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Original Research Paper

The Influence of Patient Demographics, Stage of Disease, and History of Corticosteroid Injections on the Effectiveness of Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis

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Objective: The purpose of our study was to determine the effect of PRP administrations, on pain, Cincinnati Knee Rating System and the Lysholm Knee Score in patients with osteoarthritis of the knee. In addition, we wanted to explore the relation of PRP treatment with the stage of osteoarthritis, BMI, age, gender, and intraarticular steroid administration within the last 6 months. Materials and Methods: This study was done on 371 osteoarthritic knees of 295 patients, who were 40 to 65 years of age. The patients were interviewed for age, gender, BMI, and history of intraarticular steroid injections within the last 6 months. The patients were evaluated using VAS, the Cincinnati Knee Rating System, and the Lysholm Knee Score at 1, 3, and 6 months following two intraarticular PRP injections with an interval of 4 weeks. The relation of these results with demographic data was investigated. Results: This study shows that PRP treatment is a safe and effective method that can be used in the treatment of knee osteoarthritis. Reduction of pain and clinical improvement were observed in all patients after the treatment, and the stage of knee osteoarthritis, BMI, age, and intraarticular steroid injections within 6 months were directly related to the effectiveness of PRP treatment. Conclusion: The stage of knee osteoarthritis, BMI, age, and intraarticular steroid injections within 6 months are important demographic data that require evaluation in patients for whom PRP treatment is planned. These parameters should be taken into account when selecting the patients for PRP injections.

Keywords: Osteoarthritis,knee, platelet-rich plasma, Physician's Practice Patterns

INTRODUCTION

Osteoarthritis is the most common type of non-inflammatory arthritis usually affecting the knee joint (1). As the population ages and the rate of the population participating in sports activities increases, complaints related to knee osteoarthritis increase (1). Healing can occur through regeneration of the avascular cartilage tissue(2,3). While pharmacological treatment, weight management, lifestyle changes, and physical therapy can improve symptoms in early osteoarthritis, surgical treatment can be recommended in late stages (3,4,5). Nonoperative treatments that accelerate regeneration are intended to promote healing in the periarticular tissue and prevent the progression of the disease, and hence increase the patient's quality of life. The goal is to help preserve the patient's independence in activities of daily living for as long as possible using nonoperative treatment methods.

PRP is a nonoperative treatment method that promotes soft tissue and cartilage regeneration through injection of high concentrations of platelets into the knee joint. In

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contrast with conventional treatments, the main idea in this treatment is "triggering" inflammation instead of "suppressing" it, and PRP's effect is considered to stem the acceleration of cell proliferation, collagen synthesis, and vascularization (4,5,6). PRP contains many growth factors such as transforming growth factor- β (TGF- β), insulin-like growth factors 1 and 2 (IGF 1 and 2), basic fibroblast growth factor (bFGF), hepatocyte growth factor (HGF), and vascular endothelial growth factor (VEGF) (7). In the treatment of osteoarthritis, supraphysiological doses of growth factors obtained through concentration of a patient's own platelets, stimulate the growth and differentiation of chondrocytes.

Growth factors also increase proteoglycan synthesis while decreasing the breakdown, and they play an active role in cartilage regeneration and metabolism (8). With regard to PRP's effect on cartilage degeneration, PRP has been shown to inhibit the inflammatory process induced by interleukin-1 beta and reduce the activation of nuclear factor kappa B, which plays an important role in the pathogenesis of osteoarthritis (9). Appropriate patient selection is crucial to the effectiveness and sustainability of this treatment. This study was designed to identify the patients for whom PRP treatment would predictably be successful through clinical evaluations in addition to a simple staging system. Therefore, the purpose was to contribute to the literature by providing a method of standardization for patient selection in PRP treatment. Identifying this standardization is important because it provides us with a method to avoid unnecessary treatments (cost and unnecessary procedure) and to offer an effective treatment (whether it is an operation or pharmacological treatment) in a timely fashion.

MATERIALS AND METHODS

This study was done on 371 knees of 295 patients who had osteoarthritis, who were 18 to 65 years of age, and who applied to Dumlupınar University, Physical Medicine and Rehabilitation Clinic between March 2015 and February 2016. Informed consent forms were received from all patients.

Patients with a grade of more than 3 on Kellgren-Lawrence grading scale, inflammatory arthritis, a severe deformity, a psychological disorder, and a history of drug addiction were excluded from this study. Furthermore, patients who had a cardiac disease, who were using antiplatelet medications, who had positive hepatitis markers, and who were either pregnant or nursing were also excluded.

Knee pain was measured using the visual analogue scale (VAS). The VAS is a psychometric response scale which can be used in questionnaires, and respondents specify their level of agreement to a statement by indicating a position along a continuous line between two end-points. Usually, the VAS score is determined by measuring in millimeters from the left-hand end of the line to the point that the patient marks. Knee function was assessed using the Cincinnati Knee Rating System and the Lysholm Knee Score. The Cincinnati Knee Rating System includes a functional assessment based on six abilities that are considered important for participation in sports. This can help evaluate any change following surgery or other interventions. The Lysholm Knee Scoring Scale has eight sections that are rated to produce an overall score of 0 to 100. The items of limp, support and locking are worth a possible score of 25 points; pain and instability, 25 points each; swelling and stair-climbing, 10 points each; and squatting, 5 points.

Blood Sample Collection and PRP Production

From all patients who participated in the clinical trial, 27 mL of blood was obtained with a 20-6 needle from an antecubital vein to achieve a blood to the anticoagulant ratio of 10:1. The blood samples were centrifuged at a speed of 3,000 RPM for three minutes. The buffy coat layer and the plasma in the upper portion were transferred to a concentration kit using a 10-mL syringe. The tubes were centrifuged again at a speed of 3,300 RPM for three minutes in order to obtain a concentrated PRP. The injection site was sterilized with an antiseptic solution, and 3 to 4 mL of PRP was injected into the knee joint. The patients were asked to bend and stretch their knees several times so that the PRP could spread evenly. After the second injection, stretching exercises were allowed. One month after the injections, patients were recommended to begin a strengthening program as tolerated.

Follow-up after PRP injections

PRP was injected twice, with an interval of 4 weeks, by the same physician. There were no complications after the injections. Baseline evaluation was done during the examination of the patient before the PRP injection. The second evaluation was done one month after the second PRP injection. The third evaluation was done 3 months after the second PRP injection. The fourth evaluation was done 6 months after the second PRP injection. The patients were evaluated for pain using VAS and for function using the Cincinnati Knee Rating System and the Lysholm Knee Score. The relation of these results to the stage of the knee, patient's age, gender, BMI, and additional diseases of the patient was analyzed.

Statistical Reviews

While the descriptive statistics were shown as a mean ± standard deviation for numerical data, a number of cases and percentages were used for categorical variables. Friedman test was used to determine the statistical significance of differences in VAS, Lysholm, and Cincinnati knee scores between measurement times. When the p-value from Friedman test statistics was found as statistically significant, Wilcoxon Sign Rank test was used to determine the measurement time that differed from the others.

The differences between two independent groups were compared using Mann–Whitney U test, and Kruskal-Wallis test was used for comparisons of more than two independent groups. When the p-value from Kruskal-Wallis test statistics was found to be statistically significant, Conover's multiple comparison tests was used

to determine the group that differed from others. Degrees of association between numerical data were evaluated using Spearman's Rank Correlation analyses.

Data analysis was performed using IBM SPSS Statistics version 17.0 software. A p-value less than 0.05 was considered as statistically significant. However, for all possible multiple comparisons, the Bonferroni Correction was performed in order to avoid a Type I error.

RESULTS

Two hundred and ninety-five patients were included in the study, and the average age was 51.5 ± 6.4. Of those patients included in the study, 65.8% were women, and 34.2% were men. 49.8% of patients had an osteoarthritis of the right knee. There were no additional diseases in 95.3% of our patients, and 4.7% of the patients had a history of intraarticular injection within the last 6 months.
Descriptive statistics regarding the demographic and clinical characteristics of the patients are shown in Table 1.

Table 1:

Data regarding the VAS, Lysholm, and Cincinnati scores according to follow-up times are given in **Table 2**. From baseline to 6-month follow-up, there was a statistically significant cumulative decrease in the VAS scores ($p<0.001$) (Figure 1). In the same period, both the Lysholm knee score and the Cincinnati knee score showed statistically significant cumulative increases ($p<0.001$) (Figure 1 and Figure 2, respectively). Statistically, significant differences between follow-up times were noted in the table using symbols such as "a," "b," and "c."

The VAS, Lysholm, and Cincinnati scores according to stages of patients are given for each follow-up time in **Table 3.** After the Bonferroni Correction, there were no statistically significant differences between stages, except for the baseline Lysholm and baseline Cincinnati scores, regarding the clinical scores ($p<0.0125$). The scores at various follow-up times and broken down according to stages are given in the following figures: VAS score in Figure 4, Lysholm score in Figure 5, and Cincinnati score in Figure 6. Statistically, significant differences were noted using symbols such as "a," "b," and "c."

VAS, Lysholm, and Cincinnati scores are broken down according to body mass index at each follow-up time are given in **Table 4.** After the Bonferroni Correction, the differences between BMI groups were found to be statistically significant, except for the baseline VAS, baseline Lysholm, and baseline Cincinnati scores ($p<0.0125$). VAS scores at each follow-up time within each category of BMI are shown in Figure 7. Similarly, Lysholm knee scores were given in Figure 8, and Cincinnati knee scores were shown in Figure 9. Statistically, significant differences were noted using symbols such as "a," "b," and "c."

Data related to VAS, Lysholm, and Cincinnati scores at each follow-up time in patients who did and did not receive intraarticular steroid injections within the last 6 months are shown in **Table 5.** Except for baseline scores of VAS, Lysholm, and Cincinnati, all other Bonferroni corrected scores were found to be statistically significant between other follow-up times ($p<0.0125$). With respect to intraarticular steroid injections within the last 6 months, data in each follow-up time are shown in Figure 10 for VAS score, Figure 11 for Lysholm score, and Figure 12 for Cincinnati knee score.

Table 6 shows the results of analysis of the correlation between age and changes in VAS, Lysholm, and Cincinnati scores: first month to baseline, 3rd month to baseline, 6th month to baseline, 3rd month to 1st month, 6th month to 1st month, and 6th month to 3rd month.

Table 6. Correlation coefficients and levels of significance between age and VAS, Lysholm, and Cincinnati scores according to follow-up times

Table 7 shows the comparisons between gender and changes in VAS, Lysholm, and Cincinnati scores: first month to baseline, 3rd month to baseline, 6th month to baseline, 3rd month to 1st month, 6th month to 1st month, and 6th month to 3rd month. There were no statistically significant differences between clinical scores and gender after Bonferroni Correction was performed ($p>0.0083$).

Table 7. Comparison of VAS, Lysholm, and Cincinnati scores according to follow-up times with respect to gender
Correlation coefficients and levels of significance between the amount of change in Lysholm scores and the amount of change in Cincinnati scores for each follow-up time is shown in Table 8. The increase in Lysholm scores was associated with an increase in Cincinnati scores for baseline to 1st month, baseline to 3rd month, baseline to 6th month, 1st month to 3rd month, and 3rd month to 6th month ($p<0.001$).

Table 8. Correlation coefficients and levels of significance between the amount of change in Lysholm scores and the amount of change in Cincinnati scores at each follow-up time

DISCUSSION

According to the results of this study, PRP treatment is an effective method of relieving the symptoms of knee osteoarthritis. It also has a significant effect on clinical improvement. PRP treatment was tolerated well by all patients, and no allergic reactions were seen.

In the literature, PRP was found to be promising as a treatment method in early-stage knee osteoarthritis (10, 11). Nevertheless, there are studies reporting its effectiveness in improving pain and functions in all ages and stages (11, 12, 13). We found PRP to be effective in all ages and stages although its effect was more pronounced on clinical scores in the early stages. Jang et al. (2013) reported that the effectiveness of PRP decreased with advancing age and increasing degeneration (14). Although we observed improvement in pain and functional scores in all age groups, the improvement was especially noticeable in young patients.
We showed that in addition to age and degeneration, BMI and intraarticular steroid injection within the last 6 months were critical factors affecting the degree of improvement.
It is important to know that the effect of PRP treatment is less in intensity and shorter in duration especially in overweight, obese, and morbidly obese patients so that the patients can be advised of the importance of weight

loss, sports activities, and lifestyle changes in order to improve their participation in treatment. There is a need for studies using different approaches regarding the frequency and timing of PRP injections for these patients.
Our study suggests that the results of PRP treatment are negatively affected in patients with a history of intraarticular steroid injections within the last 6 months for the treatment of osteoarthritis, and there are studies in the literature reporting the same results in patients with tendon injuries (15).

Reviewing the frequency and the dose of intraarticular steroid treatment before the PRP treatment can be beneficial in order to obtain effective results. This can be explained with the mechanism of action of corticosteroids in that they affect the intracellular signals especially by negatively affecting the growth factors, which play a role in the mechanism of action of PRP. In the case of tendons, for example, corticosteroids negatively affect tenocyte viability and proliferation; thus, they cause an increase in tendon injuries due to a decrease in matrix production (15,16).

In randomized controlled studies comparing HA and PRP, both disease-modifying osteoarthritis drugs (DMOADs), PRP is reported to be more effective than HA. Sanchez et al. (2008), in their retrospective study comparing intraarticular hyaluronic acid with PRP, found a statistically significant improvement in the PRP group (17). Spaková et al. and Cerza et al. compared PRP with a control group of patients receiving hyaluronic acid injections, and they reported better pain scores and functional improvement in the PRP group in patients with osteoarthritis (18, 19). On the other hand, Filardo et al. were unable to show any significant difference between the two methods of treatment (20).

Gobbi et al. compared patients receiving surgical treatment with patients receiving PRP injections, and they reported that return to daily activities was quicker in the PRP group (21).

İlhanlı et al., in their study comparing physical therapy with PRP injections, found a more pronounced decrease in knee pain and increase in knee functions in the PRP group (22).

Halpern et al. reported an improvement in knee pain and knee functions in patients with knee osteoarthritis, and they showed a significant decline in the progression of disease (23).

Sampson et al. reported a positive effect in 14 patients after receiving 3 PRP injections with intervals of 4 weeks. They showed an increase in cartilage thickness with ultrasound, but this study needed to be supported by studies with a larger cohort because it was done on a small number of patients (24). Furthermore, there are studies stating that evaluations based on cartilage thickness would not be reliable, that knee complaints could be present in patients with adequate cartilage thickness, and that patients could be asymptomatic even though they have thin cartilages (25). Therefore, we preferred to score pain and function instead of ultrasound measurements.

There are also studies reporting that PRP is effective for a limited period of time. In a study by Patel et al, the authors compared patients who received a single PRP injection, two PRP injections, and saline injection. They observed improvement in pain and function in patients who received PRP injections, but they reported that the improvement lasted for 6 months (26). Kon et al. found that both pain and function improved in 100 patients who had three PRP injections with an interval of 3 weeks. Despite an improvement in parameters in the first year, results deteriorated in the second year, and the authors calculated a median value of 9 months for the asymptomatic period (27). We followed up our patients for a period of 6 months. During this follow-up period, we observed a significant improvement; however, studies with longer follow-up are needed.

CONCLUSION

Our study is meaningful in terms of identifying the relation of risk factors in osteoarthritis such as BMI, age, gender, and the severity of degeneration with the results of PRP treatment, along with indicating the negative effect of corticosteroid treatment administered within 6 months on the results of PRP treatment. With regard to its contribution to current literature, our study can be expected to contribute to future studies on standardization of PRP treatment.

LIMITATIONS OF THE STUDY

The limitations of our study are a lack of a control group and reliance on patient evaluations in a self-preferred treatment.

CONFLICT OF INTERESTS

We declare that we have no conflicts of interest.

Figure 1

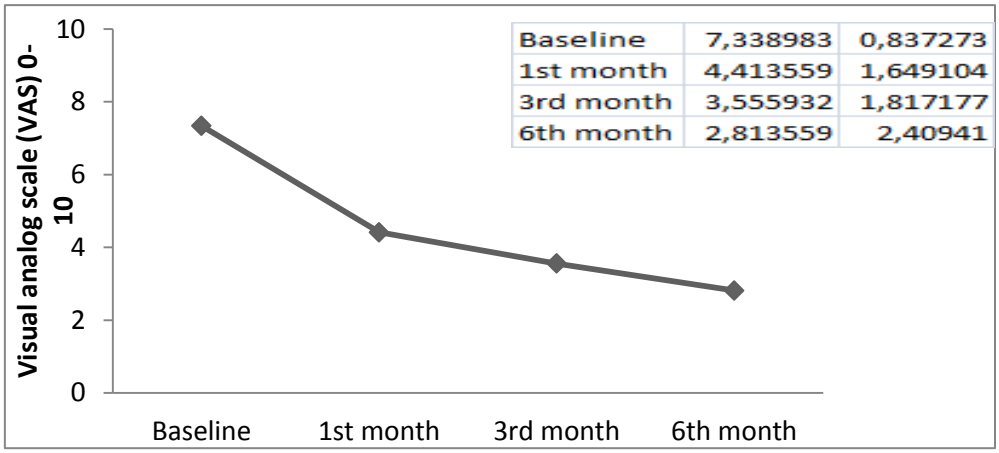


Figure 2

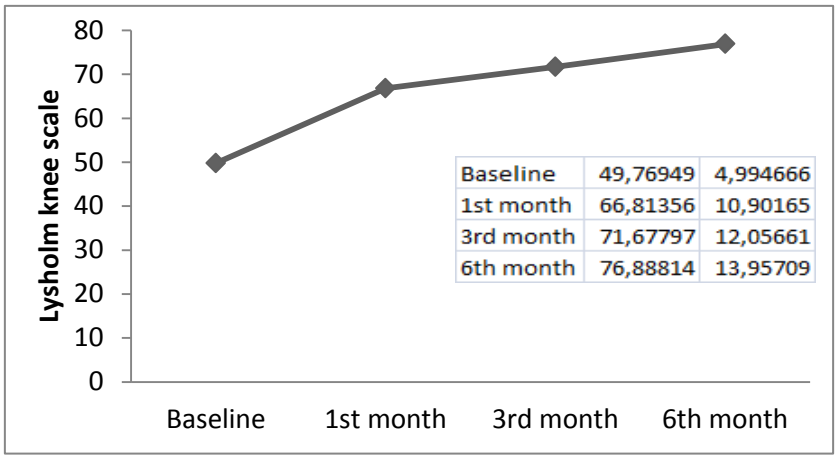
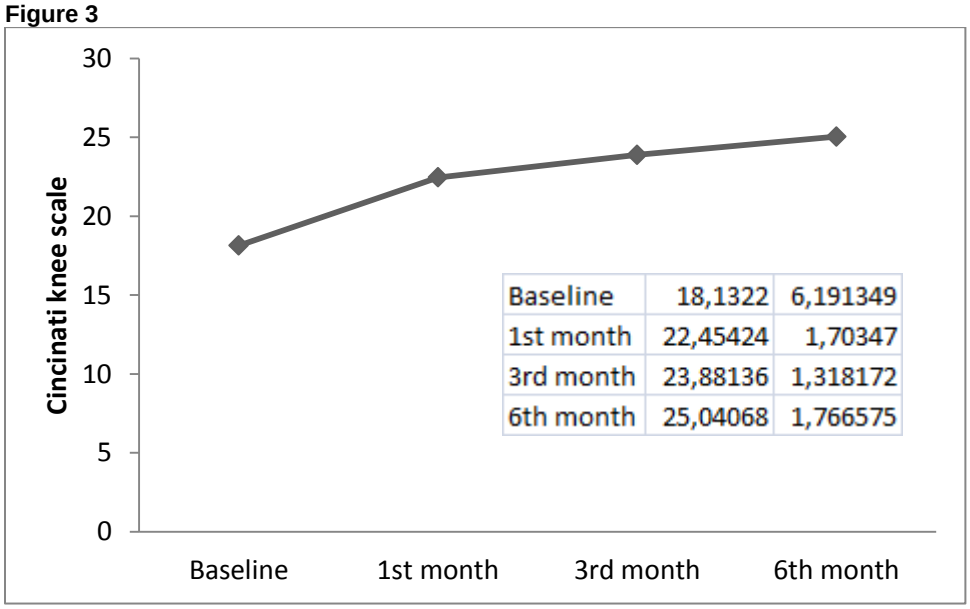
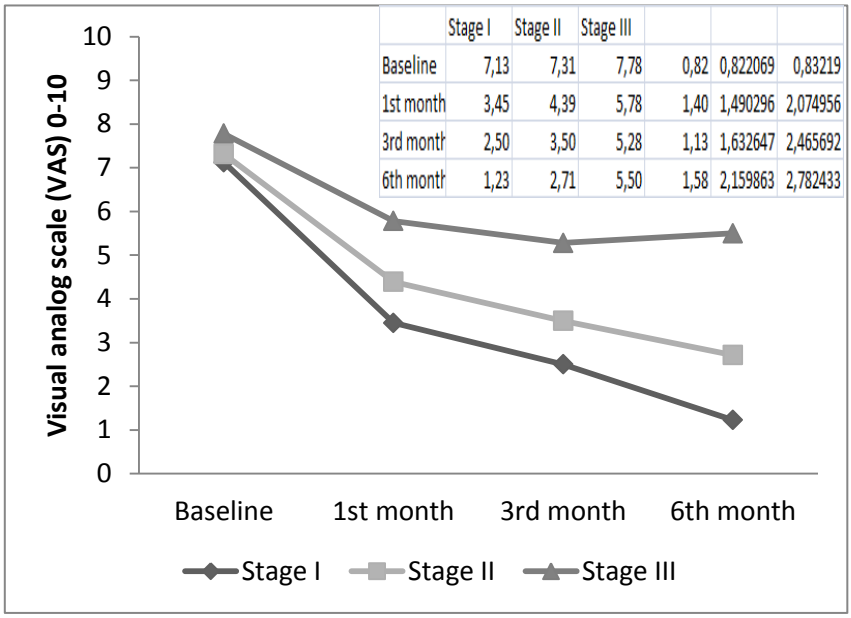


Figure 3

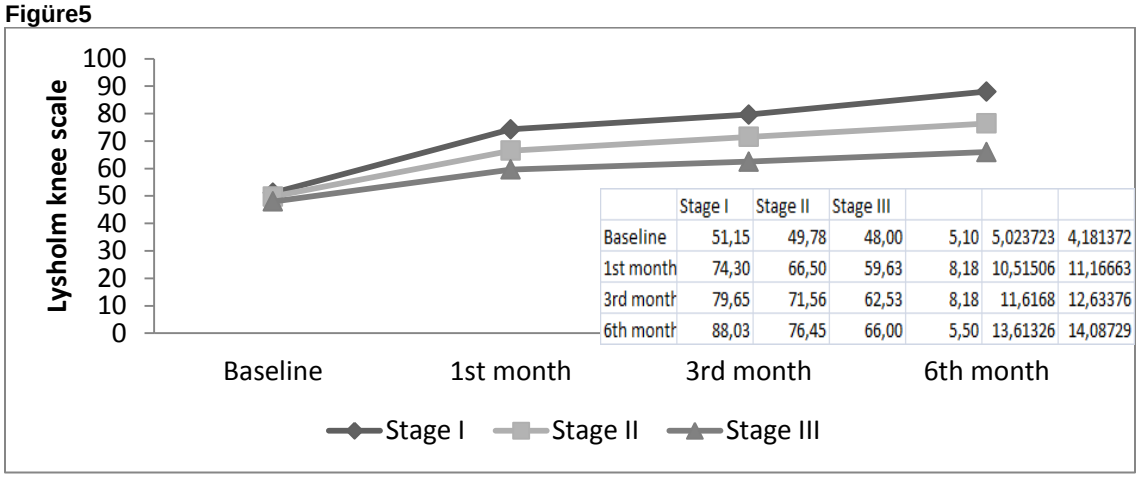


Figüre 4



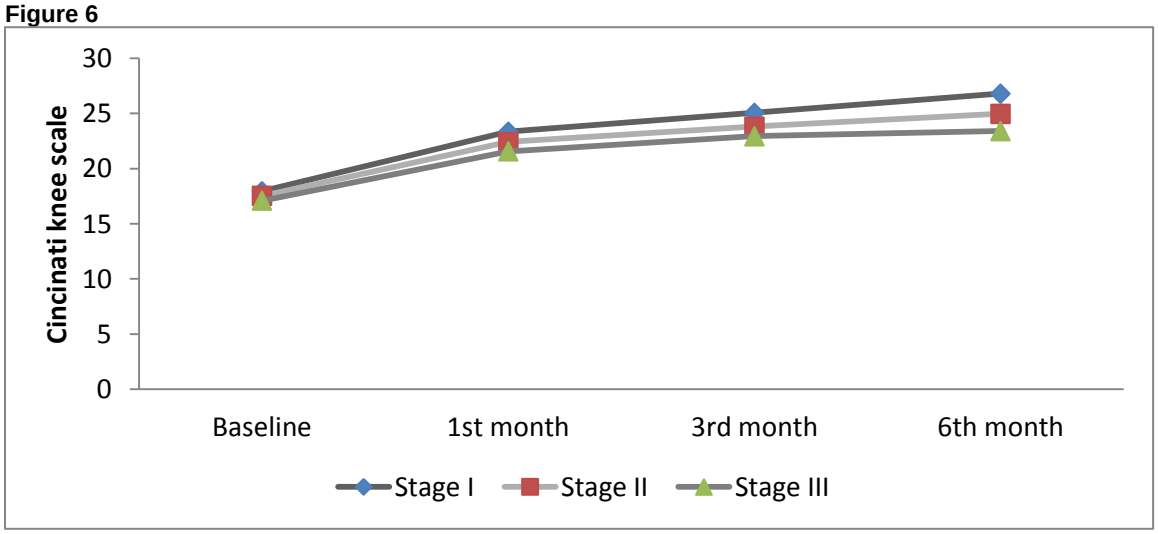
	Stage I	Stage II	Stage III			
Baseline	7,13	7,31	7,78	0,82	0,822069	0,83219
1st month	3,45	4,39	5,78	1,40	1,490296	2,074956
3rd month	2,50	3,50	5,28	1,13	1,632647	2,465692
6th month	1,23	2,71	5,50	1,58	2,159863	2,782433

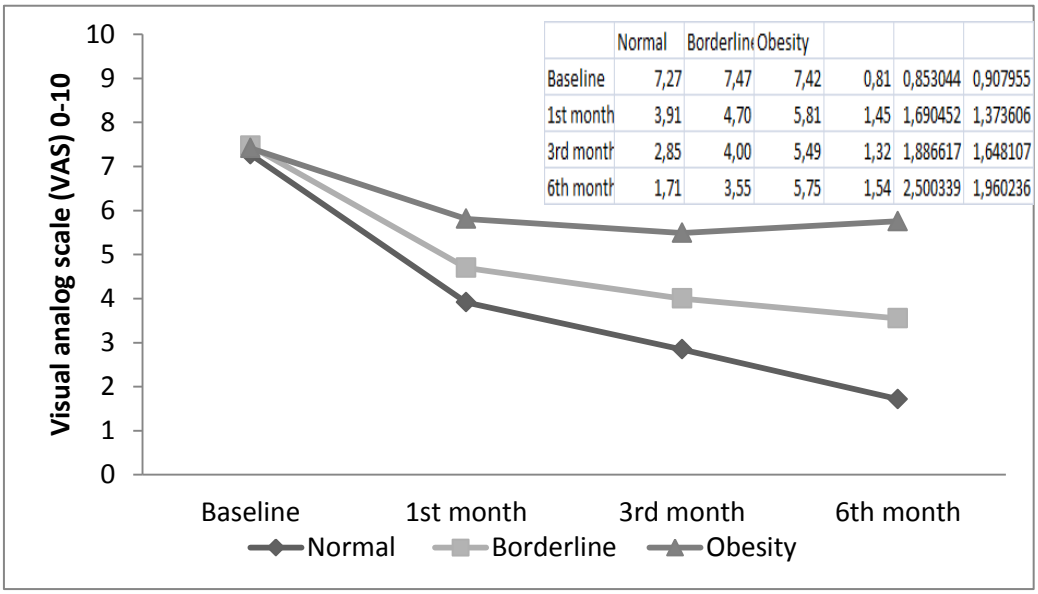
Figüre5



	Stage I	Stage II	Stage III			
Baseline	51,15	49,78	48,00	5,10	5,023723	4,181372
1st month	74,30	66,50	59,63	8,18	10,51506	11,16663
3rd month	79,65	71,56	62,53	8,18	11,6168	12,63376
6th month	88,03	76,45	66,00	5,50	13,61326	14,08729

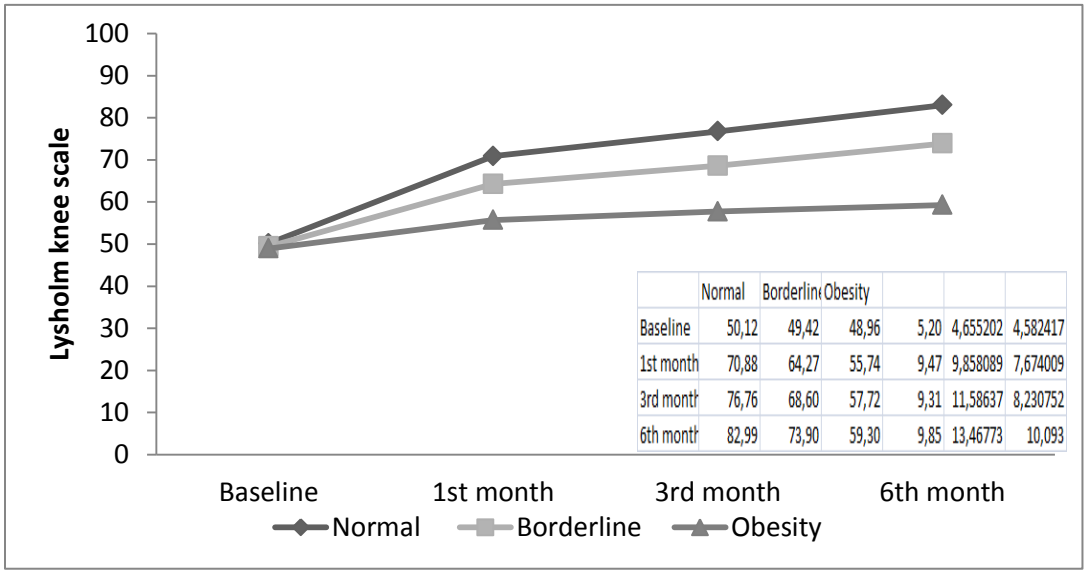
Figure 6





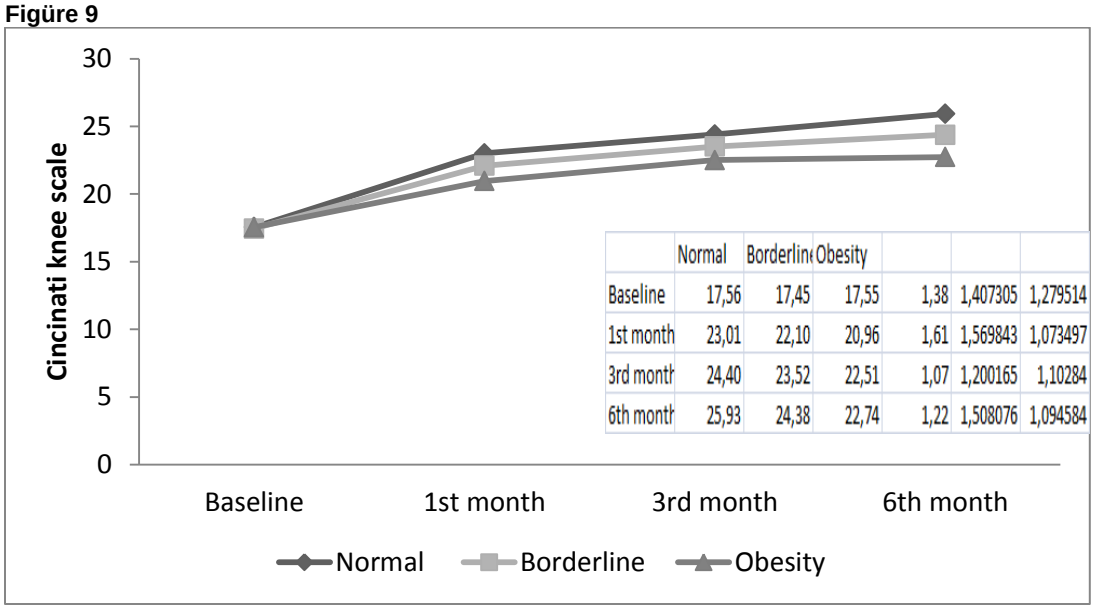
	Normal	Borderline	Obesity			
Baseline	7,27	7,47	7,42	0,81	0,853044	0,907955
1st month	3,91	4,70	5,81	1,45	1,690452	1,373606
3rd month	2,85	4,00	5,49	1,32	1,886617	1,648107
6th month	1,71	3,55	5,75	1,54	2,500339	1,960236

Figüre 8



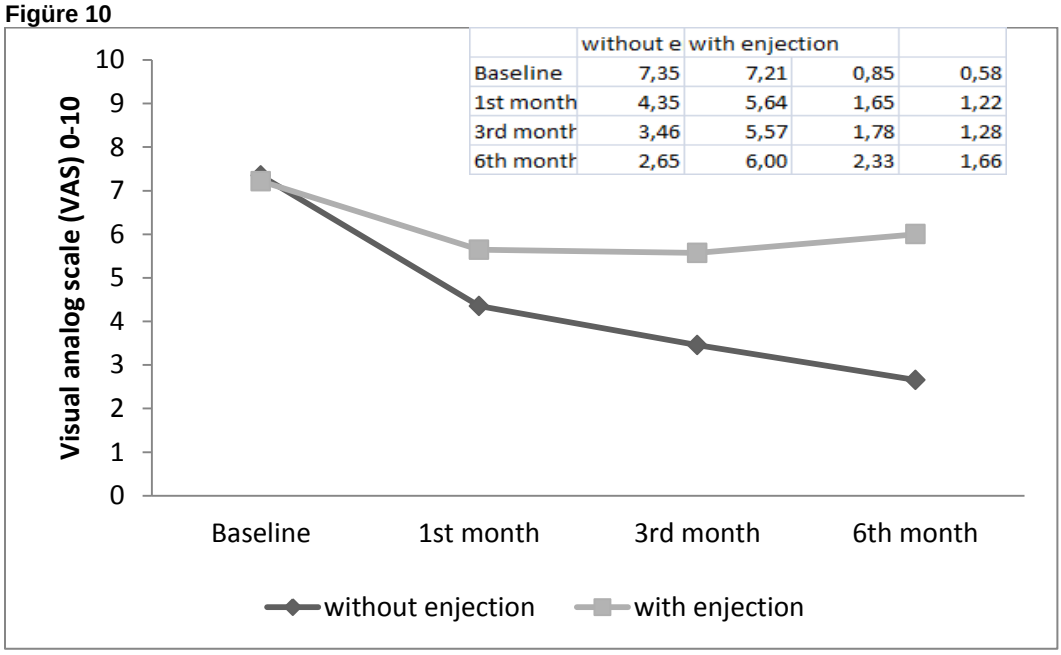
	Normal	Borderline	Obesity			
Baseline	50,12	49,42	48,96	5,20	4,655202	4,582417
1st month	70,88	64,27	55,74	9,47	9,858089	7,674009
3rd month	76,76	68,60	57,72	9,31	11,58637	8,230752
6th month	82,99	73,90	59,30	9,85	13,46773	10,093

Figüre 9



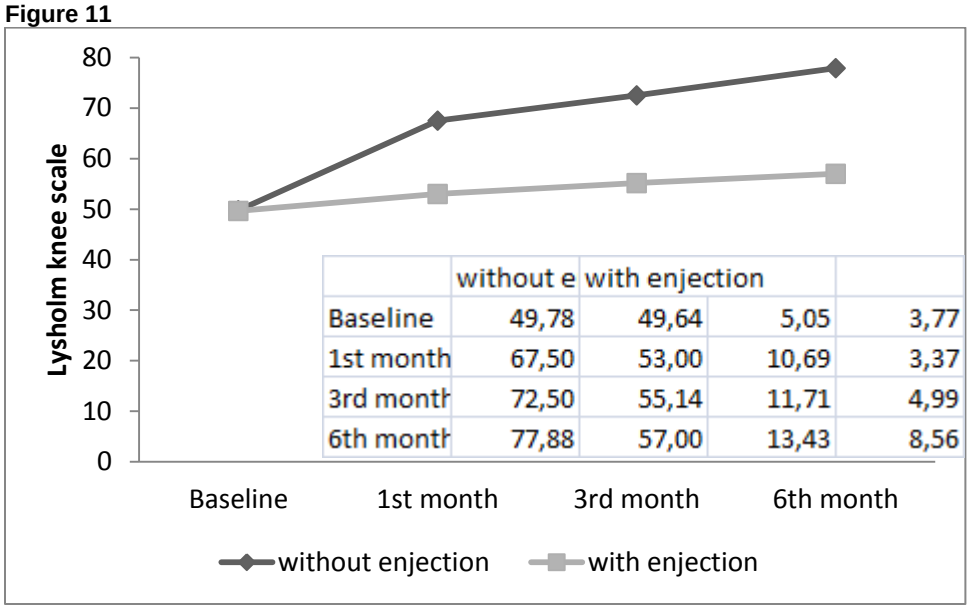
	Normal	Borderlin	Obesity			
Baseline	17,56	17,45	17,55	1,38	1,407305	1,279514
1st month	23,01	22,10	20,96	1,61	1,569843	1,073497
3rd month	24,40	23,52	22,51	1,07	1,200165	1,10284
6th month	25,93	24,38	22,74	1,22	1,508076	1,094584

Figüre 10



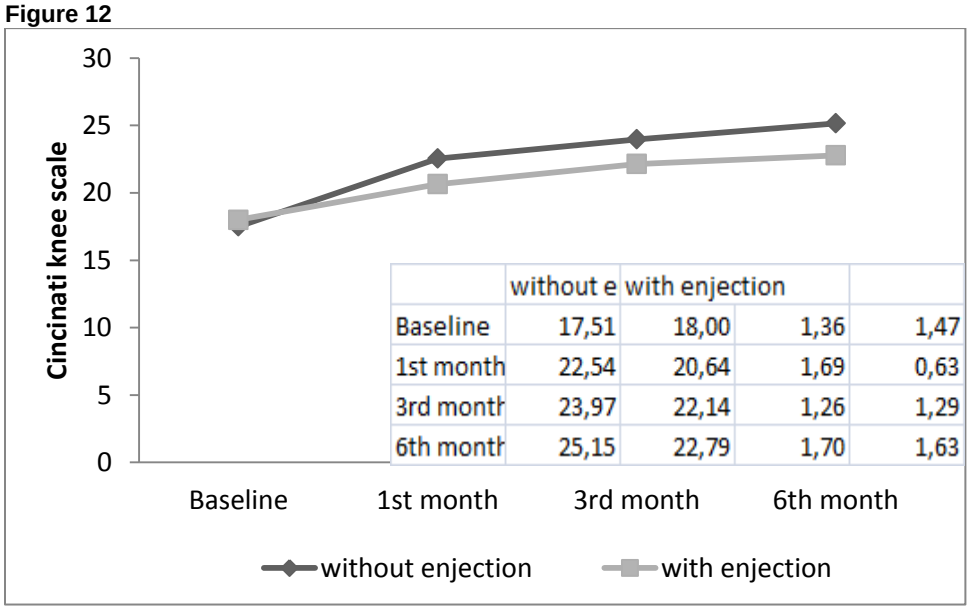
	without e	with enjection		
Baseline	7,35	7,21	0,85	0,58
1st month	4,35	5,64	1,65	1,22
3rd month	3,46	5,57	1,78	1,28
6th month	2,65	6,00	2,33	1,66

Figure 11



	without e	with enjection		
Baseline	49,78	49,64	5,05	3,77
1st month	67,50	53,00	10,69	3,37
3rd month	72,50	55,14	11,71	4,99
6th month	77,88	57,00	13,43	8,56

Figure 12



	without e	with enjection		
Baseline	17,51	18,00	1,36	1,47
1st month	22,54	20,64	1,69	0,63
3rd month	23,97	22,14	1,26	1,29
6th month	25,15	22,79	1,70	1,63

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