Retrospective Study

Plasma Rich in Growth Factors (PRGF) in the Treatment of Cervical and Lumbar Back Pain: A Retrospective Observational Clinical Study

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Background: Plasma rich in growth factors (PRGF) is a leukocyte-free platelet-rich plasma (PRP) that is an effective biological approach to tissue repair and has been demonstrated to significantly improve multiple conditions, including low back pain and degenerative disc pathology.

Objectives: The objective of this retrospective study was to analyze the effectiveness of treating both cervical and lumbar spine pain with minimally invasive infiltrations of PRGF-Endoret.

Study Design: Retrospective study design.

Setting: Outpatient private practice facility.

Methods: The effectiveness of PRGF has been assessed by patient-reported outcomes (PRO) through validated questionnaires, namely Numeric Rating Scale (NRS) for back pain, Spine Tango Core Outcome Measure Index (COMI) Questionnaire for lumbar and cervical pain, and OSWESTRY Disability Index questionnaire for lumbar pain cases. Score differences between pre- and post-treatment have also been assessed stratified for multiple sub-groups of patients based on the sector of the column treated, gender, and age.

Results: This study includes 65 patients (18 with cervical pain and 47 with lumbar back pain). The average time of back pain evolution was 10 years. Patients received at least 2 PRGF infiltration series about one month apart. Each patient received intervertebral disc and epidural infiltrations, root infiltrations, in case of radicular injury, and intraarticular infiltrations, in case of osteoarthritis of the facet joints. Results show statistically significant ($P < 0.05$) improvements on all analyzed scores. Regarding the stratified analyses, 249 (99%) sub-groups showed an improvement in all tests (252 cases overall). From the 249 improving cases, 154 (62%) showed a statistically significant difference between the pre- and the post- treatment periods.

Limitations: This research is a retrospective study with a relatively small sample cohort. Only PRO have been assessed.

Conclusions: According to the results obtained in this study, and taking into account their limitations, PRGF infiltrations are an effective and minimally invasive biological strategy in the treatment of both cervical and lumbar pain, evaluated according to PRO.

Key words: Back pain, degenerative disc disease, growth factors, intervertebral disc degeneration, plasma rich in growth factors, platelet-rich plasma, regenerative medicine, tissue engineering

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Cervical and low back pain are conditions that affect an increasing number of individuals, in part, as a result of the increase in life span, as well as sedentary lifestyles (1). According to the last Global Burden of Disease, back and neck pain present the world's largest disease burden related to years lived with disability and is overall the fourth leading cause of disability adjusted life years (2,3). The overall point

prevalence mean in the general population is estimated at approximately 7% for cervical pain and 14% for low back pain (4,5); both conditions have high recurrence rates (6). From the economic standpoint and taking into account the data from the US, neck and low back pain account for the third-highest amount of health care spending ($87.6 billion in 2013), and is the second-leading condition that increased its spending between 1996 and 2013, with $64.4 billion spent over 18 years (7). Therefore, there is a need to find cost-effective treatments for these conditions.

Minimally invasive biological approaches have emerged to overcome the limitations of current treatments and speed up recovery times (8,9). Among them, autologous platelet-rich plasma (PRP) therapies have been included in the treatment of chronic low back pain (10), being applied through minimally invasive techniques to specific spinal structures for the treatment of degenerative disc pathology (11-16), in order to suppress the low-grade inflammation and restore homeostasis (17). However, to the best of our knowledge, the description of treatment of cervical spine pain with PRP is limited to one case report (18).

Plasma rich in growth factors (PRGF) technology has been widely used as a minimally invasive biological approach to induce tissue repair and improve numerous clinical conditions of musculoskeletal system (19), including spinal structures (20,21). The treatment of spine pathologies with PRGF, namely protrusion and herniated intervertebral disc (IVD); spinal roots; neuritis produced by radicular compression, due to the direct compressive effect of the herniated disc; etc, provides pain attenuation, chondroprotection, and anti-inflammatory effect (17).

We have previously published a retrospective study evaluating only low back pain, using a simple score, visual analogue scale (21). The aim of the current retrospective study was to analyze the effectiveness of treating both cervical and lumbar spine pain with PRGF infiltrations, as assessed by patient-reported outcomes (PRO), through validated questionnaires, namely Numeric Rating Scale (NRS) for back pain, the Spine Tango Core Outcome Measure Index (COMI) Questionnaire for lumbar and cervical pain cases, and the Oswestry Disability Index questionnaire for lumbar cases.

Methods

Study Design and Patients

This retrospective study was performed according to the STROBE Statement guidelines (22). Anonymized database of patients with lumbar and cervical pain due to different lesions and who received medical treatment with PRGF infiltrations in the Barcelona Traumatology Institute and Eduardo Anitua Clinic between January 2016 and June 2019, were retrospectively reviewed. Patients provided informed written consent and were treated according to the clinical protocol of the centres. This study was performed in accordance with the international ethical standards from the latest revised World Medical Association Declaration of Helsinki (Brazil, 2013) (23).

The inclusion criteria are as follows: patients of both genders, aged between 18 and 76 years, with symptoms of low back pain or cervicalgia, of at least 3 months of evolution, that have not responded to drug treatment, diagnosed by Magnetic Resonance Imaging (RMI), with a minimum of one month of follow-up, and who have completed all baseline and follow-up questionnaires. Patients with the following scenarios are included: 1) degeneration of the lumbar IVD, classified in the Pfirrmann's system between 3 and 4 (24); 2) degeneration of the cervical IVD according to the classification of Miyazaki (25) or Suzuki (26); 3) positive signs visible on MRI, including rupture of the annulus fibrosus, annular fissure, with or without a herniated disc; 4) presence of sciatica or brachialgia produced by radicular compression, due to the direct compressive effect of the herniated disc; 5) patients with indirect trauma with mechanical disc overload; 6) patients who have finally relapsed after previous treatments with analgesic medications, muscle relaxants, and anti-inflammatories; 7) lumbar fracture, extruded herniated discs, and hernias with signs of calcification; 8) endplate lesions as Modic changes (MC) type 1-3, or other subchondral lesions (hernias of Shmörl); and 9) patients who have undergone previous spinal surgery or rhizolysis.

Exclusion criteria includes patients with severe cardiovascular diseases, central nervous system diseases, epilepsy, coagulopathies, immunological diseases, infectious diseases, morbid obesity, cancer, etc; history of drug use and mental illness or psychological conditions related to pain; pregnant or breastfeeding women; and pathologies that produce alteration of coagulation or platelets.

PRP Preparation

PRP was prepared according to the PRGF-Endoret method (27,28). Peripheral venous blood was with-

drawn (72 mL) and collected in 9-mL tubes containing sodium citrate (3.8% wt/vol) (Endoret Traumatology kit, BTI Biotechnology Institute, S.L., Vitoria, Spain). Subsequently, the tubes were centrifuged in the PRGF-Endoret System centrifuge. The 2 mL plasma fraction located just above the buffy coat (F2 fraction) was collected without aspirating leukocytes or erythrocytes. Activation of PRGF was performed just before infiltration by adding PRGF activator (10% calcium chloride).

Antibiotic Prophylaxis and Sedation

After the blood collection, 2 g of cefazolin was administered. An anaesthetist performed mild intravenous sedation with a combination of 2.5 mg of Midazolan hydrochloride (1 mg/mL, Normon Laboratories, Madrid, Spain) and 3.2 mg/kg of fentanyl citrate (0.05 mg/mL, Kern Pharma, Barcelona, Spain) in 100 mL of saline. Additionally, depending on the duration of the procedure, a single dose, or repeated doses of 1-2 mg/kg Propofol (1%, BBraun Medical, Barcelona, Spain) were administered.

Contrast Agent

An iodinated contrast agent was used (Iohexol 300 mg/mL, Omnipaque, GE-Healthcare, Madrid, Spain) in order to get a better view of the structures to infiltrate. Contrast was only used when strictly necessary and always diluted (20% in saline).

Cervical Infiltration Protocol

The patient was placed in supine position and their head was fixed with a frond to the cranial extension of the special table for fluoroscopy. The patient was then immobilized with wide, cross-shaped plasters, leaving the entire neck free to ensure the precision of the infiltration in the objective. IVDs were first infiltrated for reasons of asepsis, which are accessed through the anterolateral route of Smith. A small skin surgical incision was open and a 22G x 90 mm needle (Spinal Needle Quincke) with the last 15 mm curved towards the bevel plane was inserted. Infiltrations of the IVD were performed under a C-arm fluoroscope, using an oblique angle at 25°-30° and tilted towards podalic about 7°-10°, until finding the parallelism with the 2 endplates next to the disc to be infiltrated. Once the disc was reached, controls were performed in anterior-posterior and lateral view to determine the correct depth of the needle. Then, 1.0 - 1.5 mL of activated PRGF were infiltrated in the nucleus pulposus (Fig. 1a). This infiltration produced intervertebral diastasis, which helped grant the access needed to perform epidural infiltration. It was advanced to the posterior wall, passing 1 - 1.5 mm behind it, and then very slowly 1.5 mL of activated PRGF was infiltrated. In the case of the joints, the lateral approach was taken under fluoroscopic control and 1 mL of activated PRGF was infiltrated with a short needle (Spinal Needle Quincke).

Finally, intraosseous intravertebral infiltration (20) was performed when the injured disc (protrusion, hernia, or intervertebral collapse) was in close contact with one or both of the neighbouring vertebrae, whose endplates also showed lesions, such as large Schmorl's nodes on one endplate or both (29), detectable osseous subchondral edema, recent or old fractures, or endplate lesions with advanced MC 1-3 signs. The approach

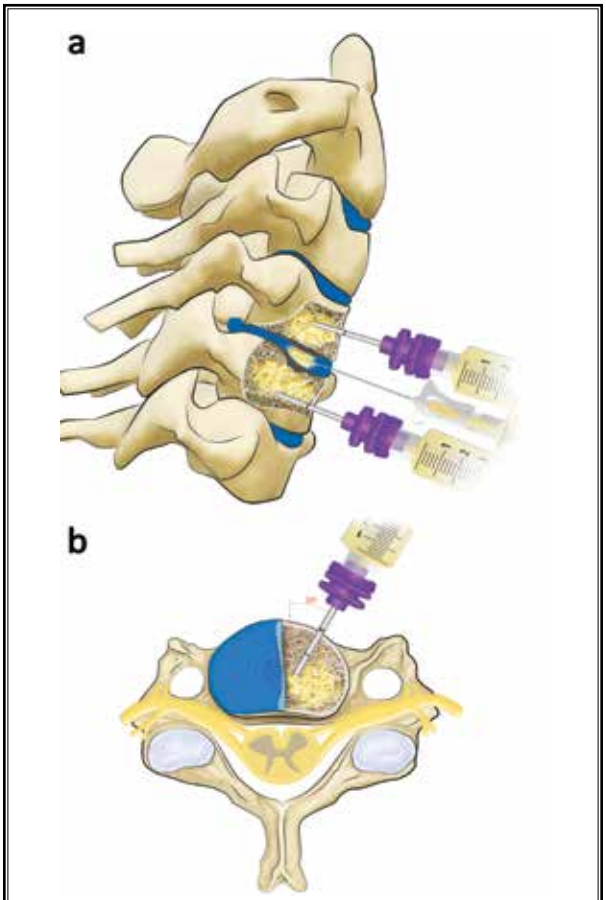

Fig. 1. *Illustration of the technique used for PRGF infiltration in the cervical spine. a) Sagittal view showing the intradiscal (C4-C5) and intraosseous infiltration in the 2 vertebral bodies adjacent to the disc (C4 and C5). b) Axial view demonstrating the infiltration with a 30° needle approach to reach the intraosseous level of the vertebral body*

was via the anterior route (Fig. 1), infiltrating 2 mL of PRGF directly in the middle of the spongy area of the vertebral body.

Lumbar Infiltration Protocol

The intradiscal infiltration technique is based on procedure published by Kirchner & Anitua (21). Briefly, IVD infiltrations were performed under a C-arm fluoroscope. A small skin surgical incision was opened at the point of entry of the spinal needle of 22G x 178 mm long (BD Spinal Needle Quincke, BD Spain, Madrid, Spain). The infiltration process was performed using an oblique angle of between 30º to 35º, in the lateral margin of the superior articular process of the lower vertebra and tilted towards the Scottie dog´s head, about 10º to 15º, until finding the parallelism with the 2 endplates next to the disc to be infiltrated, between the lower endplate of the superior vertebra and the upper endplate of the lower vertebra, and lateral to the neuroforamen, for the preservation of the nerve root. The position of the spinal needle, which was manually bent at the tip (15º - 20º), was guided and its position confirmed under fluoroscopic view in the 3 usual incidences: oblique, for the approaching; anterior-posterior (AP), to confirm the needle inside the disc; and lateral, to measure the depth of the needle on the disc. Once the tip of the spinal needle was located in the degenerated disc (depth of the nucleus pulposus), and checking under fluoroscopy by an infiltration of a small amount of contrast, 3 mL of activated PRGF was injected into the nucleus pulposus of each injured lumbar disc and 2 mL in the nearby nerve roots (Fig. 2). The epidural infiltration was performed in the lateral fluoroscopic incidence taking into account the posterior wall of the body and, using the same procedure, 2 mL of activated PRGF were infiltrated. Intraosseous infiltrations were performed according to the protocol described by Kirchner, et al (20) (Fig. 2).

Postoperative Protocol

Once the procedure was finished, the patient was transferred from the operating room to the resuscitation room and observed for 1 to 2 hours to monitor evolution and any possible adverse reaction. An ice pack was kept on the treated area to avoid possible inflammation. A solution of 100 mL of saline was administered intravenously. According to the immediate clinical evolution, the anaesthetist could indicate Paracetamol (1 g) and/or Dexketoprofen (25 g).

Outcome Measures

The efficacy of the treatment was assessed by means of PRO: 1) NRS for back pain, 2) COMI Questionnaire for lumbar and cervical cases and 3) the OSWESTRY Disability Index questionnaire solely for the lumbar cases. Patients fulfilled the questionnaires in the pre- and the post-treatment stages, which provided 6 different scores: NRS, COMI, COMI Disability Score (CDS), COMI Pain Score (CPS), OSWESTRY Pain Score (OPS) and OSWESTRY Disability Index (ODI) (the latter 2 being valid only for lumbar cases). In addition to the overall scores, results from 3 relevant questions contained in the questionnaires relating to the daily life of the patients were also individually addressed, namely the quality of life in the last week ("QoL," question 5 at the COMI questionnaire), the capability to go to work in the last 4 weeks ("Work," question 7 at COMI), and the capability to sleep ("Sleep," contained in the OSWESTRY questionnaire). In addition, adverse events data were also extracted from each patient's medical records.

Statistical Analysis

All analyses were conducted using RStudio-Integrated Development for R software, version 1.2.1335 (RStudio, Inc. Boston, US). Descriptive statistics were used to summarize data. In addition to considering the whole cohort, score differences between pre- and post-treatment were assessed for multiple sub-groups of patients (sub-cohorts) resulting from the stratification and clustering based on 3 different parameters: 1) the sector of the column treated, namely lumbar and cervical, 2) gender, and 3) age, which was divided into 3 age ranges (young, 18 - 40; middle, 41 - 60; and elderly, 61 - 76), producing up to 36 subgroups. The 3 subgroup age ranges were established following educated, medical criteria of subgroup similarity. Nine clinical scores were considered for study. A Wilcoxon signed-rank test (30) was performed to each resulting group within each score and question. A P value < 0.05 was considered statistically significant.

Results

Patient characteristics

This study includes 65 patients (27 women and 38 men) treated with PRGF technology for cervical and lumbar pain. Eigthteen patients had cervical pathology, 11 women and 7 men, aged between 39 and 73 years (average age of 54 years). With respect to patients with

lumbar back pain, there are 47 patients (16 women and 32 men) between 19 and 76 years old (average age of 51 years).

The average time of back pain evolution was 10 years (range between 0.5 - 40 years). All patients received at least 2 infiltration series about one month apart, 60 patients (92%) received 3, 9 patients (14%) were treated with 4 series, and one patient (1.5%) received 5. All patients in this study were subjected to IVD infiltrations. In the cervical sector, 9 of the patients received infiltrations on 2 discs, while 8 of them received infiltrations on 3 discs, and only one patient was infiltrated on 4 discs. With respect to the lumbar area, 4 out of 47 patients received IVD infiltrations on one disc, 24 on 2 discs, and in 5 patients 4 IVD had to be infiltrated.

Regarding intraosseous injections, only 2 patients received injections in the cervical spine, while 5 received them in the low back. All 7 patients received intraosseous infiltrations in only 2 vertebrae. The criterion for this type of infiltration was the presence of lesions in the endplate or subchondral bone in 2 vertebrae separated by an injured disc. For the rest of the structures, and as an integral approach, 80% of the total patients received root infiltrations. Intraarticular infiltrations were carried out in case of osteoarthritis of the facet joints; in the cervical sector this was seen in 44% of the patients, while in the lumbar sector it was seen in 74%. Epidural infiltration was carried out in 83% of all patients.

The patients' follow-up time had a range of 1 to 24 months with a mean of 5 months. Two patients were excluded from the "Work" question due to ineligibility causes.

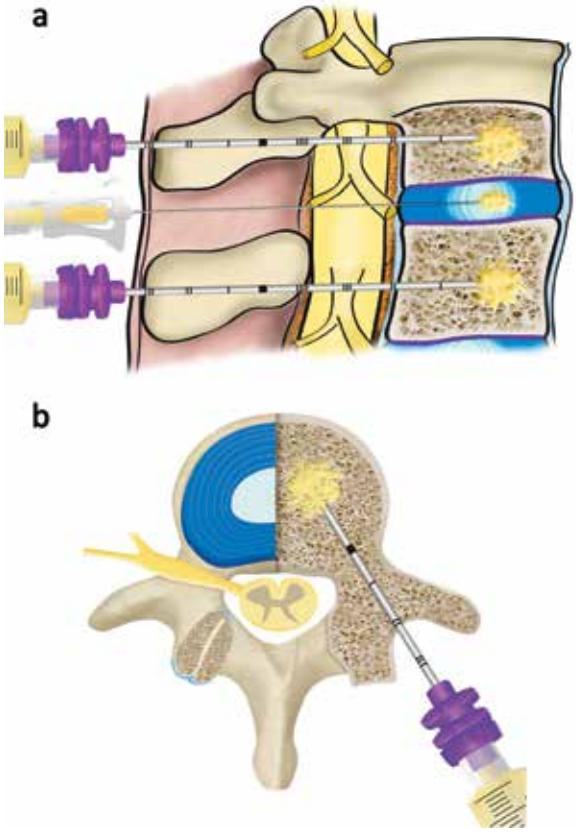

Fig. 2. *Illustration of the technique used for the infiltration of PRGF in the lumbar section. a) Sagittal view showing intradiscal and intraosseous infiltration in the 2 vertebral bodies adjacent to the disc. b) Axial view showing the transpedicular approach of the needle that will finally reach the intraosseous level of the vertebral body. Reproduced with permission from (20).*

Outcome Measures

The first column of Figs. 3-10 show boxplots for pre- and post-treatment statistics and their difference for the 9 scores considered. Results show statistically significant ($P < 0.05$) improvements (negative differences, ie, smaller post- than pre-treatment scores) on all 9 scores, when all patients (without stratification) are considered. The minimal clinically important difference (MCID) was achieved in all subgroups for NRS and ODI.

Spine Sector, Age, and Gender Stratification Strategies

The results are stratified and analyzed by spine sector, age, and gender (Figs. 3-10). Considering sub-groups in all tests (252 cases overall) showed an improvement in 249 cases (99%). Three cases showed no change (with n values equal 1, 1, and 3). From the 249 improving cases, 154 (62%) showed a statistically significant difference between the pre- and the post-treatment stages (Supplementary tables 1-36).

First, results were assessed from the perspective of the 3 variables compared (spine sector, gender, and age), thus, considering all patients. Results reveal that men had more improvement, compared to women, with a larger score decrease on all 9 scores. Regarding the sector of column treated, patients with lumbar pathology show more improvement than the ones with cervical lesions, with significant score decreases in 5 out of 6 comparable scores. Finally, results comparing the patients age show that the elderly group experienced the largest improve-

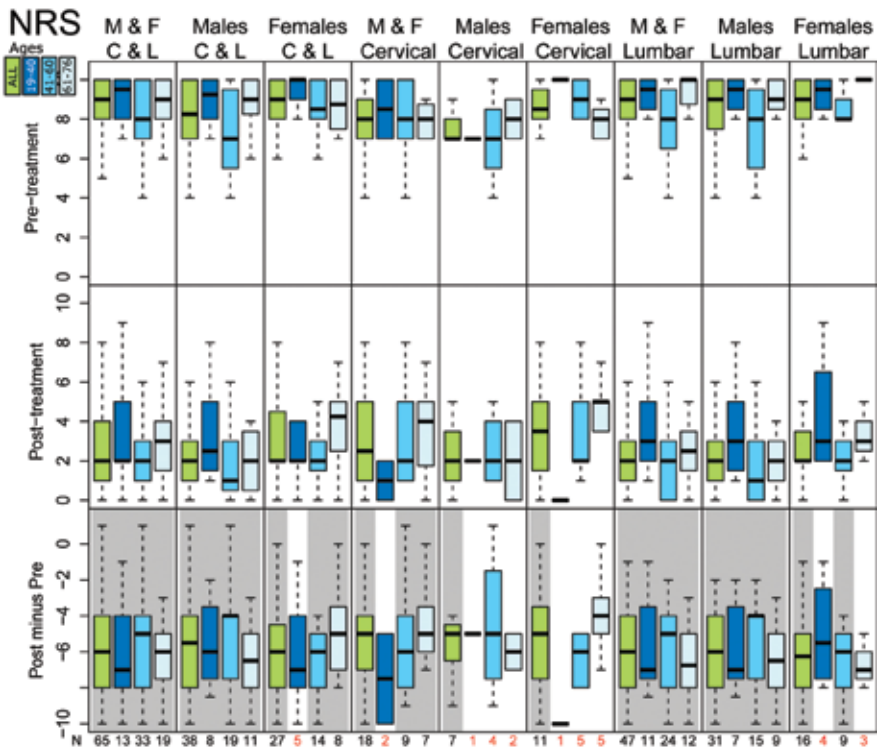

Fig. 3. *Boxplots of the NRS results for the 36 sub-groups considered, showing Pre-treatment (top), Post-treatment (center) and difference (Post- minus Pre-treatment) results (bottom). A grey background denotes statistical significance ($P < 0.05$) in the difference. Sample sizes for each group are shown at the bottom (N). N values smaller than 6 are shown in red. Groups are colour-distributed according to the defined age ranges (all ages for green, and 19-40, 41-60, 60-76 from dark to light blue, respectively).*

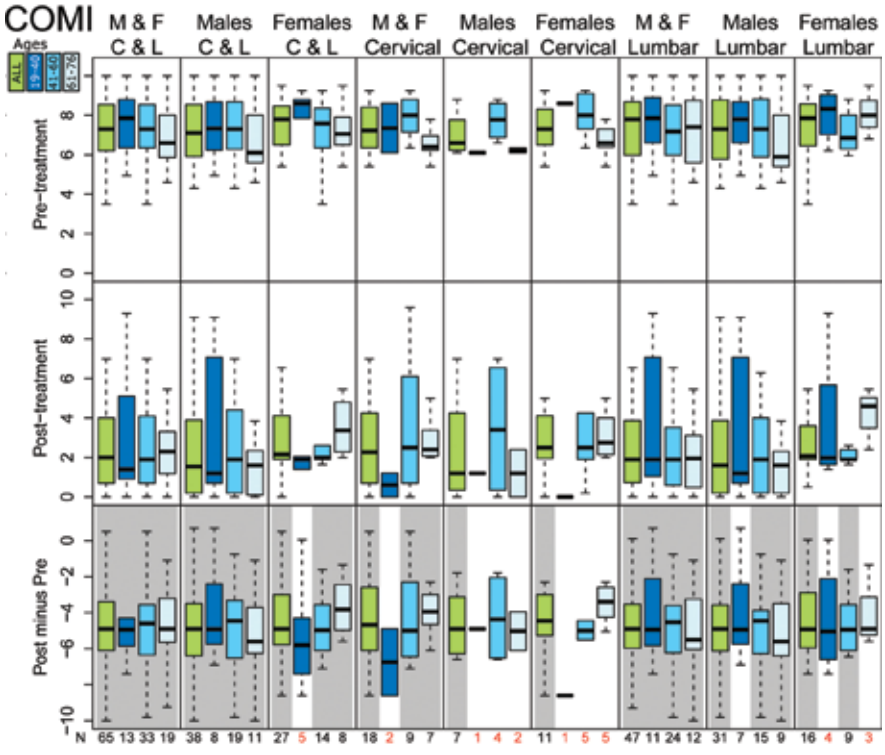

Fig. 4. *Boxplots of the COMI results for the 36 sub-groups considered, showing Pre-treatment (top), Post-treatment (center) and difference (Post- minus Pre-treatment) results (bottom). A grey background denotes statistical significance ($P < 0.05$) in the difference. Sample sizes for each group are shown at the bottom (N). N values smaller than 6 are shown in red. Groups are colour-distributed according to the defined age ranges (all ages for green, and 19-40, 41-60, 60-76 from dark to light blue, respectively).*

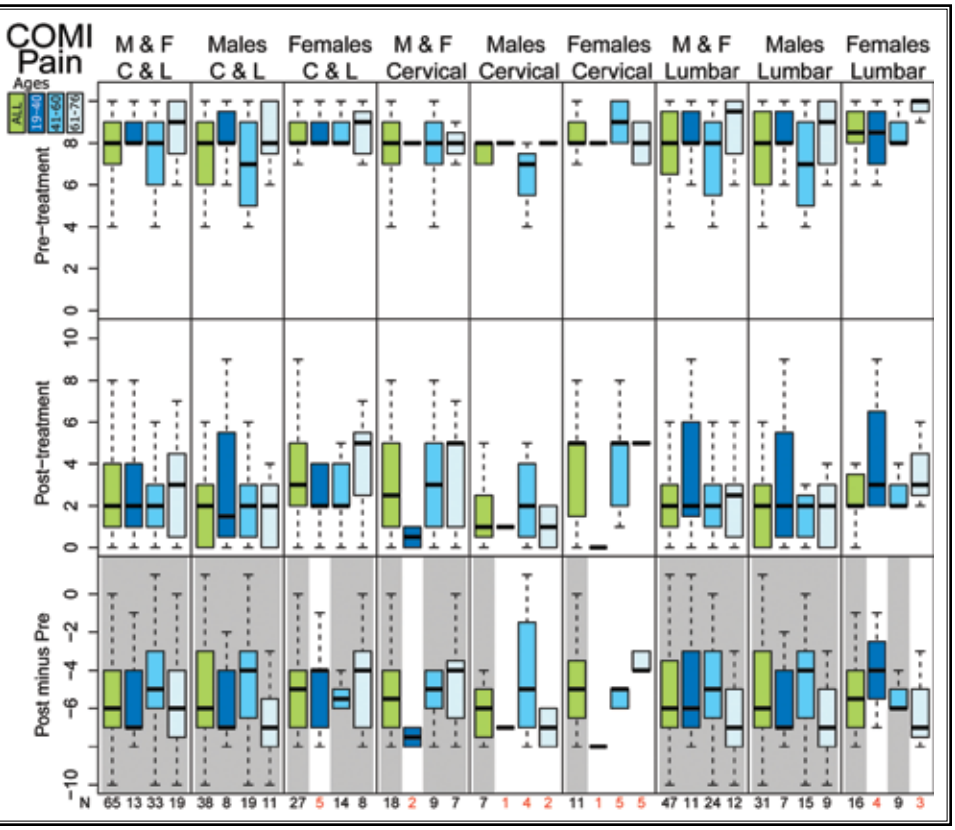

Fig. 5. *Boxplots of the COMI - Pain Score results for the 36 sub-groups considered, showing Pre-treatment (above), Post-treatment (center) and difference (Post- minus Pre-treatment) results (bottom). A grey background denotes statistical significance ($P < 0.05$) in the difference. Sample sizes for each group are shown at the bottom (N). N values smaller than 6 are shown in red. Groups are colour-distributed according to the defined age ranges (all ages for green, and 19-40, 41-60, 60-76 from dark to light blue, respectively).*

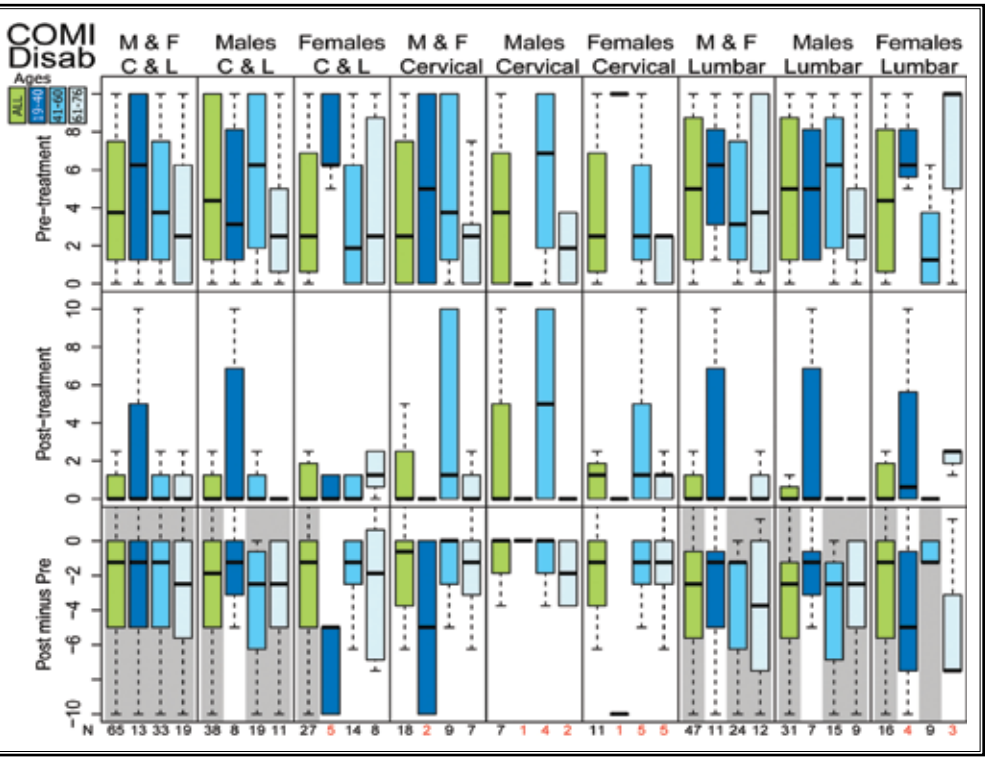

Fig. 6. *Boxplots of the COMI - Disability Score results for the 36 sub-groups considered, showing Pre-treatment (top), Post-treatment (center) and difference (Post- minus Pre-treatment) results (bottom). A grey background denotes statistical significance ($P < 0.05$) in the difference. Sample sizes for each group are shown at the bottom (N). N values smaller than 6 are shown in red. Groups are colour-distributed according to the defined age ranges (all ages for green, and 19-40, 41-60, 60-76 from dark to light blue, respectively).*

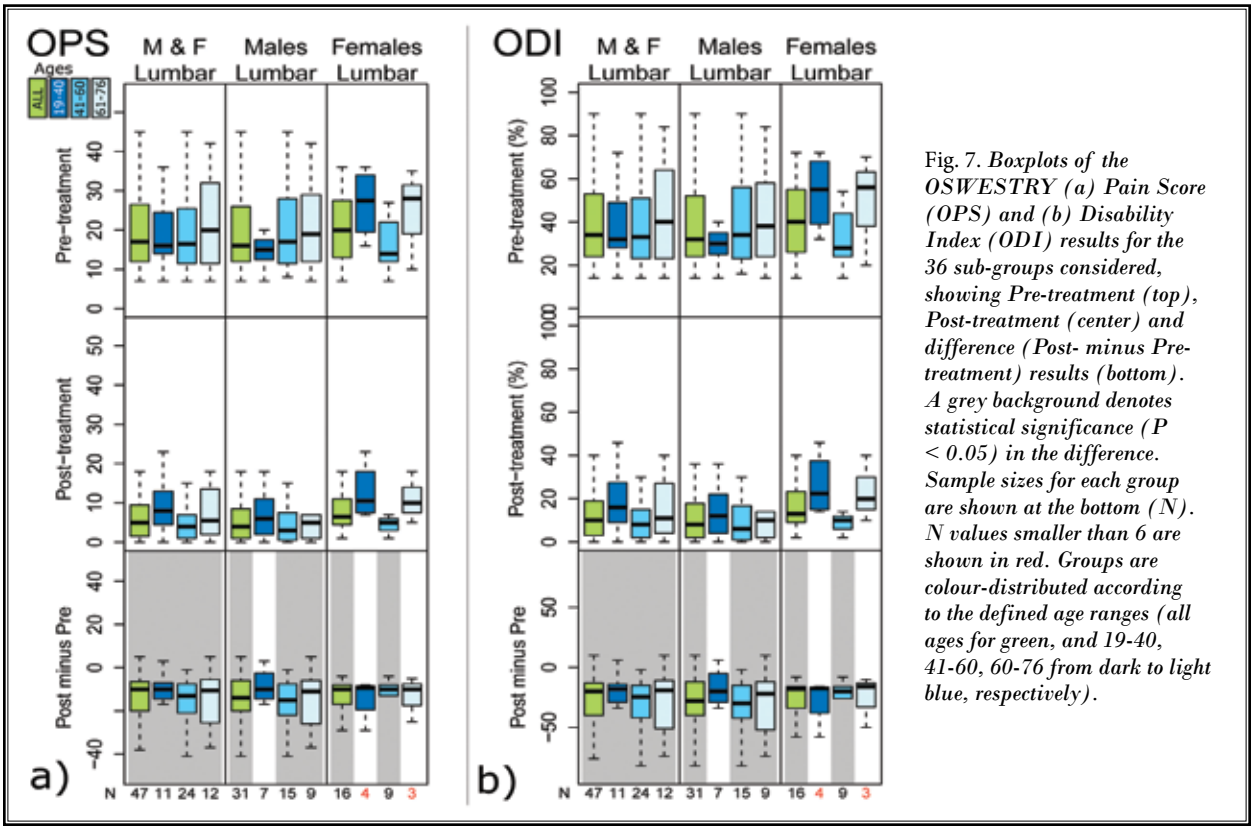

Fig. 7. *Boxplots of the OSWESTRY (a) Pain Score (OPS) and (b) Disability Index (ODI) results for the 36 sub-groups considered, showing Pre-treatment (top), Post-treatment (center) and difference (Post- minus Pre-treatment) results (bottom). A grey background denotes statistical significance ($P < 0.05$) in the difference. Sample sizes for each group are shown at the bottom (N). N values smaller than 6 are shown in red. Groups are colour-distributed according to the defined age ranges (all ages for green, and 19-40, 41-60, 60-76 from dark to light blue, respectively).*

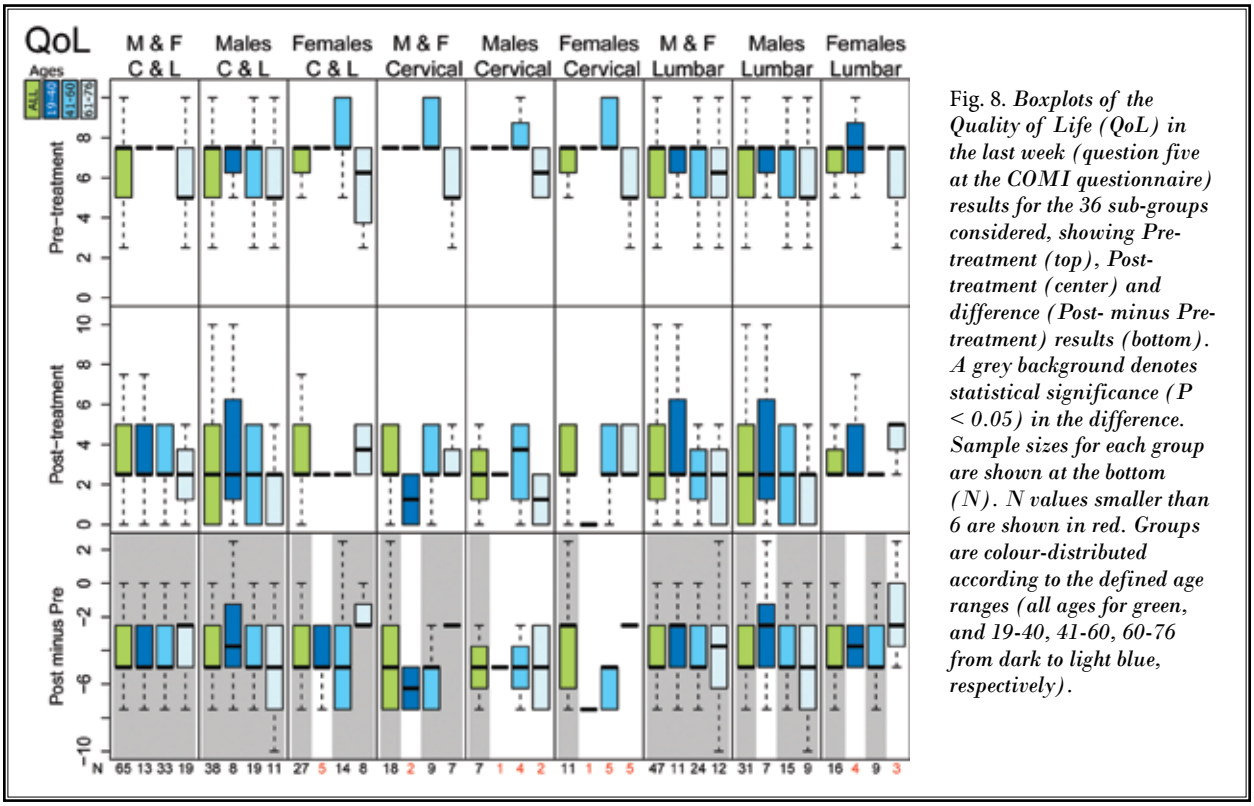

Fig. 8. *Boxplots of the Quality of Life (QoL) in the last week (question five at the COMI questionnaire) results for the 36 sub-groups considered, showing Pre-treatment (top), Post-treatment (center) and difference (Post- minus Pre-treatment) results (bottom). A grey background denotes statistical significance ($P < 0.05$) in the difference. Sample sizes for each group are shown at the bottom (N). N values smaller than 6 are shown in red. Groups are colour-distributed according to the defined age ranges (all ages for green, and 19-40, 41-60, 60-76 from dark to light blue, respectively).*

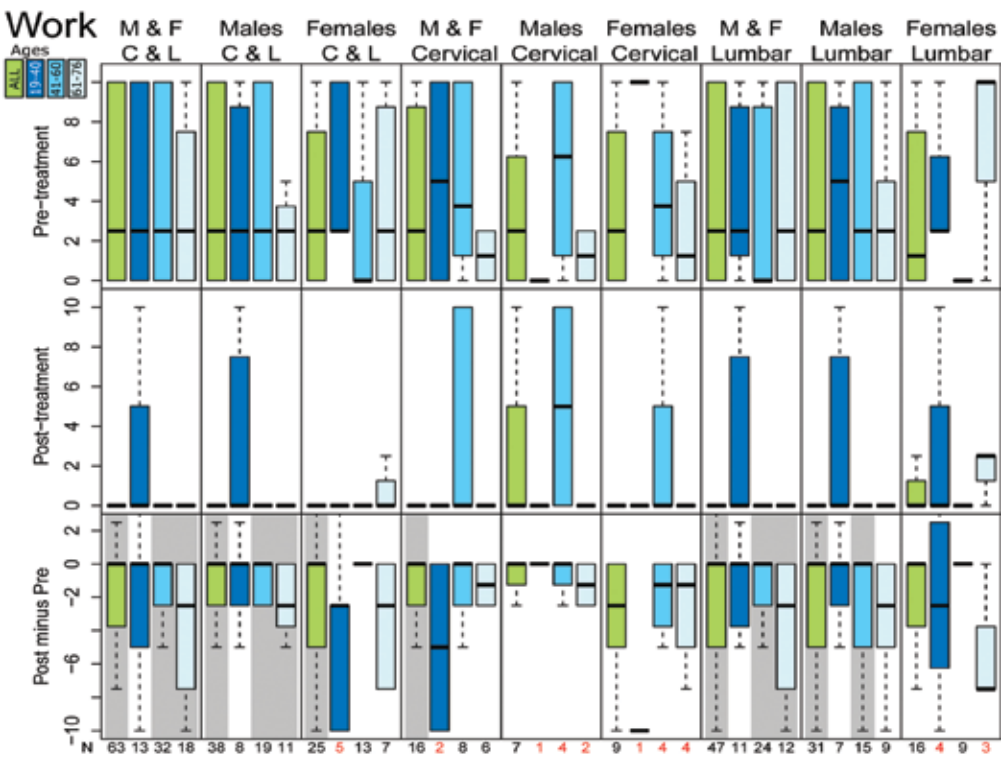

Fig. 9. *Boxplots of the capability to go to work in the last 4 weeks (question seven at the COMI questionnaire) results for the 36 sub-groups considered, showing Pre-treatment (top), Post-treatment (center) and difference (Post-minus Pre-treatment) results (bottom). A grey background denotes statistical significance ($P < 0.05$) in the difference. Sample sizes for each group are shown at the bottom (N). N values smaller than 6 are shown in red. Groups are colour-distributed according to the defined age ranges (all ages for green, and 19-40, 41-60, 60-76 from dark to light blue, respectively).*

ment on 5 scores, followed by the middle (4 maximum scores), and the young group (1 maximum score). Most sub-groups show an n (≤ 7) that was too small to extract reliable conclusions from. The group of men in the lumbar sector presented all subgroups with n > 7, with 5 scores showing the greatest improvement in the middle age range (41-60), compared to 4 scores in the elderly group, and none in the young group.

Considering the different scores, NRS, COMI, CPS, OPS, ODI, and QoL show more than 69% sub-groups with statistically significant improvements. Among these scores, all non-significant sub-groups have a sample size ≤ 7. A smaller statistically significant amount of improvements were obtained for "Sleep" (50%), "CDS" (44%), and "Work" (36%). In these cases, results also show sensibility to the sample size, as 33 out of 55 non-significant differences have a sample size ≤ 7. Overall, results show that most of the non-significant cases (80%, 78 out of 97) have a sample size smaller or equal to 7, of those included in this study, which encourages us to expect a higher statistical significance, if their n is increased.

Adverse events

PRGF infiltrations were well tolerated and no serious adverse events were observed.

Discussion

The results of this retrospective study show that a minimally invasive treatment consisting of PRGF infiltrations in the cervical and lumbar spine contributed to a statistically significant reduction in all patient reported outcomes. Broadly, the groups show a statistically significant improvement in all areas at the end of the follow-up, especially in terms of pain and overall quality of life. These results are consistent with previous studies and highlight the minimally invasive treatment of back pain through PRP infiltrations (11-16,20,21). It is noteworthy that the MCID was achieved in all subgroups for NRS scale, namely, an improvement equal to or greater than 2 points that corresponds to a decrease in pain of 2 points or more (31,32). The MCID was also reached for the ODI (difference of 10 points) (31).

Breaking down the results, the elderly group was found to have better results in terms of return to work, compared to the other 2 age groups, and the middle-aged group had a better result than the younger group. In contrast, the younger and middle-aged groups had a better result in sleeping hours at the end of the follow-up, compared to the elderly group. This is probably due to the fact that the elderly population already tends to

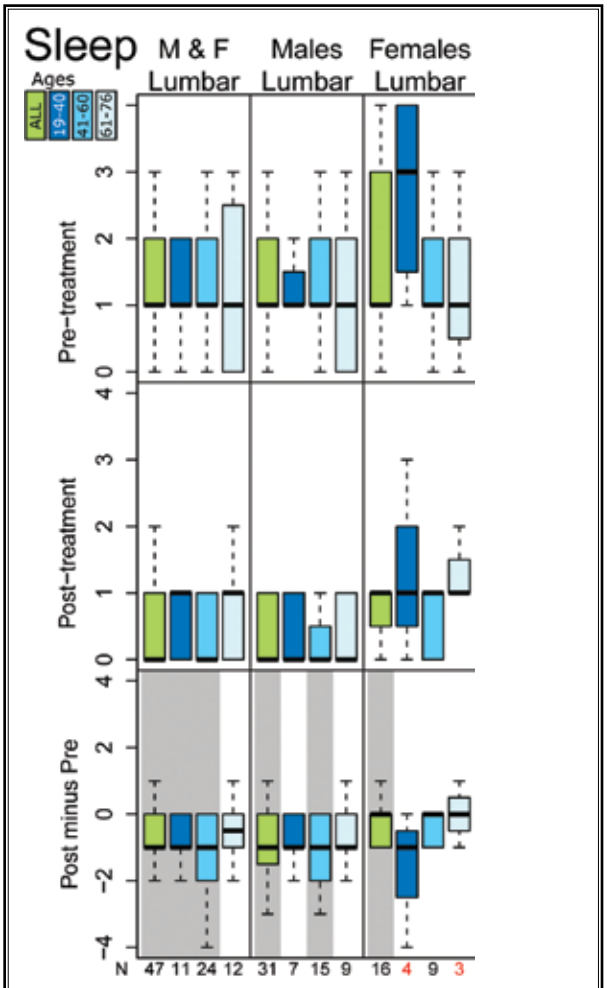

Fig. 10. *Boxplots of the capability to sleep (Sleep, contained in the OSWESTRY questionnaire) results for the 36 sub-groups considered, showing Pre-treatment (top), Post-treatment (center) and difference (Post- minus Pre-treatment) results (bottom). A grey background denotes statistical significance ($P < 0.05$) in the difference. Sample sizes for each group are shown at the bottom (N). N values smaller than 6 are shown in red. Groups are colour-distributed according to the defined age ranges (all ages for green, and 19-40, 41-60, 60-76 from dark to light blue, respectively).*

have more sleep problems than the younger population (33), due to among other causes, respiratory problems, such as apnea-hypopnea syndrome.

On the other hand, the men studied show a greater improvement than the women. Even so, the sample size was significantly higher in men (28) than in women (12), so it cannot be stated that women cannot recover their sleep after treatment. The cervical spine group did not show a statistically significant improvement in terms of social and occupational disability, whereas the lumbar spine group did (with the exception of the middle age group). By independently analyzing the capability to go to work in the last 4 weeks, the cervical group obtained a statistically significant result, when analyzed as an entire group; therefore, there was improvement in terms of work disability, but there was less improvement in terms of social disability. On the other hand, low back pain patients obtained an improvement in both areas equally (work and daily activities); therefore, there is a need to increase the sample size in some subgroups in order to perform stratification, since no definitive conclusions can be drawn with samples ≤ 7. With sample sizes greater than 7, a significant result was obtained almost systematically. The literature recommends that the Wilcoxon signed-rank test should have sample sizes greater than 7 to measure statistical significance (34). Therefore, we believe that the non-significant results are related to the sample size and not to the treatment (in the cases that n ≤ 7). However, when the subgroup sample size is larger than 7 and the result is not statistically significant, it may also be due to a small sample (n = 7-13). There are also large differences in the sample size in each subgroup of patients, which prevents us from making comparisons between them. With larger sample sizes, more powerful conclusions could be drawn and more meaningful comparisons could be made between subgroups.

Recent studies support the hypothesis of a global approach to back pain pathologies, since changes in the vertebral bone, especially in the endplates, influence the transport of nutrients to the disc and its eventual degeneration (35). The appropriate crosstalk between the IVD and the subchondral bone is a key feature of the homeostasis of the intervertebral joint functional unit (IVD, the upper and lower vertebrae, and the facet joints) (17).

Together, growth factors, fibrin, and the rest of the bioactive molecules contained in PRGF (36-38) play a key role in the physiology of IVD cells by promoting the synthesis of the extracellular matrix, while exerting an anti-inflammatory and antiapoptotic effect, which attempts to re-establish homeostasis (17,39). Therefore, as in other pathologies of the musculoskeletal system (40), PRGF intravertebral infiltrations can contribute to the integral approach to back pain.

It should be noted, no significant adverse events were found due to PRGF infiltrations in the 65 patients. In the 10-year history series of about 1000 patients, the percentage of adverse effects was 0.7%, with dis-

citis and neuritis as the most relevant. These findings were consistent with a recent systematic review that included 3 randomized clinical trials and in which no increase in adverse events due to PRP infiltrations was observed (41).

Limitations

This study has several limitations. As a retrospective study, not all patients had the same follow-up period, nor the same number of infiltrations. However, this study highlights how the treatment of cervical and lumbar back pain (a very prevalent pathology with multiple etiologies) with a cost-effective, minimally invasive procedure based on PRGF technology, is feasible, clinically promising, and safe. Another limitation is the low number of cases of cervical pathology compared to the lumbar ones. This corresponds to the higher prevalence of lumbar back pain than the cervical pain (1,5). In line with this, it would be convenient to increase the sample size of the study, so that stratification by spine sector, age, and gender was effective in all subgroups and had adequate statistical power. In addition, it would have been helpful to have included body mass index values in the study, since being overweight and/or obese are factors that can influence back pain, especially in the lumbar area (42,43).

Conclusion

In conclusion, taking into account the limitations of the study, PRGF infiltrations are an effective and minimally invasive tool in the treatment of both cervical and lumbar pain, evaluated according to validated questionnaires. These encouraging results obtained in routine clinical practice should be validated in future randomized clinical trials.

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Supplemental Table 1. *Results for the subgroup considering both sexes, for both cervical and lumbar treatments and for all ages (19-76).*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	65.0	65.0	65.0	65.0	65.0	63.0
Mean Pre	8.4	8.0	4.5	7.3	6.9	3.8
Mean Post	2.6	2.7	1.8	2.7	2.8	1.6
Difference	-5.7	-5.3	-2.8	-4.6	-4.0	-2.3
Significance (%)	100.0	100.0	100.0	100.0	100.0	100.0

Supplemental Table 2. *Results for the subgroup considering both sexes, for both cervical and lumbar treatments and for ages ranging 19-40.*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	13.0	13.0	13.0	13.0	13.0	13.0
Mean Pre	9.1	8.3	5.6	7.7	7.1	4.6
Mean Post	3.4	3.2	2.7	3.2	3.5	2.7
Difference	-5.7	-5.2	-2.9	-4.5	-3.7	-1.9
Significance (%)	99.8	99.8	96.5	99.7	99.5	82.0

Supplemental Table 3. *Results for the subgroup considering both sexes, for both cervical and lumbar treatments and for ages ranging 41-60.*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	33.0	33.0	33.0	33.0	33.0	32.0
Mean Pre	7.8	7.5	4.5	7.4	7.3	3.8
Mean Post	2.2	2.5	2.0	2.7	2.8	1.9
Difference	-5.6	-5.0	-2.6	-4.7	-4.5	-1.9
Significance (%)	100.0	100.0	100.0	100.0	100.0	99.7

Supplemental Table 4. *Results for the subgroup considering both sexes, for both cervical and lumbar treatments and for ages ranging 61-76.*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	19.0	19.0	19.0	19.0	19.0	18.0
Mean Pre	8.7	8.5	3.8	7.30	6.1	3.5
Mean Post	2.8	2.7	0.7	2.3	2.5	0.3
Difference	-5.9	-5.8	-3.1	-4.7	-3.6	-3.2
Significance (%)	100.0	100.0	99.6	100.0	99.9	99.5

Supplemental Table 5. *Results for the subgroup considering male patients, for both cervical and lumbar treatments and for all ages (19-76).*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	38.0	38.0	38.0	38.0	38.0	38.0
Mean Pre	8.1	7.7	4.7	7.2	6.8	4.0
Mean Post	2.3	2.2	1.7	2.4	2.5	1.7
Difference	-5.8	-5.5	-3.0	-4.8	-4.3	-2.3
Significance (%)	100.0	100.0	100.0	100.0	100.0	99.9

Supplemental Table 6. *Results for the subgroup considering male patients, for both cervical and lumbar treatments and for ages ranging 19-40.*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	8.0	8.0	8.0	8.0	8.0	8.0
Mean Pre	8.9	8.4	4.4	7.4	6.9	4.1
Mean Post	3.4	3.0	3.0	3.4	3.8	3.1
Difference	-5.6	-5.4	-1.4	-4.0	-3.1	-0.9
Significance (%)	98.6	98.1	79.8	96.1	95.1	58.6

Supplemental Table 7. *Results for the subgroup considering male patients, for both cervical and lumbar treatments and for ages ranging 41-60.*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	19.0	19.0	19.0	19.0	19.0	19.0
Mean Pre	7.3	6.9	5.5	7.4	7.0	4.6
Mean Post	2.0	2.2	2.0	2.6	2.5	2.1
Difference	-5.3	-4.7	-3.5	-4.8	-4.5	-2.5
Significance (%)	100.0	100.0	99.9	100.0	100.0	98.7

Supplemental Table 8. *Results for the subgroup considering male patients, for both cervical and lumbar treatments and for ages ranging 61-76.*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	11.0	11.0	11.0	11.0	11.0	11.0
Mean Pre	8.8	8.5	3.6	6.8	6.4	3.0
Mean Post	2.1	1.6	0.2	1.4	1.6	0.0
Difference	-6.7	-6.8	-3.4	-5.5	-4.8	-3.0
Significance (%)	99.6	99.6	97.8	99.5	99.5	96.6

Supplemental Table 9. *Results for the subgroup considering female patients, for both cervical and lumbar treatments and for all ages (19-76).*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	27.0	27.0	27.0	27.0	27.0	25.0
Mean Pre	8.8	8.4	4.3	7.4	7.0	3.6
Mean Post	3.1	3.4	1.8	3.1	3.3	1.4
Difference	-5.7	-5.0	-2.5	-4.4	-3.7	-2.2
Significance (%)	100.0	100.0	99.5	100.0	100.0	98.2

Supplemental Table 10. *Results for the subgroup considering female patients, for both cervical and lumbar treatments and for ages ranging 19-40.*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	5.0	5.0	5.0	5.0	5.0	5.0
Mean Pre	9.4	8.2	7.5	8.1	7.5	5.5
Mean Post	3.4	3.4	2.2	2.9	3.0	2.0
Difference	-6.0	-4.8	-5.2	-5.2	-4.5	-3.5
Significance (%)	93.8	94.2	89.8	87.5	94.3	72.4

Supplemental Table 11. *Results for the subgroup considering female patients, for both cervical and lumbar treatments and for ages ranging 19-40.*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	14.0	14.0	14.0	14.0	14.0	13.0
Mean Pre	8.6	8.3	3.2	7.3	7.7	2.5
Mean Post	2.5	2.9	1.9	2.9	3.2	1.5
Difference	-6.1	-5.4	-1.3	-4.4	-4.5	-1.0
Significance (%)	99.8	99.8	94.4	100.0	99.8	82.6

Supplemental Table 12. *Results for the subgroup considering female patients, for both cervical and lumbar treatments and for ages ranging 61-76.*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	8.0	8.0	8.0	8.0	8.0	7.0
Mean Pre	8.7	8.6	4.1	7.2	5.6	4.3
Mean Post	3.8	4.1	1.4	3.5	3.8	0.7
Difference	-4.9	-4.5	-2.7	-3.7	-1.9	-3.6
Significance (%)	97.8	97.8	85.1	99.2	95.1	91.1

Supplemental Table 13. *Results for the subgroup considering both sexes, for a cervical treatment and for all ages (19-76).*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	18.0	18.0	18.0	18.0	18.0	16.0
Mean Pre	8.1	7.9	3.9	7.3	7.2	3.9
Mean Post	3.0	3.1	2.3	2.9	3.1	1.9
Difference	-5.1	-4.9	-1.6	-4.4	-4.2	-2.0
Significance (%)	99.9	99.9	92.6	100.0	99.9	98.0

Supplemental Table 14. *Results for the subgroup considering both sexes, for a cervical treatment and for ages ranging 19-40.*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	2.0	2.0	2	2.0	2.0	2
Mean Pre	8.5	8.0	5	7.3	7.5	5
Mean Post	1.0	0.5	0	0.6	1.2	0
Difference	-7.5	-7.5	-5	-6.8	-6.2	-0.9
Significance (%)	0.0	0.0	0	0.0	0.0	0

Supplemental Table 15. *Results for the subgroup considering both sexes, for a cervical treatment and for ages ranging 41-60.*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	9.0	9.0	9.0	9.0	9.0	8.0
Mean Pre	8.1	7.9	4.9	7.9	8.3	5.0
Mean Post	3.1	3.3	4.0	3.6	3.6	3.8
Difference	-5.0	-4.6	-0.8	-4.3	-4.7	-1.2
Significance (%)	97.9	98.0	50.2	99.2	98.6	82.6

Supplemental Table 16. *Results for the subgroup considering both sexes, for a cervical treatment and for ages ranging 61-76.*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	7.0	7.0	7.0	7.0	7.0	6.0
Mean Pre	7.9	8.0	2.3	6.6	5.7	2.1
Mean Post	3.5	3.4	0.7	2.6	2.9	0.0
Difference	-4.4	-4.6	-1.6	-3.9	-2.9	-2.1
Significance (%)	96.5	96.4	77.7	98.4	97.4	86.6

Supplemental Table 17. *Results for the subgroup considering male patients, for a cervical treatment and for all ages (19-76).*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	7.0	7.0	7.0	7.0	7.0	7.0
Mean Pre	7.3	7.1	3.9	7.1	7.5	3.6
Mean Post	2.3	1.7	2.9	2.5	2.5	2.9
Difference	-5.0	-5.4	-1.1	-4.6	-5.0	-0.7
Significance (%)	96.6	96.6	65.4	98.4	97.9	65.4

Supplemental Table 18. *Results for the subgroup considering male patients, for a cervical treatment and for ages ranging 19-40.*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	1	1	1	1.0	1.0	1
Mean Pre	7	8	0	6.1	7.5	0
Mean Post	2	1	0	1.2	2.5	0
Difference	-5	-7	0	-4.9	-5.0	0
Significance (%)	0	0	0	0.0	0.0	0

Supplemental Table 19. *Results for the subgroup considering male patients, for a cervical treatment and for ages ranging 41-60.*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	4.0	4.0	4.0	4.0	4.0	4.0
Mean Pre	7.0	6.5	5.9	7.7	8.1	5.6
Mean Post	2.5	2.2	5.0	3.4	3.1	5.0
Difference	-4.5	-4.2	-0.9	-4.3	-5.0	-0.6
Significance (%)	75.0	75.0	0.0	87.5	90.2	0.0

Supplemental Table 20. *Results for the subgroup considering male patients, for a cervical treatment and for ages ranging 61-76.*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	2	2	2.0	2.0	2.0	2.0
Mean Pre	8	8	1.9	6.2	6.2	1.2
Mean Post	2	1	0.0	1.2	1.2	0.0
Difference	-6	-7	-1.9	-5.0	-5.0	-1.2
Significance (%)	0	0	0.0	0.0	0.0	0.0

Supplemental Table 21. *Results for the subgroup considering female patients, for a cervical treatment and for all ages (19-76).*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	11.1	11.1	11.0	11.0	11.0	9.0
Mean Pre	8.6	8.5	3.9	7.5	7.0	4.2
Mean Post	3.5	3.9	1.9	3.1	3.4	1.1
Difference	-5.1	-4.5	-1.9	-4.3	-3.6	-3.1
Significance (%)	99.1	99.1	82.9	99.8	98.7	94.2

Supplemental Table 22. *Results for the subgroup considering female patients, for a cervical treatment and for ages ranging 19-40.*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	1	1	1	1.0	1.0	1
Mean Pre	10	8	10	8.6	7.5	10
Mean Post	0	0	0	0.0	0.0	0
Difference	-10	-8	-10	-8.6	-7.5	-10
Significance (%)	0	0	0	0.0	0.0	0

Supplemental Table 23. *Results for the subgroup considering female patients, for a cervical treatment and for ages ranging 41-60.*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	5.0	5.0	5.0	5.0	5.0	4.0
Mean Pre	9.0	9.0	4.0	8.0	8.5	4.4
Mean Post	3.6	4.2	3.2	3.7	4.0	2.5
Difference	-5.4	-4.8	-0.8	-4.3	-4.5	-1.9
Significance (%)	90.2	90.2	28.7	87.5	89.8	62.9

Supplemental Table 24. *Results for the subgroup considering female patients, for a cervical treatment and for ages ranging 61-76.*

	NRS	COMI	CDS	CPS	QoL	Work
Sample Size (N)	5.0	5.0	5.0	5.0	5.0	4.0
Mean Pre	7.9	8.0	2.5	6.7	5.5	2.5
Mean Post	4.1	4.4	1.0	3.2	3.5	0.0
Difference	-3.8	-3.6	-1.5	-3.5	-2.0	-2.5
Significance (%)	90.0	90.2	53.9	93.8	92.8	62.9

Supplemental Table 25. *Results for the subgroup considering both sexes, for a lumbar treatment and for all ages (19-76).*

	NRS	COMI	CDS	CPS	OPS	ODI	QoL	Work	Sleep
Sample Size (N)	47.0	47.0	47.0	47.0	47.0	47.0	47.0	47.0	47.0
Mean Pre	8.5	8.0	4.8	7.3	20.1	40.3	6.8	3.8	1.4
Mean Post	2.5	2.5	1.5	2.6	6.4	13.2	2.8	1.5	0.6
Difference	-6.0	-5.4	-3.2	-4.7	-13.7	-27.1	-4.0	-2.3	-0.9
Significance (%)	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0

Supplemental Table 26. *Results for the subgroup considering both sexes, for a lumbar treatment and for ages ranging 19-40.*

	NRS	COMI	CDS	CPS	OPS	ODI	QoL	Work	Sleep
Sample Size (N)	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0	11.0
Mean Pre	9.2	8.4	5.7	7.8	19.5	39.1	7.0	4.5	1.7
Mean Post	3.8	3.6	3.2	3.7	9.2	18.6	3.9	3.2	0.7
Difference	-5.4	-4.7	-2.5	-4.1	-10.4	-20.5	-3.2	-1.4	-1.0
Significance (%)	99.6	99.4	93.6	98.6	99.1	99.5	98.7	65.2	98.2

Supplemental Table 27. *Results for the subgroup considering both sexes, for a lumbar treatment and for ages ranging 41-60.*

	NRS	COMI	CDS	CPS	OPS	ODI	QoL	Work	Sleep
Sample Size (N)	24.0	24.0	24.0	24.0	24.0	24.0	24.0	24.0	24.0
Mean Pre	7.8	7.3	4.4	7.2	19.5	38.9	6.9	3.3	1.4
Mean Post	1.9	2.2	1.2	2.4	4.7	9.6	2.5	1.2	0.4
Difference	-5.9	-5.2	-3.2	-4.8	-14.8	-29.3	-4.4	-2.1	-1.0
Significance (%)	100.0	100.0	100.0	100.0	100.0	100.0	100.0	98.7	99.9

Supplemental Table 28. *Results for the subgroup considering both sexes, for a lumbar treatment and for ages ranging 61-76.*

	NRS	COMI	CDS	CPS	OPS	ODI	QoL	Work	Sleep
Sample Size (N)	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
Mean Pre	9.2	8.8	4.7	7.2	22.0	44.0	6.2	4.2	1.2
Mean Post	2.4	2.2	0.7	2.1	7.5	15.3	2.3	0.4	0.7
Difference	-6.8	-6.6	-4.0	-5.2	-14.5	-28.7	-4.0	-3.8	-0.6
Significance (%)	99.8	99.8	98.7	99.7	99.5	99.5	99.2	97.8	87.6

Supplemental Table 29. *Results for the subgroup considering male patients, for a lumbar treatment and for all ages (19-76).*

	NRS	COMI	CDS	CPS	OPS	ODI	QoL	Work	Sleep
Sample Size (N)	31.0	31.0	31.0	31.0	31.0	31.0	31.0	31.0	31.0
Mean Pre	8.2	7.8	4.9	7.3	19.9	39.7	6.6	4.1	1.3
Mean Post	2.3	2.3	1.5	2.4	5.6	11.4	2.5	1.5	0.4
Difference	-5.9	-5.5	-3.5	-4.9	-14.2	-28.3	-4.1	-2.7	-0.9
Significance (%)	100.0	100.0	100.0	100.0	100.0	100.0	100.0	99.9	100.0

Supplemental Table 30. *Results for the subgroup considering male patients, for a lumbar treatment and for ages ranging 19-40.*

	NRS	COMI	CDS	CPS	OPS	ODI	QoL	Work	Sleep
Sample Size (N)	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0	7.0
Mean Pre	9.2	8.4	5.0	7.6	15.4	30.9	6.8	4.6	1.1
Mean Post	3.6	3.3	3.4	3.7	7.1	14.3	3.9	3.6	0.4
Difference	-5.6	-5.1	-1.6	-3.9	-8.3	-16.6	-2.9	-1.1	-0.7
Significance (%)	97.8	96.7	79.8	92.2	92.2	92.2	91.1	58.6	91.1

Supplemental Table 31. *Results for the subgroup considering male patients, for a lumbar treatment and for ages ranging 41-60.*

	NRS	COMI	CDS	CPS	OPS	ODI	QoL	Work	Sleep
Sample Size (N)	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0	15.0
Mean Pre	7.3	7.0	5.4	7.3	21.1	42.3	6.7	4.3	1.3
Mean Post	1.8	2.1	1.2	2.4	4.5	9.3	2.3	1.3	0.3
Difference	-5.5	-4.9	-4.2	-4.9	-16.6	-33.0	-4.3	-3.0	-1.1
Significance (%)	99.9	99.9	99.8	99.9	99.9	99.9	99.8	97.9	99.5

Supplemental Table 32. *Results for the subgroup considering male patients, for a lumbar treatment and for ages ranging 61-76.*

	NRS	COMI	CDS	CPS	OPS	ODI	QoL	Work	Sleep
Sample Size (N)	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0
Mean Pre	8.9	8.6	4.0	7.0	21.2	42.4	6.4	3.3	1.2
Mean Post	2.1	1.8	0.3	1.4	6.3	12.7	1.7	0.0	0.4
Difference	-6.8	-6.8	-3.8	-5.5	-14.9	-29.8	-4.7	-3.3	-0.8
Significance (%)	99.1	99.1	96.5	99.6	98.8	98.8	98.6	94.3	89.4

Supplemental Table 33. *Results for the subgroup considering female patients, for a lumbar treatment and for all ages (19-76).*

	NRS	COMI	CDS	CPS	OPS	ODI	QoL	Work	Sleep
Sample Size (N)	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0	16.0
Mean Pre	8.9	8.3	4.5	7.4	20.6	41.2	7.0	3.3	1.8
Mean Post	2.8	3.0	1.7	3.0	8.0	16.6	3.3	1.6	0.9
Difference	-6.2	-5.3	-2.8	-4.4	-12.6	-24.7	-3.8	-1.7	-0.9
Significance (%)	100.0	100.0	98.8	100.0	100.0	100.0	99.9	85.3	96.3

Supplemental Table 34. *Results for the subgroup considering female patients, for a lumbar treatment and for ages ranging 19-40.*

	NRS	COMI	CDS	CPS	OPS	ODI	QoL	Work	Sleep
Sample Size (N)	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0	4.0
Mean Pre	9.2	8.2	6.9	8.0	26.8	53.5	7.5	4.4	2.8
Mean Post	4.2	4.2	2.8	3.7	12.8	26.2	3.8	2.5	1.2
Difference	-5.0	-4.0	-4.1	-4.4	-14.0	-27.3	-3.8	-1.9	-1.5
Significance (%)	87.5	90.2	80.3	75.0	87.5	87.5	90.5	41.9	82.6

Supplemental Table 35. *Results for the subgroup considering female patients, for a lumbar treatment and for ages ranging 41-60.*

	NRS	COMI	CDS	CPS	OPS	ODI	QoL	Work	Sleep
Sample Size (N)	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0
Mean Pre	8.4	7.9	2.8	6.9	16.7	33.3	7.2	1.7	1.6
Mean Post	1.9	2.2	1.1	2.4	4.9	10.1	2.8	1.1	0.7
Difference	-6.5	-5.7	-1.7	-4.5	-11.8	-23.3	-4.4	-0.6	-0.9
Significance (%)	99.1	99.1	96.9	99.6	99.1	99.6	98.7	0.0	81.9

Supplemental Table 36. *Results for the subgroup considering female patients, for a lumbar treatment and for ages ranging 61-76.*

	NRS	COMI	CDS	CPS	OPS	ODI	QoL	Work	Sleep
Sample Size (N)	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Mean Pre	10.0	9.7	6.7	8.1	24.3	48.7	5.8	6.7	1.3
Mean Post	3.3	3.7	2.1	4.2	11.0	23.3	4.2	1.7	1.3
Difference	-6.7	-6.0	-4.6	-3.9	-13.3	-25.3	-1.7	-5.0	0.0
Significance (%)	75.0	75.0	58.6	75.0	75.0	75.0	41.4	65.4	0.0