically significant difference between the mean number of sessions according to the gender of the patients ($p<0.001$). There was a significant relationship between the age of the patients and the treatment results according to the results of the one-way analysis of variance (Anova) ($p<0.001$). There is a significant difference between the mean of sessions according to the diagnosis distribution of patients ($p<0.001$).
Conclusions: Better results can be obtained with the right patient selection and informing the patient correctly. Epidemiological studies are of great importance to learn these.
Keywords: Prolotherapy, Musculoskeletal Disorders, Pain, Epidemiology

INTRODUCTION

Prolotherapy is a regenerative injection-based treatment that is commonly used for damaged or degenerated connective tissue healing of musculoskeletal disorders [1–3]. The word "prolotherapy" was used first by Dr. George Hackett in 1950 [1]. Chronic musculoskeletal pain occurs due to inadequate repair of connective tissue. Prolotherapy is used to improve this inadequate healing process for eliminating pain [1,4]. This is based on the idea of relieving pain by enhancing the ligaments with injections of irritating, cell proliferation-stimulating solutions. Prolotherapy injections are typically administered in or near the area with connective tissue dysfunction [5–7]. It is thought that the main mechanism of action of the solutions used in prolotherapy is that they increase fibroblast proliferation and collagen synthesis by stimulating the wound healing mechanism after ligament injections. In this way, the strength and thickness of the tendons and ligaments increase, thus stability can be achieved in joints with laxity [4,6,8,9].

The natural wound healing process underlies the mechanism of action of prolotherapy. In prolotherapy injections, local inflammation occurs in the area where the proliferate solution is applied, which triggers the release of growth factors and collagen deposition. Growth factors play a major role in tissue repair and cell proliferation in wound healing; angiogenesis, cell proliferation, extracellular matrix formation, cell differentiation. Proliferation occurs in human cartilage cells

exposed to a mixture of transforming growth factor (TGF), insulin-like growth factor-1 (IGF-1), basic fibroblast growth factor (bFGF). Human cartilage cells have the potential to form many growth factors. In addition, since the cells in the region secrete growth factors during the repair process after tendon and ligament injury, if the secretion of these factors is stimulated, a similar healing process will be initiated [4,10]. This is the basic logic in the mechanism of action of prolotherapy injections. Following prolotherapy, the healing process begins as a result of triggering inflammation or directly secreted growth factors and stimulated cytokines. By providing proliferation and strengthening of newly formed connective tissue, it also stabilizes the joint and causes pain and disability to decrease [4,8,11].

Irritant solutions are used for injections and performed into tender ligamentous and tendinous attachments [1213]. The most commonly used injectant solution in prolotherapy is hypertonic dextrose [3,5,14–16] Dextrose is an ideal proliferative solution for prolotherapy injections. It is a very safe substance because it is soluble in water and is included in the normal content of blood biochemistry. Being easy to obtain and being economical has been effective in its spread. Dextrose prolotherapy affects many mechanisms such as direct effect, osmotic effect, and inflammatory growth effect [4,8,15].

Our Traditional and Complementary Medicine Center of our hospital was opened on 1 January 2017 and were started to perform prolotherapy. Our standard procedure at the first examination of the patients, following the routine physical examination, complete blood, liver and bleeding serum biomarkers and direct radiographs are requested. Patients whose complaints continue despite conservative treatment were accepted for treatment. Patients with unstable hypertension/diabetes and treat with antithrombotic medicine cannot be discontinued through a cardiology consultation were not included in the treatment. All patients were reminded at each contact to avoid NSAIDs and to limit the overuse of the relevant area. Standard home exercise programs were prescribed for all areas. The range of motion and stretching exercises of the relevant area were started. After 2 weeks, strengthening exercises were added. The stretching and isotonic strengthening exercises were prescribed and patients have continued this program until the next control. Activities above the daily level might cause pain, so patients were restricted from activities in the first three days after the injection.

The epidemiological studies about traditional and complementary medicine are president in the literature, although, there is no epidemiologic prolotherapy study founded. This study aimed to classify age, gender, pain areas, diagnosis, number of sessions in patients with musculoskeletal disorders who applied to our center for prolotherapy.

MATERIALS AND METHODS

This was a retrospective epidemiologic study. Ten thousand three hundred nineteen patients who were applied to our outpatient clinic between January 1, 2017 and 2021 were included in the study. A local Ethics Committee approved the study protocols. (Study number: 2021/47, date:23.07.2021)

Forty one thousand nine hundred fifty six patients' registrations were done between 1 January 2017 and 2021. The patient is examined at the first application. If the treatment is not suitable for the patients (uncontrolled diabetes mellitus/ hypertension, antithrombotic medicine usage etc), their examinations and consultations are requested. At the next visit, it is decided whether it is suitable for treatment with these results or further examination is requested. As a result, the patient were classified as not received/ continue to the treatment, waiting for the treatment, the patient stopped treatment, the patient's treatment was terminated, and completed the treatment.

Not received: Immunodeficiency; cancer; active inflammatory or connective tissue disease; unstable hypertension; active endocrine disorder; and active neurological disorder; and usage of anticoagulants were the exclusion criteria's of the prolotherapy treatment. These patients are not appropriate for the treatment.

Continue: It refers to the patients whose treatment has not yet been completed as of January 1, 2021, and who are continuing the treatment.

Waiting for the treatment: The patient is appropriate for the treatment. The treatment is explained. If the patient does not take any conservative treatment, first of all, received associate policlinics. If conservative treatments used and did not sufficient, the exercises are described and the patient waits for his/her turn.

The patient stopped treatment: The prolotherapy treatment is a difficult application for the patient. Sometimes patients cannot tolerate the injections and give up the treatment.

The patient's treatment was terminated: Sometimes the patient does not do what is called and does not

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follow their follow-up so physicians terminate the treatment.

Completed the treatment: When the patient recovered, three follow-ups were done two months apart and was removed from follow-ups.

The recurrent records of the same patients with the same reason and records for acupuncture were excluded. Also, the records for the diagnosis and treatments of trigeminal neuralgia that requiring long treatment sessions were excluded in order not to affect the number of sessions.

Statistical analyses

Statistical Package for Social Sciences software (IBM 25.0) was used for the statistical analyses. The nominal variables were presented as number, percent and frequency, and continuous variables were presented as mean ± SD. The normality tests were performed first. The t-test (Independent Samples t Test), Anova (One-Way Variance Analysis) and Pearson Correlation test analysis were performed to evaluate the significance of the means' difference between two parametric independent groups as a result of the normal distribution of the data. The Post-Hoc Tukey test was conducted for the difference between the groups with significant differences. Chi-square analysis was used to compare categorical data. p significance value was accepted as 0.05 and 0.01.

RESULTS

The number of patients' injured area was 10319 with the age range of 2-103 (mean 54.2±13.8). Frequency of age is shown in Figure 1. 2886 male (28.0%) and 7433 females (72.0%) were evaluated, and 844 of these patients (8.2%) did not receive the treatment. 2094 patients' treatment (20.3%) were continuing, 715 were waiting for the treatment (6.9%), 642 patients (6.2%) stopped the treatment, 176 patients' treatment (1.7%) was terminated, and 5848 patients (5.7%) completed the treatment. The reasons for admission / treatment of the patients were 35.3% (3647) low back and hip pain, 33.9% (3503) osteoarthritis of the knee, 13.3% (1369) neck pain and 3.7% (384) back pain, 1.0% (106) synovitis-tenosynovitis, 2.0% (209) sprain, 0.6% (65) lateral epicondylitis, 0.4% (37) calcaneal spur, 0.03% (4) avascular necrosis, 0.5% (52) headache, 0.3% (33) fibromyalgia, 0.1% (10) trigger finger, 1.3% (138) other knee disorders, 2.1% (218) shoulder disorders, and 5.3% (544) other joints disorders. The number of sessions was 3,90±2.0 for completed treatments.

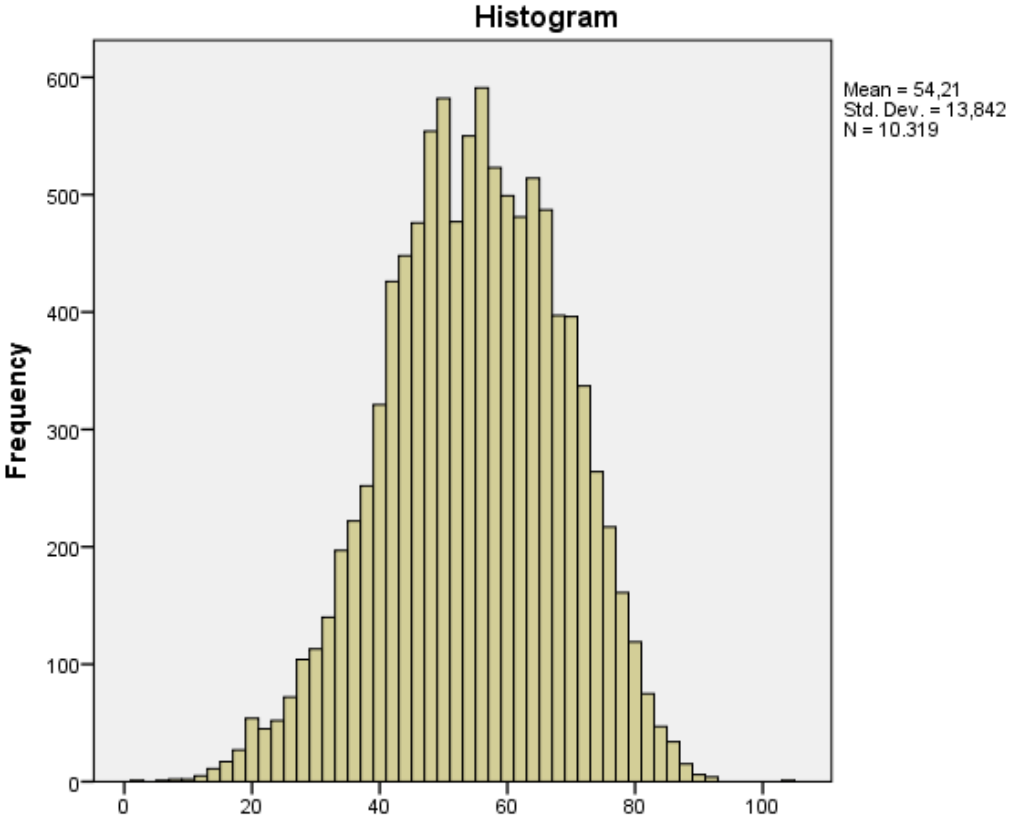

Figure 1. Frequency of Age

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Treatment results of the patients showed a significant difference according to gender (p<0.001) (Table 1). There was a statistically significant difference between the mean number of sessions according to the gender of the patients (p<0.001) (Table 2). There was a significant relationship between the age of the patients and the treatment results according to the results of the one-way analysis of variance (Anova) (p<0.001) (Table 3).

Table 1. Comparison of Treatment Results by Gender

Treatment Results	n / %	Gender		Total
		Male	Female	
Not received	n	304	540	844
	%	36.0	64.0	100.0
Continue	n	631	1463	2094
	%	30.1	69.9	100.0
Waiting for the treatment	n	221	494	715
	%	30.9	69.1	100.0
The patient stopped treatment	n	185	457	642
	%	28.8	71.2	100.0
The patient's treatment was terminated	n	42	134	176
	%	23.9	76.1	100.0
Completed the treatment	n	1503	4345	5848
	%	25.7	74.3	100.0
Total	n	2886	7433	10319
	%	28.0	72.0	100.0
Chi-Square: 51.719		p- value: <0.001		

n: Number

Table 2. Comparison of the mean number of sessions according to the gender

	Gender	n	Mean	SD	t	p
The number of sessions for overall treatments	Male	2886	2.77	2.279	-6.319	<0.001
	Female	7433	3.09	2.295		
The number of sessions for completed treatments	Male	1506	3.77	2.086	-2.848	0.004
	Female	4342	3.95	2.086		

n: Number; SD: Standard deviation

Table 3. Correlation of Patient Results with Age

	n	Mean	SD	F	p
Not received	844	50.73	17.1	45.264	<0.001
Continue	2094	52.60	12.9		
Waiting for the treatment	715	50.58	14.3		
The patient stopped treatment	642	54.70	13.5		
The patient's treatment was terminated	176	60.93	13.1		
Completed the treatment	5848	55.47	13.3		

n: Number; SD: Standard deviation

There is a significant difference between the mean of sessions according to the diagnosis distribution of patients (p<0.001) (Table 4).

Table 4. Comparison of the mean of sessions according to the diagnosis distribution of patients.

	Overall patients					Completed patients		
	n	Mean	SD	F	p	n	Mean	SD
Low back and hip pain	3647	3.17	2.4			1572	4.74	1.9
Osteoarthritis of the knee	3502	2.94	2.1			2620	3.35	2.0
Neck pain	1369	3.31	2.3			741	4.58	1.8
Synovitis-tenosynovitis	106	2.10	1.7			66	2.8	1.6
Back pain	384	2.48	1.8			118	3.4	1.7
Sprain	209	2.66	2.2			104	3.8	2.0
Other joints disorders	544	2.81	2.1			336	3.6	1.9
Headache	52	1.21	1.8	13.456	<0.001	5	3.5	1.7
Other knee disorders	138	1.96	1.7			80	2.6	1.6
Fibromyalgia	33	.79	1.4			6	2.3	1.0
Shoulder disorders	218	2.89	2.0			125	3.5	1.9
Lateral epicondylitis	65	2.65	1.9			38	3.6	1.7
Calcaneal spur	37	3.00	1.7			28	3.3	1.6
Avascular necrosis	4	2.25	1.5			3	3.0	0.0
Trigger finger	11	3.09	2.0			6	4.0	2.2

n: Number; SD: Standard deviation

DISCUSSION

This study tried to eliminate the lack of prolotherapy epidemiological studies that we could not find in the literature. Our center is in high demand in terms of prolotherapy. We did not find any other prolotherapy study with this amount of patient data in the literature. Ten thousand three hundred nineteen injured areas were evaluated in 3 years and 5848 were completed the prolotherapy treatment in our center. Although women prefer prolotherapy treatment 2.5 times more than men, the number of sessions required in the treatment of men was found to be less than women. The most common reasons to prefer the prolotherapy treatments were low back and hip pain and osteoarthritis of the knee nearly with the same ratio. Almost one out of three patients were preferred the treatment because of low back and hip pain, one for osteoarthritis of the knee, and one for remaining reasons. The most common remaining reason was neck pain. The area that needed the most sessions in the treatment was the neck.

The literature showed that the complementary and alternative medicine treatment users were mostly women (78.6%)[17]. Similarly in our study, 72% of the prolotherapy users were women. The patient's age range was wide, 2-103 years old (A two years old child was brought by his family due to his unresolved restlessness). The physicians did all patients' physical examinations, but injection applications were not preferred under fifteen years-old.

The most common pain along the spine belongs to the lumbar region. Chronic low back pain is one of the most common diseases and is one of the leading causes of labor loss in public[18]. It causes temporary or permanent disability[18,19]. Chronic low back pain is one of the most common indications for prolotherapy based on the repair and strengthening of the spinal ligaments. There is a debate in the literature about injection and exercise protocols for chronic low back pain, and studies have conflicting results[20]. Intra-articular prolotherapy injection is significantly superior to corticosteroid injection in sacroiliac joint pain. Although there was no significant difference in pain compared to intra-articular steroid injection, it was reported that long-term pain did not recur in the prolotherapy group[21]. In a randomized controlled study on sclerosing injections, it was reported that prolotherapy had similar results with lignocaine administered in combination with saline in chronic low back pain[22]. Injections were given once a week for 3 weeks, unlike normal administration. Another randomized controlled trial with 2x2 factorial for nonspecific chronic low back pain compared prolotherapy with saline injection and flexion exercise with no exercise therapy. All ligament injections caused significant decreases in pain and disability scores during follow-up. The results were found to be similar for prolotherapy and saline or for flexion exercises and daily life[20]. When integrated with spinal manipulation, exercise, and other interventions, prolotherapy may have a better effect on chronic low back pain and disability, but prolotherapy alone is not seen as an effective treatment for chronic low back pain[19]. Solmaz et al. used prolotherapy and exercise therapy together in failed back surgery syndrome and achieved success[8]. Another study of Solmaz et al. reported that 654 patients with low back pain or lumbar disc herniation were treated with prolotherapy and the Visual Analogue Scale (VAS) scores decreased from 7.2±1.1 before the treatment to 0.9±0.9 after 1 year of the treatment and only 34 patients had poor clinical results. A home exercise program was given with to the patients with the prolotherapy treatment in this study[23]. We are routinely used prolotherapy and exercise together and get good results.

A review of spinal pain mentions 26 observational cohorts and 5 randomized controlled 31 clinical prolotherapy trials conducted up to 2005. Indications in these studies were low back pain (22), neck pain (3), cervical headache (3), and back or chest pain (3). A total of 20 sclerosing solutions were used in these studies. The most commonly used sclerosing solution is a mixture of 12.5% dextrose, 12.5% glycerin, 1.25% phenol, and 0.25% lidocaine. It has been stated that there are wide differences in treatment protocols such as dose, number of treatments, and use of adjunct therapies. Most cohort studies were of only moderate quality, and they were found to differ greatly in terms of injectables and co-interventions[24]. The limitations in the methodologies of studies on prolotherapy treatment in mechanical low back pain and the heterogeneity of clinical protocols make it difficult to evaluate these studies collectively[19,25]. In most clinical studies, it has been demonstrated that although the differences between treatment and control groups are not always statistically significant, they report positive results such as reduced pain or disability[24]. In addition, Miller et al. the response to leg pain secondary to moderate to severe lumbar degenerate disc disease appears

promising in a case series[26]. We are using dextrose as prolotherapy solution in our center. Treatment is not completed when there is at least 50% improvement from baseline. When we complete the treatment, 3 control examinations are performed at 2-month intervals, pain complaints and physical examination and palpation are checked for pain, and when the improvement is confirmed, the treatment is considered to be completed.

There are 1921 regions (18.6%) whose sessions have not started regardless of the diagnosis. Some of them are those who were waiting for their turn to start the session, others were those who have applied from several regions at the same time and were waiting for their turn for the region. In addition, those who did not receive the prolotherapy, or had not received any medical treatment before, or/and where the only exercise was sufficient were included in this group.

The mean of sessions was found to be approximately 3. However, the range is very wide 1-13. The enthesofascial prolotherapy is applied 6 times at the most, but the neurofascial prolotherapy can be performed up to 13 times[4]. We prefer the neurofascial prolotherapy in older patients, we already have patients up to the age of 103.

Although the number of treatments terminated or stopped by patients due to the corona pandemic increases in 2020 data, it is still low compared to the total number. This treatment application is difficult for the patients, but that means pain is more difficult for them.

CONCLUSION

There are few studies in the literature on prolotherapy treatment demanded due to chronic musculoskeletal pain. As with other complementary and alternative medicine treatments, it is more preferred by women. Better results can be obtained with the right patient selection and informing the patient correctly. Epidemiological studies are of great importance to learn these. There is still a need for epidemiological prolotherapy studies, which are lacking in the literature.

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