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Research Article

Quality of Life in Patients with Lumbosacral Radicular Syndrome and Complete Rehabilitation Program (PRISUM PHSD/1/2022)

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Abstract

Worldwide, Lumbosacral Radicular Syndrome (L.R.S.) represents one of the most common lumbar spine problems, inducing disability, reduced quality of life, and working capability. We performed a prospective, double-blind, randomized study in the Departments of Physical Medicine and Rehabilitation, Filantropia Hospital, Craiova, and Techirghiol Balneal and Rehabilitation Sanatorium from June to October 2022. We analyzed the effects of ProHumano+ SpineDinamic (PHSD) on the severity reduction of radicular pain and improvement of quality of life in patients with L.R.S. over three months. A total of 247 patients were randomly divided into two groups: Group 1 (151 patients) received 10 sessions of the rehabilitation program and PHSD (daily, three months), and Group 2 (96 patients) received ten sessions of the rehabilitation program and placebo (daily, three months). Conventional physical therapy (transcutaneous nerve stimulation, ultra-sound, and low-intensity laser treatment) and kinetic program represented the components of a rehabilitation program. Statistical analysis was performed using Microsoft Excel (Microsoft Corp., Redmond, WA, U.S.A.), together with the XLSTAT add-on (Addinsoft SARL, Paris, France). All patients had a favorable evolution, but the difference was significantly statistic for G1 patients. These results concluded that daily PHSD for three months naturally affected clinical and functional status in L.R.S.

Keywords: Radicular; Pain; PHSD; Rehabilitation

Introduction

Globally, Lumbosacral Radicular Syndrome (L.R.S.) is among the most prevalent issues affecting the lumbar spine, significantly reducing the quality of life for patients and is one of the most encountered pathologies in primary care [1]. It is noted that approximately 3 to 5% of adults will encounter L.R.S. during their lifetime [2,3], serving as a primary contributor to prolonged disability [4], absenteeism from work, and increased utilization of long-term healthcare services with corresponding costs [5]. Lumbar Disk Hernia (L.D.H.), degenerative spondyloarthropathies, or lumbar spinal stenosis, including Lateral Recess Stenosis (L.S.S.), are frequent causes of L.R.S. [1,6,7]. Validated instruments indicate that the rate of radiculopathy resulting from lumbar disk prolapse is between 17% and 50% [8]. A clinical examination aims to identify common symptoms, such as radiating pain frequently accompanied by numbness, paraesthesia, and/or muscular weakness, and to determine if a nerve root has been mechanically impinged upon [9,10]. A neuropathic component of pain is often present in 36% to 55% of patients with spinal diseases, including L.R.S. Regarding mechanism, neuropathic pain syndromes are defined by the maladaptive plasticity of neurons, immune cells and neuroimmune inter-actions throughout the pain pathway, the causative mechanisms of which remain in-completely understood [11,12].

After a complete assessment of the L.R.S. patient, a complex rehabilitation program will be applied to regain and maintain the patient's quality of life and well-being. Treatment options for L.R.S. are diverse and may encompass medication as well as physical and kinetic programs (physiotherapy interventions are prescribed as first-line treatment, but their effectiveness remains controversial) [13] or surgical decompression (suggested for patients experiencing persistent symptoms such as progressive/ severe neurological impairment, including cauda equina syndromes, and/or enduring pain) [14,15]. The primary tasks in assessing and managing L.R.S. are to exclude signs and/ or symptoms of possible underlying severe pathology, focus on an active approach to promote natural recovery, and prevent chronicity through early tailored rehabilitation [16].

Typically, the selection of therapy involves integrating clinical recommendations with the unique status of the individual patient [17,18]. There is consensus (systematic reviews and clinical practice guidelines) that the first six to eight weeks of L.R.S. therapy should be conservative [19]. However, it's unclear precisely what the conservative approach entails at this point [20,21]. Recent research has highlighted the potentially complex roles of B vitamins in the maintenance of nervous system function, and deficiencies of which may result in peripheral nervous system disorders, as an adjunct to NSAID therapy, or in the treatment of neuropathic pain and symptoms of neuropathic conditions [22-26]. It has demonstrated the effectiveness of administering medications containing pyrimidine nucleotides (uridine triphosphate – U.T.P., cytidine monophosphate - C.M.P.) in reducing pain intensity associated with diabetic neuropathy, back pain, cervical pain, and trauma-compressive disorders [27], with neuro regenerative properties in the medium term [28]. The use of uridine and cytidine nucleotides associated with hydroxocobalamin had positive control of the intensity of chronic neuropathic low back pain, with a reduction in the consumption of rescue analgesics, thus improving and enhancing the quality of treatment [27,29], and in reducing the pain and improving the motor activity of the patients with alcoholic polyneuropathy [30]. Another combination - uridine monophosphate, folic acid, and hydroxycobalamin has been controlled in pain for patients with peripheral neuropathy and neuropathic pain and reduced the adjunctive use of analgesic or anti-inflammatory drugs [31].

Despite its classical role in calcium and phosphorus metabolism, vitamin D plays a vital role in the etiology and progression of various chronic pain conditions and associated comorbidities by exerting anatomic, hormonal, neurological, and immunological influences on pain expression [32,33]. This vitamin is involved in modulating neuroinflammation, maintaining neuroplasticity, and expressing neurotrophins in various physiological and pathological contexts. In the adult brain, vitamin D has both genomic and non-genomic actions on various neurological functions [34].

Taking into consideration all these recent studies, we performed a prospective study. We analyzed the effects of ProHumano+ SpineDinamic (PHSD) on reducing the severity of radicular pain and improving the quality of life in patients with L.R.S. over a three-month period. PHSD is a complex of nucleotides and vitamins B1, B6, B12, and D3, manufactured and supplied by PharmaLinea Ltd. (Ljubljana, Slovenia). The effectiveness of this product in controlling the clinical-dysfunctional status of patients with L.R.S. has yet to be studied. By combining nucleotides, vitamins B1, B6, B12, and D in a single tablet at the optimal dose, with the summation of the therapeutic effects of each vitamin, easy to ad-minister, we tried to prove the product's effectiveness in conditions of increased compliance.

Materials and Methods

Ethical approval

Before being included in the study, the details of the present research were explained to the patients. Written informed consent was obtained from each patient. The protocol was conducted in accordance with the Declaration of Helsinki and Good Clinical Practices and was approved by the local independent ethics committee (approval no. 9057/ 3rd May 2022).

Study Design

Our prospective, double-blind, randomized study was conducted in the Departments of Physical Medicine and Rehabilitation, Filantropia Hospital, Craiova, and Techirghiol Balneal and Rehabilitation Sanatorium from June 2022 to October 2022. Prior to the study, the clinical-paraclinical evaluation

protocol and the rehabilitation program were established in agreement with the specialists from the two centers. Therefore, there were no differences in approach.

A total of 300 patients with L.R.S. lasting more than three months were enrolled in this study, with a 2:1 ratio between the treatment groups. All patients have been previously diagnosed with L.D.H., degenerative spondyloarthropathies, or L.S.S. The study blinded both patients and investigators. Randomization was generated using the medication code, made by an independent physician.

Following the initial evaluation, 247 patients were randomly allocated into two groups: Group 1 (G1) underwent ten sessions of a rehabilitation program along with PHSD (daily, for three months), while Group 2 (G2) underwent ten sessions of a rehabilitation program along with a placebo (daily, for three months) (Figure 1).

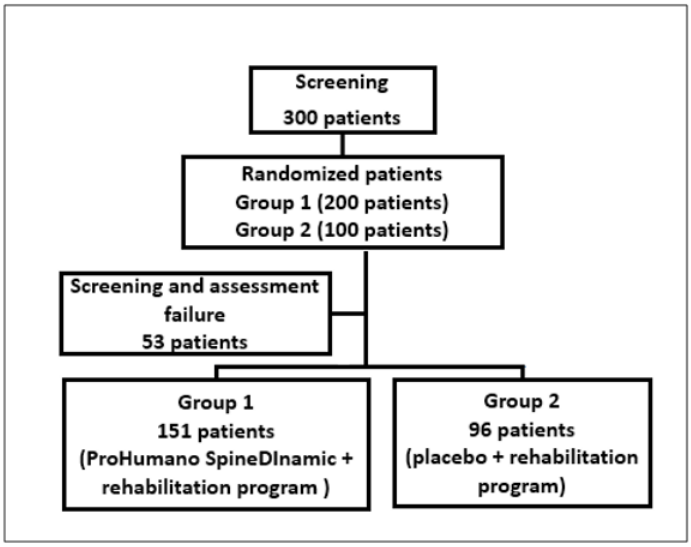

Figure 1: Diagram of our study.

The patients were included in the study in the order of presentation at admission. After the diagnosis, each patient was given a tablet without him or the attending physician being informed about the meaning of the code on the received tablet. The placebo and PHSD forms were identical but with a different code on the packaging. The rehabilitation program was carried out by an independent physiotherapist. The study team was the only one that grouped the patients, according to the diagram.

Each PHSD capsule contained 75.3 mg of Qspine® complex. Qspine® is a proprietary complex consisting of nucleotide complex and vitamins B1, B6, B12, and D3. Starch-based placebo products matched the size and weight of PHSD capsules to maintain blinding. Both products were developed, manufactured, and supplied by PharmaLinea Ltd. (Ljubljana, Slovenia). All subjects were instructed to take one capsule per day.

Conventional physical therapy (transcutaneous nerve stimulation, ultrasound, and low-intensity laser treatment) and kinetic program (stretching and postural control, lumbar strengthening, and stabilizing exercises) represented the components of the re-habilitation program performed by all patients.

All patients were followed daily for ten days, with the electrotherapy session in the morning and the kinetic program in the afternoon. The electrotherapy session included the three procedures applied at the lumbosacral level. The parameters for each procedure were those for analgesia, with a duration of 15 min for transcutaneous nerve stimulation, 10 min for ultrasound, and 5 min for low-intensity laser treatment.

The kinetic program had a duration of 30-40 minutes. Initially, it was applied passively so that the patient could learn the movement correctly, and later, it was actively assisted. Stretching was carried out for the paravertebral muscles, hamstrings, and adductors of the rib, as well as toning for the abdominal muscles and gluteus medius muscle. Postural control was achieved through walking and coordination exercises for the lower body. Inclusion and exclusion criteria are mentioned in Table 1.

Inclusion criteria	Exclusion criteria
patients over 18 years old	pregnancy or breastfeeding
lasting more than three months and diagnosed with L.R.S. confirmed by M.R.I. in the last six months;	need for surgical treatment
absence of other significant and disability lower limb osteoarthritis	intolerance to any component of the ProHumano+ SpineDinamic
patients with stable cardiovascular and respiratory function without unstable medical conditions;	use of other analgesic / AINS drugs
Compliance with physical exercise during the healthcare program.	malignancy
	modified laboratory test (ALT, AST, or Urea >2x% reference range, Creatinine >3x% reference range)

Table 1: Inclusion and exclusion criteria.

The study included two visits: pretreatment (Visit 1 / T1 - initial) and after three months (Visit 2 / T2 - final). These specific time points were selected to gauge the rate of improvement across all outcome measures effectively.

Patient's assessment

A precise evaluation of L.S.R. patients is essential to deliver appropriate management and treatment promptly upon initial presentation [35].

So, each study visit consisted of a clinical and functional assessment, vital signs measurement, and laboratory testing. After careful anamnesis (age, comorbid diseases), the clinical assessment included:

- General physical examination (body mass index – B.M.I.);
- musculoskeletal and neurological assessment involves a somatotopic examination, systematic palpation of all regions of the vertebral column, evaluation of range of motion (such as finger-to-floor distance - FFD, measured and recorded in centimeters; Schober test), assessment of tenderness and stability, manual muscle testing of the trunk and lower limb muscles, chronic lumbar root irritation and dysfunction (including straight leg raise - S.L.R. test, identification of radicular syndrome symptoms such as sensory loss, weakness, pain location, reflex loss, and myofascial syndrome);
- Evaluation of equilibrium and walking pattern (tip-toe walking).

During the examination, we conducted standard laboratory tests (screening, inflammation tests – fibrinogen and C reactive protein) and imagistic examination of the lumbar column (radiologic and M.R.I. exams).

The functional evaluation included:

- the VAS - Visual Analogue Scale (from 0 to 10, 0 = absence of pain and 10 = maxi-mum pain score; other values between 0 and 10 are directly proportional to the intensity of pain, depending on the individual pain threshold);
- The short-form McGill Pain Questionnaire (SF-MPQ) - a comprehensive tool for evaluating pain, comprising a sensory subscale with 11 items and an affective subscale with four items. Each item is rated on an intensity scale ranging from 0 (none) to 3 (severe) [36].
- the Katz Index of Independence in Activities of Daily Living (A.D.L.) - the most appropriate instrument to assess functional status as a measurement of the patient's ability to perform activities of daily living independently (the six functions of bathing, dressing, toileting, transferring, continence, and feeding are scored yes/no). A score of 6 indicates full function, 4 indicates moderate impairment, and two or less indicates severe functional impairment [37,38].

Safety was evaluated through the occurrence of adverse reactions throughout the treatment period.

Statistical analysis

Statistical analysis was performed using Microsoft Excel (Microsoft Corp., Redmond, WA, U.S.A.), together with the XLSTAT add-on for M.S. Excel (Addinsoft SARL, Paris, France). Data were recorded using Microsoft Excel files, and then it was statistically analyzed to find the relationship between the variables of interest for the two groups of patients.

To assess the normality of the data, we employed the Anderson-Darling and Shapiro-Wilk tests. Given that the data from the study did not follow a normal (Gaussian) distribution and involved numerical comparisons between two groups of patients, we predominantly utilized the nonparametric Mann-Whitney-Wilcoxon test instead of Stu-dent's t-test to identify significant differences among the values in the compared data sets.

We also used the nonparametric Spearman's rank correlation test to measure the strength of association between two ranked variables.

Results

We included a total of 247 LRS patients in our study; all patients followed the same re-habilitation program, but only 151 patients were treated with PHSD (G1). The remaining 96 patients received placebo treatment (G2).

Females and urban patients were dominant in both groups. Most patients were over-weight and between 50 and 79 years old (mean value - 61.33 years for G1 and 62.44 years for G2). All patients had chronic pain and a disability status of their A.D.L.s.

After the initial evaluation of the patients, the finalization of the two groups resulted in an unequal number of patients for the two groups. Although unequal in number, the two batches are homogeneous in the distribution for biographical data, maintaining a ratio of 1.5 (Table 2).

	Gender		Own Place		Age						Total
	F	M	U	R	<40	40-49	50-59	60-69	70-79	80-89	
G1	100	51	103	48	7	16	41	47	31	9	151
	66.23%	33.77%	57.29%	42.71%	4.64%	10.60%	27.15%	31.13%	20.53%	5.96%	100.00%
G2	62	34	55	41	6	10	17	32	26	5	96
	64.58%	35.42%	68.21%	31.79%	6.25%	10.42%	17.71%	33.33%	27.08%	5.21%	100.00%
Total	162	85	158	89	13	26	58	79	57	14	247
	65.59%	34.41%	63.97%	36.03%	5.26%	10.53%	23.48%	31.98%	23.08%	5.67%	100.00%
	p-value 0.7912		p-value 0.0814		p-value 0.5842						
	Profession		Previous Rehabilitation Program		BMI (kg/m^2)						Total
	A	R	Yes	No	UW	NW	OW	O1	O2	O3	
G1	61	90	103	48	1	40	58	35	11	6	151
	40.39%	59.60%	68.21%	31.79%	0.66%	26.49%	38.41%	23.18%	7.28%	3.97%	100.00%
G2	31	65	65	31	2	16	36	30	7	5	96
	32.29%	67.70%	67.71%	32.29%	2.08%	16.67%	37.50%	31.25%	7.29%	5.21%	100.00%
Total	92	155	168	79	3	56	94	65	18	11	247
	37.24%	62.75%	68.02%	31.98%	1.21%	22.67%	38.06%	26.32%	7.29%	4.45%	100.00%
	p-value 0.0534		p-value 0.9341		p-value 0.3990						

G1: ProHumano+SpineDinamic group, G2: Placebo Group; F: Female, M: Male, U: Urban, R: Rural, BMI: Body Mass Index, A: Active, R: Retired, UW: Underweight, NW: Normal Weight, OW: Overweight, O1: Obesity class 1, O2: Obesity class 2, O3: Obesity class 3

Table 2: Demographic parameters of patients.

For none of the analyzed qualitative variables, socio-demographics, or related to the history of the condition, we did not identify distribution differences between the two groups. Therefore, the two groups are perfectly compatible from the point of view of gender distribution, residential environment, age, profession, previous rehabilitation, and weight status (B.M.I.).

We noted a significant difference between G1 and G2 for B.M.I. in both moments of evaluation (Figure 2). In T1, the mean value (S.D.) was 28.57 (5.53) for G1 and 29.65 (5.07) for G2; in T2, the mean value (S.D.) was 28.34 (5.27) for G1 and 29.54 (4.89) for G2. These average values of B.M.I. were located in the overweight interval, which means that our patients were not obese but did not fit into the normal weight range.

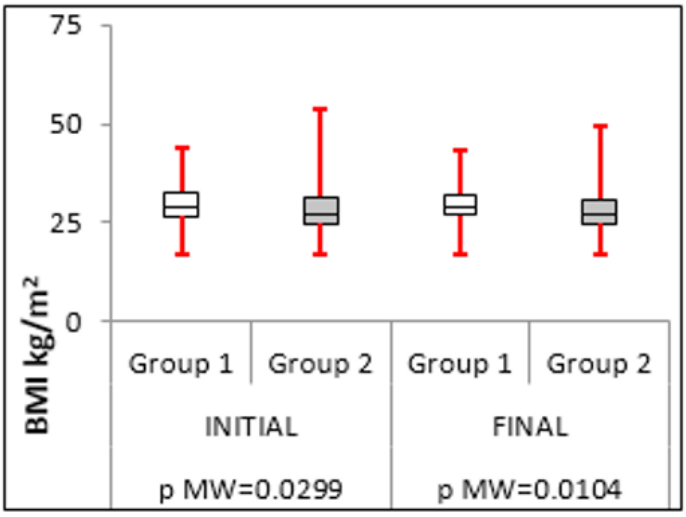

Figure 2: Body Mass Index - B.M.I. (kg/m^2) values in T1 (initial) and T2 (final) evaluation moments.

We prescribed a rehabilitation program (physiotherapy and kinetic program) as first-line management in L.R.S. Because physiotherapy and kinetic interventions are less effective in reducing pain at the medium term and disability at short- and medium-term time points, as mentioned in medical data [13], pain and functioning patients in G1 had been controlled with PHSD. No serious adverse events were reported during the study, so we have noted no treatment discontinuation in any of the groups.

In our study, patients in both treatment groups displayed significant improvement in all parameters in T2 compared to pretreatment status (T1) (Tables 3 and 4). With a few exceptions, the recorded variables did not follow a normal Gaussian distribution, as assessed with the Anderson-Darling normality test.

Vas scale de la 7.60 la 4.65, Short-form McGill Pain Questionnaire (SF-MPQ) de la 21.45 la 12.20, Katz Index of Independence in Activities of Daily Living (ADL) de la 3.83 la 4.15, and Clinical assessment. We considered six clinical parameters to follow in our research. All values are mentioned in Table 3.

G1 = PHSD patients G2 = placebo patients	**SCHOBER test**				**Finger-to-floor distance (FFD)**				**Manual muscle testing of the trunk (T.M.M.)**			
	Initial (T1)		**Final (T2)**		**Initial (T1)**		**Final (T2)**		**Initial (T1)**		**Final (T2)**	
	G1	**G2**	**G1**	**G2**	**G1**	**G2**	**G1**	**G2**	**G1**	**G2**	**G1**	**G2**
Minimum	1	0.5	1	2	0	0	0	0	0	4	0	0
Cuartila 1	3	2.5	3	3	17	14	12	12.5	4	4	4	4
Mediana	4	3	4	3	27	25	21	20	4	4	4	4
Cuartila 3	12.75	12.25	12.375	4.5	30	30	27	29.5	4	4	4	4
Maximum	24	16	20	20	73	55	70	60	5	5	5	4
G1 vs G2	NS	0.0994	**HS**	**0.0004**	NS	0.3536	NS	0.8282	NS	0.8618	NS	0.0913
Initial vs. Final G1	NS	0.1382			**HS**	**0.0004**			NS	0.2743		
Initial vs. Final G2	NS	0.4864			NS	0.0756			NS	0.1615		
Mean	6.90	6.26	6.88	5.37	25.30	22.88	20.94	20.28	3.98	4.01	4.02	3.95
Standard deviation	4.98	4.98	4.75	4.22	12.70	12.02	12.29	10.97	0.42	0.12	0.46	0.46

G1 = PHSD patients G2 = placebo patients	Straight Leg Raise test (S.L.R.)				Radicular Syndrome (R.S.)				Myofascial Syndrome (M.S.)			
	Initial (T1)		Final (T2)		Initial (T1)		Final (T2)		Initial (T1)		Final (T2)	
	G1	G2	G1	G2	G1	G2	G1	G2	G1	G2	G1	G2
Minimum	0	0	0	0	0	0	0	0	0	0	0	0
Cuartila 1	0	0	0	0	1.5	1.75	0.5	1	1	1	0	0
Mediana	0	0	0	0	2	2	1	1.5	1	1	0.5	1
Cuartila 3	1	0	0	0	2	2	1	2	1	1	1	1
Maximum	1	1	1	1	3	3	2	2	1	1	1	1
G1 vs G2	S	0.0029	NS	0.4259	NS	0.4896	S	0.0321	NS	0.1250	S	0.0237
Initial vs. Final G1	**HS**	**0.0000**			**HS**	**0.0000**			**HS**	**0.0000**		
Initial vs. Final G2	**HS**	**0.0003**			**HS**	**0.0000**			**HS**	**0.0003**		
Mean	0.40	0.22	0.07	0.04	1.73	1.72	0.86	0.95	0.82	0.90	0.61	0.68
Standard deviation	0.49	0.42	0.25	0.20	0.62	0.56	0.56	0.63	0.38	0.31	0.49	0.47

Table 3: Clinical parameters values in all studied patients.

Analyzing the differences between the values obtained between the patients from the two groups (Figure 3), we noticed that, for the T1 moment, there was a statistically significant difference only for the S.L.R. test (those from the G2 group having lower values, p Mann-Whitney=0.0029>0.05). At the T2, statistically significant changes between G1 and G2 were recorded for the Schober test (p Mann-Whitney=0.0004<0.001), radicular syndrome (p Mann-Whitney=0.0321<0.05), and myofascial syndrome (p Mann-Whitney=0.0237<0.05). In the straight leg raise test, G1 patients recovered more than those from G2, but the difference between groups didn't reach statistical significance (p Mann-Whitney=0.4259>0.05).

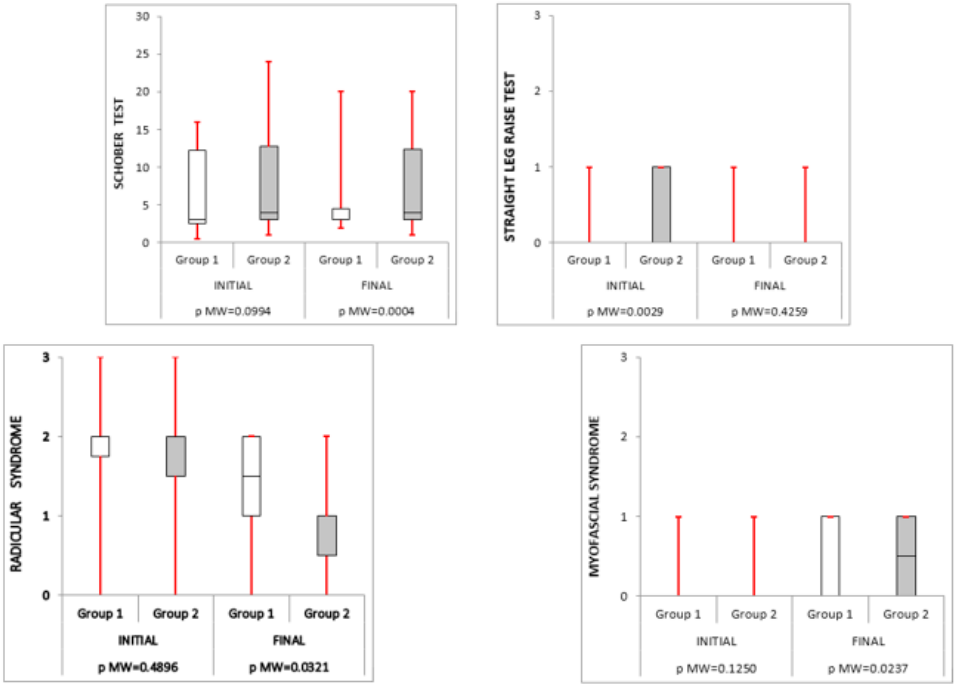

Figure 3: The six clinical parameters are values in the T1 (initial) and T2 (final) evaluation moments. Schober test - S.T., a finger-to-floor distance – FFD, manual muscle testing of the trunk – T.M.M., straight leg raise test - S.L.R., radicular syndrome - R.S., myofascial syndrome - M.S.

Within the group comparison between both time points revealed that a statistically significant difference was achieved in the finger-to-floor distance test for G1 (p test Wilcoxon<0.001), while the same group achieved better improvements in the Schober test, but the difference wasn't significant (p Wilcoxon=0.1382).

Both groups scored highly statistically significant changes in the straight leg raise test (p test Wilcoxon<0.001), radicular syndrome (p Wilcoxon test<0.001), and myofascial syndrome difference (p test Wilcoxon<0.001). We consider the clinical relevance of the obtained results necessary for the category of patients studied. No other pharmaceutical products were administered to control the pain parameter, with the exception of Pro Humano+SpineDinamic. By reducing the pain status, the kinetic program was optimally performed, with a favorable clinical and functional impact.

The lab data was followed by other parameters studied. There were no significant differences in biochemical and inflammatory parameters between the groups. This aspect permitted the application of rehabilitation programs in safe conditions.

Functional assessment was performed with three scales, mentioned in Table 4. All patients had moderate impairment; the mean value of Katz Index of Independence in Activity of Daily Living (A.D.L.) was nearly 4, with mention that after three months of PHSD treatment, the value was 4.15.

G1 = PHSD patients G2 = placebo patients	VAS scale				Short-form McGill Pain Questionnaire (SF-MPQ)				Katz Index of Independence in Activities of Daily Living (A.D.L.)			
	Initial (T1)		Final (T2)		Initial (T1)		Final (T2)		Initial (T1)		Final (T2)	
	G1	G2	G1	G2	G1	G2	G1	G2	G1	G2	G1	G2
Minimum	0	2	0	2	2	4	0	0	0	0	0	0
Cuartila 1	7	7	4	4.75	16	17	8	11	4	3	4	2
Mediana	8	8	5	6	21	23	12	17	4	4	5	5
Cuartila 3	8	8.25	6	7	28	28.25	15.5	22	5	5	6	5
Maximum	10	10	8	8	38	39	29	37	6	6	6	6
G1 vs G2	NS	0.8162	HS	0.0000	NS	0.2952	HS	0.0000	NS	0.3804	S	0.0183
Initial vs. Final G1	HS	0.0000			HS	0.0000			NS	0.1515		
Initial vs. Final G2	HS	0.0000			HS	0.0000			HS	0.0002		
Mean	7.60	7.59	4.65	5.55	21.45	22.45	12.20	16.03	3.83	3.68	4.15	3.71
Standard deviation	1.50	1.33	1.68	1.53	8.55	8.37	6.91	7.54	1.69	1.70	2.09	2.02

Table 4: Functional parameter values in all studied patients.

Analyzing the differences between the values obtained between the patients from the two groups (Figure 4), we noticed that, for the moment T1, there was no statistically significant difference for any of the three parameters. By the T2, participants in G1 reached highly significant improvements in the VAS scale (p Mann-Whitney<0.001), SF-MPQ (p Mann-Whitney<0.001), and A.D.L. scale values (p Mann-Whitney=0.0183<0.05), when compared to patients in G2.

Within the group, the comparison revealed that both groups recorded highly significant differences through VAS (p Wilcoxon test<0.001) and SF-MPQ measurements (p Wilcoxon test<0.001). Only G1 reached a highly significant difference by T2 on the A.D.L. scale (p Wilcoxon test=0.0002<0.001), while for outcomes of G2, no significance has been found in the difference from T1 to T2 (p=0.1515>0.05).

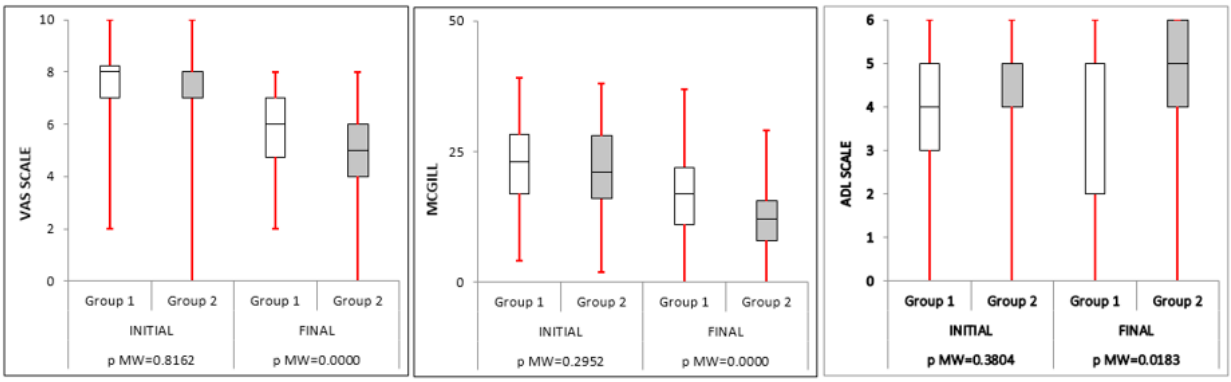

Figure 4: Functional parameter values in T1 (initial) and T2 (final) evaluation moments. VAS SCALE = Visual Analogue Scale, MCGILL = the short-form McGill Pain Questionnaire (SF-MPQ), ADL SCALE = the Katz Index of Independence in Activities of Daily Living.

We analyzed the correlation between the imagistic aspects (X-ray and M.R.I.) and the functional parameters variables (VAS, SF-MPQ, A.D.L.) with the aid of Spearman's correlation coefficient. The values in Table 5 represent Spearman's rho coefficient of correlation.

G1 in T1						**G1 in T2**					
Variables	**M.R.I. 1**	**X-RAY 1**	**A.D.L. 1**	**VAS 1**	**SF-MPQ 1**	**Variables**	**M.R.I. 2**	**X-RAY**	**A.D.L. 2**	**VAS 2**	**SF-MPQ 2**
M.R.I. 1	**1**	**-**	0.0698	0.2136	0.1570	MRI 2	**1**	-	-0.1239	0.2185	0.1408
X-RAY 1	-	**1**	**0.2663**	-0.0263	**0.1944**	X-RAY 2	-	**1**	0.1261	**-0.2658**	-0.1335
ADL 1	0.0698	**0.2663**	**1**	0.1252	-0.0996	ADL 2	-0.1239	0.1261	**1**	**0.2312**	0.1071
VAS 1	0.2136	-0.0263	0.1252	**1**	**0.5906**	VAS 2	0.2185	**-0.2658**	**0.2312**	**1**	**0.6499**
SF-MPQ 1	0.1570	**0.1944**	-0.0996	**0.5906**	**1**	SF-MPQ 2	0.1408	-0.1335	0.1071	**0.6499**	**1**
G2 in T1						**G2 in T2**					
Variables	M.R.I. 1	X-RAY 1	A.D.L. 1	VAS 1	SF-MPQ 1	Variables	M.R.I. 2	X-RAY 2	A.D.L. 2	VAS 2	SF-MPQ 2
M.R.I. 1	**1**	**-**	-0.0141	-0.1564	-0.3135	MRI 2	**1**	-	0.2466	-0.2999	-0.2259
X-RAY 1	**-**	**1**	0.0364	-0.0034	0.2223	X-RAY 2	-	**1**	0.0327	0.1116	0.2454
ADL 1	-0.0141	0.0364	**1**	0.1828	-0.0474	ADL 2	0.2466	0.0327	**1**	**0.5156**	0.1846
VAS 1	-0.1564	-0.0034	0.1828	**1**	**0.6568**	VAS 2	-0.2999	0.1116	**0.5156**	**1**	**0.6846**
SF-MPQ 1	-0.3135	0.2223	-0.0474	**0.6568**	**1**	SF-MPQ 2	-0.2259	0.2454	0.1846	**0.6846**	**1**
G1: PHSD patients, G2: placebo patients, T1: initial, T2: final											

Table 5: Correlation matrix (Spearman) / Group 1 and Group 2 / T1 and T2.

Values in bold are different from 0 with a significance level of 0.05 (95% confidence). For all measurements and groups, we have a highly significant correlation between VAS and SF-MPQ. For the initial data (T1), we found significant correlations between X-ray and A.D.L. (rho=0.2663) and X-ray and SF-MPQ (0.1944), and M.R.I. and VAS (rho=0.2136), for the G1 and a strong negative correlation between the M.R.I. staging and SF-MPQ (rho= - 0.3135), in the G2. For the second exam (T2), we found a significant correlation between VAS and A.D.L. (rho= 0.2312) in the G1 and a highly significant positive correlation be-tween the VAS and A.D.L. (rho= 0.5156), in the G2. Also, X-RAY and VAS (rho= -0.2658) were negatively correlated in the G1. These observations support the continued treatment for the period of 90 days among all patients with L.R.S.

Discussion

While L.R.S. guidelines emphasize the significance of clinical, functional, and imaging assessments for patients, recommendations regarding pharmacological interventions need to be more consistent. Uncertainty persists regarding their effectiveness in L.R.S. patients [39]. In cases of lumbar radicular pain accompanied by chronic nerve irritation and dysfunction, interventional procedures might be contemplated if initial attempts with physical therapy or medication prove ineffective [40]. More and more concerns are raised regarding the nerve's ability to regenerate themselves and regain their functional balance. This process can be facilitated by supplementing the diet with substances such as B vitamins, vitamin D, nucleotides (uridine monophosphate and cytidine monophosphate ribonucleotides), antioxidants, amino acids, Omega-3 fatty acids [29,41].

In our study, we approached two original aspects: the first – the type of pathology studied- and the second - the effectiveness of combination PHSD in regaining functional status and pain control in L.R.S. patients. As we mentioned previously, all patients had a favorable evolution, but the difference was a significant statistic for G1 patients. These results permitted us to conclude that daily PHSD for three months generated a natural effect on clinical and functional status in L.R.S. Based on the available literature [42], we considered three months as an optimal duration of conservative treatment to improve patient outcomes, primarily pain and functioning, especially that L.R.S. is a neuropathic pain condition, often associated with compression and inflammation of the nerve roots [43].

A large majority of patients studied had a positive outlook on pain and disability. Our study set out to demonstrate that PHSD could be included in recovery algorithms of L.R.S. patients. In addition, we also followed the inflammatory markers (C-reactive protein and fibrinogen) levels for all patients, along with screening lab tests. All lab tests had normal values without statistically significant correlation.

In the last two decades, many studies concluded the effectiveness and safety of vitamin B and nucleotides (alone or in combination with vitamin B12) in combating neuropathic pain and regeneration of peripheral nerves, but no study was performed in L.R.S. patients [28]. Furthermore, unlike other combinations, PHSD contains vitamin D, with a complex role in the human body. Although there are various studies on the complex role of vita-min D, no study exists to associate the three B vitamins (B1, B6, and B12), vitamin D, and the two nucleotide-monophosphate (uridine and cytidine) in pain control. Since we can-not refer to other similar studies, we will refer to the most critical data for each of the component elements of PHSD. Certainly, the cumulative benefit of the six components of PHSD (vitamins B1, B6, and B12, vitamin D, cytidine, and uridine monophosphate) substantiates the results obtained.

The complex role of vitamin B. In the last five years, four studies were performed and mentioned the efficacy and safety of vitamins B1, B6, and B12 in neuropathic pain and peripheral nerve regeneration:

- The B complex vitamins play a role in facilitating nerve repair by expediting nerve tissue regeneration and enhancing nerve function recovery through diverse mechanisms. A recent review has provided a succinct overview of the physiological and biochemical characteristics of vitamins B1, B6, and B12 in this context. [44].
- The high-dose combination of vitamins B1, B6, and B12 in a set dosage has demonstrated effectiveness in managing mild to moderate peripheral neuropathy of diverse origins. Additionally, it is well-tolerated and has been associated with enhanced quality of life for patients. [45].
- The neurotropic vitamins B1, B6, and B12 exhibit a biochemical synergy within various pathways of the nervous system, encompassing cellular energy processes, anti-oxidative and neuroprotective effects, as well as the synthesis of myelin and neuro-transmitters. Their combined application is beneficial in treating disorders of the peripheral nervous system. [25].
- Studies have indicated that the administration of vitamin B1, B6, and B12 forte therapy influences clinical outcomes, including pain and mobility, in patients with peripheral neuropathy stemming from diverse causes such as diabetes mellitus, nutritional deficiencies, entrapment or carpal tunnel syndrome, or idiopathic origins. [46].
- Medications containing pyrimidine nucleotides. Nucleo-cytidine-monophosphate shows promise as a new therapeutic agent that can complement conventional prescribed regimens [47]. The cytidine-uridine-hydroxocobalamin complex:
- Reduced the intensity and quality of pain in patients suffering from chronic neuropathic low back pain and was an efficacious adjuvant of the multimodal approach for treating chronic neuropathic lumbar pain [27].
- It demonstrates a beneficial impact on alleviating pain and enhancing functionality in the management of degenerative orthopedic conditions with neural compression [48].

- Was safe and effective in the treatment of patients presenting with alcoholic poly-neuropathy. At the conclusion of the treatment, there were notable decreases in the number of patients experiencing pain, paresthesia, altered motor coordination, and changes in vibration perception compared to observations made before the treatment. [30].
- The treatment proved to be both safe and efficacious in managing neuralgias resulting from neural compression linked to degenerative orthopedic conditions and trauma. [49].

The complex effects of vitamin D on the immune (reduction of the synthesis of inflammatory cytokines and an increase in anti-inflammatory cytokines), cardiovascular system, oncogenesis, cognitive functions, and nervous systems (neuropathic pain and peripheral nerve regeneration) are increasingly recognized in recent years [50]. Vitamin D has a pleiotropic function in the human body, including protection from skeletal muscle atrophy, improves proprioception, and many others [51].

A vitamin D deficiency is highly prevalent, and it is now considered a pandemic. Several studies have demonstrated the association between vitamin D deficiency, the spine, and joint morbidities [52]. Low Vitamin D levels are implicated in various chronic pain conditions. Research has shown that Vitamin D exerts anatomic, hormonal, neurological, and immunological influences on pain expression and manifestation [34,35], thereby playing a role in the etiology and maintenance of chronic pain states and associated comorbidity [53].

The researchers' interest in vitamin D therapy and conditioning for patients diagnosed with low back pain or discogenic pain is justified by clinical trials [54]. Supplementing Vitamin D in patients with chronic low back pain who are deficient may result in a reduction in pain intensity (measured by a visual analog scale) and improvement in functional ability (McGill Pain Questionnaire or Oswestry disability questionnaire) and apart from the normalization of the levels. Controlled clinical trials in the future are necessary to validate the theory [55]. Patients of all ages may be affected by vitamin D deficiency, which may be the root cause of unexplained musculoskeletal discomfort. Skeletal muscle strength is associated with vitamin D status. It is an issue that may be resolved, and supplementation may be used as a follow-up treatment for musculoskeletal pain. [56,57].

All of the investigations indicated that vitamin D is a neurosteroid and has a neuroprotective impact on a variety of neurological illnesses despite its traditional role in the metabolism of calcium and phosphorus [58]. Nevertheless, the neuroprotective mechanisms of Vitamin D remain incompletely understood in current experimental studies, and most clinical investigations in this area are observational and of limited scale, con-straining its broad application. It showed for the first time, in an animal model of nerve trauma, that cholecalciferol (vitamin D3), delivered at a high dose, induces a significant locomotor and electrophysiological recovery, with values indistinguishable from control animals [59]. In 2014, another study demonstrated that in a rabbit model of facial nerve trauma, vitamin D3 administered at a dosage of 200 IU/kg/day for 12 weeks notably enhances functional recovery and myelination. [60].

After laboratory studies, clinical trials mentioned that vitamin D (its active form – calcitriol) is involved in the regulation of neuronal-cell differentiation and axonal homogeneity of peripheral nerves [61], modulation of neuro-inflammation, maintaining neuro-plasticity, and expression of neurotrophins in various physiological and pathological contexts [34].

PHSD combination. We consider that this combination of two nucleotides, vitamin D and three important B vitamins, supports the typical operation of the peripheral nervous system due to its pyridoxine and thiamine ingredients (with optimal concentration like the necessary daily dose); vitamin B12 has an analgesic effect, controlling myelin sheath synthesis. Furthermore, PHSD contributes to a normal energy metabolism due to its pyridoxine content, an essential aspect of rehabilitation programs in patients with L.R.S. Due to Vitamin D, PHSD supports the musculoskeletal system health and neuropathic pain control. This aspect is essential and beneficial in the treatment because a neuropathic component of pain is often present in patients with spinal diseases, with a frequency ranging from 36% to 55% of patients, implying a higher occurrence correlated with lumbar spine stenosis than other causes [22].

In the last two years, the researchers mentioned [40, 62] that L.R.S. patients have mixed pain; nerve root impingement is supplied by distorted neurodynamics in the course of inflammation that accompanies every degenerative process. Vitamin D receptors are found in several parts of the nervous system, indicating that PHSD has a protective role in preventing neurotoxicity and aiding in detoxification pathways due to its vitamin D content [63].

In our study, we followed the guidelines for approaching lumbosacral radiculopathy through initial conservative management (education, physical therapy, and kinetic pro-gram) [64,65], but the replacement of anti-inflammatory medication with PHSD. We considered, like Chou et al. [66], that it is more timely first to consider conservative management for appropriate pain control and functional status rehabilitation, and we have to carefully weigh the advantages against the disadvantages before prescribing medication in our chronic L.R.S. patients. According to current guidelines, pharmacotherapy remains a mainstay in first-line treatment for neuropathic back pain [13].

Also, we approached the patients from the perspective of the biopsychosocial model. It must always be taken into account that the painful status, complex and multifactorial [67], affects the capacity to carry out everyday tasks and can cause damage to the somatosensory system, leading to long-lasting incapacity, which can have significant economic and social repercussions. [3].

Considering the physical, functional, and quality-of-life impacts of L.R.S., it is essential to explore several therapy options to identify the most suitable treatment for each patient at the appropriate stage of their illness progression. [68].

We are convinced that future studies will consider PHSD in the complete conservative management of L.R.S. patients.

LIMITS of our study

We consider that the present study has the following limitations:

- We did not perform a differentiated analysis by type of disease (L.D.H., degenerative spondyloarthropathies, or L.S.S.), considering that the disability of the patient with L.R.S. is the most important for the rehabilitation program;
- We did not dose the level of vitamins prior to the PHSD administration because their concentration in the PHSD pill does not exceed the required daily dose. If the patients had needed post-dosing vitamin supplements, the results would not have been influenced only by the studied combination;
- We did not use specific scales for the assessment of neuropathic pain [69] because the patients had mixed pain, as stated in other studies [70]. We considered that the McGill Pain Questionnaire offered a suggestive image of our patient's pain status, as other studies show [45].
- This clinical trial has not been registered in a public repository. We considered that the limited number of patients and the development in only two medical centers only contain an experimental dimension that will later be expanded accordingly.

Conclusions

- Taking into account the neuropathic dimension of the patient's pain with L.R.S. and the individual effects of each component of PHSD, we conclude that the association of vitamins B1, B6, and B12, vitamin D and the two nucleotide-monophosphate (uridine and cytidine) is an optimal and safe method in this type of pathology.
- Our results indicate that our randomized control trial is viable and has produced evidence on the appropriate therapy (PHSD and rehabilitation program) for patients with L.R.S. Larger, multicenter cohort studies with larger age groups are needed to confirm the present results.
- This recommendation should be adopted by healthcare professionals and healthcare systems worldwide to implement the most effective care, especially in age groups for which anti-inflammatory medication is not indicated.

Author Contributions

Conceptualization, M.R.T., and D.K.; methodology, M.R.T., D.K., A.M.K. AND K.K.C.; software, D.O.A.; validation, M.R.T., D.K., A.M.K., and K.K.C.; formal analysis, M.R.T., and A.M.K..; investigation, M.R.T., and D.K.; resources, M.R.T. and D.K.; data curation, M.R.T., and D.K.; writing—original draft preparation, M.R.T., and D.K.; writing—review and editing, M.R.T., A.M.K., and D.K.; visualization, M.R.T., and D.K.; supervision, M.R.T., and D.K.; project administration, M.R.T., and D.K.; funding acquisition, M.R.T. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Institutional Review Board (or Ethics Committee) of the University of Medicine and Pharmacy Craiova (approval no. 9057/ 3rd May 2022) for studies involving humans.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

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