Radiographical and clinical results of a new conservative treatment algorithm in Legg-Calvé-Perthes disease: A retrospective study

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ABSTRACT

Objective: This study aimed to establish a feasible conservative treatment algorithm for Legg-Calvé-Perthes Disease (LCPD), clarify its limitations, and evaluate the correlations between radiographical and clinical results.

Methods: Patients diagnosed with LCPD and treated conservatively were evaluated retrospectively; 39 hips from 35 patients were included. The treatment protocol consisted of intermittent manual traction, range of motion exercises, activity limitation, bed rest, NSAID (ibuprofen 100mg/5ml), and ASA (100mg/day) during attack periods. The treatment protocol was standardized, and an algorithm was established for all the patients.

Results: The mean follow-up was 13.7 (range = 8-22) years. According to the Stulberg classification, 26 (67%) hips were good, 6 (15.3%) were fair, and 7 (17%) were poor. No activity-limiting pain was detected in any patient. The mean Harris score was 90.5 ± 5.3 for Stulberg type 1, 2, and 3 hips, but 84.2 ± 8.8 for Stulberg type 4 and 5 hips. When the patients were evaluated in terms of pain, activity, and function, it was seen that pain and activity were not different, especially in the Stulberg 1, 2, 3, and 4 patients during the mid-term follow-up. The function was the main factor correlating with the Stulberg classification. Twenty-nine (82.8%) families defined the applicability of the treatment protocol as “easy,” 4 (10.3%) defined it as “moderate,” and 2 (6.2%) defined it as “difficult.”

Conclusion: The present study demonstrated that the treatment protocol was successful and easily applicable to LCPD. Although lateral pillar classification was efficient to predict radiographic results, the Stulberg classification was not correlated with the clinical results for every subgroup.

Level of Evidence: Level IV, Therapeutic Study

Introduction

Legg-Calvé-Perthes disease (LCPD) is a self-limited childhood disease involving the immature hip joint and is characterized by avascular necrosis of the femoral head. During the natural disease progression, subchondral fractures, fragmentation, revascularization, and remodeling occur at the femoral head. Although the disease begins in childhood, it may result in hip osteoarthritis later in life.

Many different treatment methods have been developed and applied in order to treat the disease at an early age. Some surgical treatments include femoral and/or pelvic osteotomies, whereas bed rest, application of traction, administration of non-steroid anti-inflammatory drugs (NSAIDs), observation of natural course, casting, orthotics, and application of adductor tenotomy are considered conservative treatments. In the early disease period, these treatments prevent the development of restrictions in hip joint movements, recover lost or restricted hip joint movements, prevent the development of early degenerative changes, and reduce pain. The main long-term objective is maintaining the congruence of the hip joint and sphericity of the femoral head.

Although conservative treatments are widely used for LCPD, there is no reported consensus on how conservative treatment would be used, for what patients it would be an appropriate choice, and at which treatment stage would it be started. Many surgeons believe that physiotherapy or observation alone is insufficient, and it may be essential to perform many treatments concurrently. Thus, we aimed to examine mid-term clinical and radiological results of patients with LCPD treated and followed between 1995 and 2012 with our conservative treatment algorithm, reveal the limitations of this treatment, and examine the applicability of the current classification systems.

Materials and Methods

We retrospectively examined the follow-up files of patients whose files were arranged in accordance with a prospective study, who were admitted to our pediatric orthopedic clinic between 1995 and 2012 and were diagnosed with LCPD. This research has been approved by the institutional review board of the authors’ affiliated institution (ID: 2013-KAEK-64-2013/0047) and was conducted in accordance with the Declaration of Helsinki. Patients were included after obtaining informed consent from their parents.

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They were included if they (1) were diagnosed in our clinic or another center but referred to us for treatment, (2) were diagnosed before reossification of the head of the femur, (3) did not receive treatment at another center, and (4) had follow-up files filled in accordance with the treatment protocol. In total, 77 patients met the inclusion criteria and were conservatively treated by the same doctor. Patients were excluded if they (1) had bilateral involvement without definite exclusion of epiphyseal dysplasia, (2) had possible chondrolysis, Gaucher's disease, hemophilia, hypothyroidism, juvenile rheumatoid arthritis, lymphoma, mucopolysaccharidosis, Meyer dysplasia, proximal femoral osteomyelitis, septic arthritis, and sickle cell anemia, (3) traumatic aseptic necrosis could not be eliminated, (4) received their first treatment in the other centers, (5) did not show up for clinical examinations after the bone development was completed, and (6) were lost during follow-up. Finally, 42 patients were excluded, leaving 35 patients for the analysis.

Treatment and follow-up
Following the initial diagnosis, all patients were administered acetylsalicylic acid (ASA, 100 mg/day) once daily while their symptoms persisted to improve blood supply to the femoral head. NSAIDs (ibuprofen 100 mg/5 mL; 2×1/2 tsp for patients aged <8 years and 2×1 tsp for those aged ≥8 years) were administered to help patients whose movements were restricted due to pain and limping to help them become active again and treat their hip synovitis.

The use of ASA continued during the first month of the fragmentation stage. Non-steroid anti-inflammatory drugs were used during the fragmentation stage to alleviate the synovitis and later during pain attacks. Patients with Herring group A hips stopped receiving these medical treatments after the disease stages were definite and children aged >7 years were recommended to swim at least once a week. In addition to medical therapy, joint range of motion (ROM) exercises and intermittent manual traction at home were started in patients with Herring group B, B/C, and C hips. Details of the applied treatment algorithm are shown in Figure 1.

The intermittent manual traction was performed in sets, with 10 repetitions comprising a set. The traction technique was practically demonstrated to all families. For the right hip, the parent stood on the right side of the patient, held their ankle, and applied traction up to 25% of the child's weight; concurrently, the hip abduction was 20°-30°, the hip flexion was 30°-40°, and the leg was rotated inward. The parent waited for 10 seconds in this position while placing the left hand on the anterior superior iliac spine to prevent the patient from falling. For the left hip, the parent moved to the left side of the patient, switched his hands, and applied traction in the same manner. Families were instructed to perform 3 sets of 10 repetitions per day in patients with Herring group B/C and C hips until the fragmentation stage ended and ossification began. In addition, these patients were shown and applied first passive-assisted and then active-assisted hip abduction, extension, and internal rotation exercises again for 5 minutes each, during the same session.

After the initial diagnosis, patients were called for a follow-up visit every 3 months until reossification began. After reossification had begun, patients were called for follow-up visits every 6 months over a span of 2 years. During each visit, x-rays were taken, and joint ROM, differences in leg length, contracture development, and treatment compliance were recorded. Patients who developed ROM restriction or femoral head lateralization during follow-up visits were called for monthly visits until ROM reached its normal limits; during these visits, patient compliance with the treatment protocol was also checked. When the ROM reached its normal limits, the follow-up visits continued again, following the normal protocol.

Evaluation
Clinical results of all patients whose bone development was completed were evaluated using the modified Harris Hip Scoring system (HHS). Subheadings of HHS—pain, activity (limping, distance walked, and stair climbing), and function (joint ROMs and muscle strengths)—were also evaluated as subgroups.

In addition, parents of patients who came to follow-up visits after the bone development was completed were asked to evaluate the applied treatment protocol subjectively, by defining it as “easy,” “moderate,” or “difficult.” Radiographs of patients were classified using the Modified lateral pillar (LP) classification during the fragmentation stage. The modified Stulberg classification was used for the last follow-up radiographs of patients who completed bone development. Stulberg 1 and 2 were evaluated as good, 3 as fair, and 4 and 5 as poor. Radiographs were classified by the same 2 surgeons using the same protocol. If the surgeons had differing opinions, a meeting was held and a decision about the classification was made by the third surgeon.

Catterall's 4 head-at-risk signs (calcification in the lateral epiphyseal, metaphyseal cyst (Gage sign), epiphyseal lateralization, and horizontal physis) were also evaluated, and the relationships between their presence and the LP and Stulberg classifications were examined. Also, correlations between age, sex, LP classification, and Stulberg classification were evaluated. In addition, correlations between the LP classification, Stulberg classification, and the HHS and HHS subgroups (pain, activity, and function) were analyzed.

Statistical analysis
The Statistical Package for the Social Sciences (SPSS) 22 program (IBM Corp., Armonk, NY, USA) was used for all statistical analyses. For quantitative data, the suitability of the normal distribution was examined using the Kolmogorov-Smirnov test, Shapiro-Wilk test, and coefficient of variation. Independent-samples t-test was used to compare independent groups. The Kendall’s Tau-c and Spearman’s rho tests were used to examine correlations between data. Pearson Chi-square and Fisher’s exact tests were used to compare categorical data. Kappa statistics were used to analyze the agreement. Data were analyzed at 95% CI, and P < 0.05 was considered significant.

Results
A total of 39 hips from 35 patients were included. The mean age at the last follow-up was 20.7 (16-27) years, and the mean follow-up duration was 13.7 (8-22) years. Detailed patients demographics can be seen in Table 1.

HIGHLIGHTS

- Although conservative treatments are widely used for Legg-Calve-Perthes Disease, there is no consensus on how conservative treatment should be utilized. This study aimed to examine mid-term clinical and radiological results of patients treated conservatively with a combination of NSAIDs and physical therapy modalities.
- At a mean follow up of 13.7 years, this treatment algorithm resulted in good or fair radiological and functional results in most of the patients.
- The results of this study suggest that this conservative treatment algorithm can be seen in Table 1.
There was a significant ($P < 0.05$) (kappa = 0.786) agreement (84.6%) between the LP class evaluations of the 2 surgeons and also a significant ($P < 0.05$) (kappa = 0.861) agreement (89.7%) between the Stulberg class evaluations of the 2 surgeons.

In total, 82.1% ($n=32$) of hips had good and fair radiological results, whereas 17% ($n=7$) had poor radiological results. A significant correlation was found between the LP and Stulberg classifications ($P < 0.001$) (Table 2). The mean HHS was 90.5 ± 5.3 (excellent) for 32 Stulberg type 1, 2, and 3 hips, and that of 7 hips classified as Stulberg type 4 and 5 was 84.6 ± 8.1 (good) (Figure 2, 3). Among the risk factors evaluated, only epiphyseal lateralization was found to be significantly higher in Stulberg stage 3, 4, and 5 group patients ($P = 0.031$). In addition, among the 4 risk factors, only lateralization of the epiphysis and the presence of horizontal physis were found to be significantly more common in Herring B/C and C hips ($P < 0.001$).

Stulberg type was found to be better after skeletal development in children diagnosed with LCPD younger than 8 years of age (Spearman's rho = 0.387, $P = 0.015$). There was no difference in age at the time of diagnosis between girls and boys ($P = 0.147$). Also, there was no difference between the mean ages of the patients among Herring group A, B and B/C, C ($P = 0.368$). Yet, it was found that the mean age of the patients with Stulberg type 4 and 5 was significantly higher ($P = 0.041$) (Tables 3 and 4). It was observed that there was impairment in internal rotation and abduction, especially in those who had the disease after the age of 8 years ($P = 0.027$ and 0.014, respectively).

However, a significant correlation between age and other items of pain, activity, and function parameters was not detected.

When Stulberg 1, 2, and 3 types were considered as a group and 4 and 5 as another, there was a significant relationship between the Stulberg classification and overall HHS scores. Patients in the Stulberg "good" and "fair" groups could walk longer distances and experienced lesser loss of abduction, internal rotation, and limb length discrepancy. However, there were no significant differences among the subgroups regarding pain and activity (Table 3).

There was a significant correlation between LP class with walking distance and abduction loss. Patients with Herring B/C and C-type hips walked less distance without pain at the last

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**Table 1. Patient demographics**

| At the time of first admission |  |
|-------------------------------|---|
| Patients (n)                  | 35 |
| Hips (n)                      | 39 |
| Gender (M/F) [patients]       | 32/3 |
| Side(R/L) [hips]              | 24/15 |
| Unilateral/bilateral [patients]| 31/4 |
| Age (mean, min-max) years     | 6.8 (2-13) |
| Under age of 6/over age of 8 [hips] | 29/10 |

| At the time of last follow-up |  |
|------------------------------|---|
| Age (mean, min-max) years    | 20.7 (16-27) |
| Follow-up duration (Mean, min-max) years | 13.7 (6-22) |
| HHS for Stulberg type 1, 2 and 3 (mean, SD) | 90.5 ± 5.3 |
| HHS for Stulberg group 4 and 5 patients (mean, SD) | 84.6 ± 8.1 |

$n$, number; $M$, male; $F$, female; $R$, right; $L$, left; HHS, Harris hip scores; SD, standard deviation.
follow-up and experienced more loss of abduction. No significant differences were found among these groups in terms of pain and activity (Table 4).

Of 19 Herring B/C and C hips, 6 were classified as stage 4 or 5, according to the Stulberg classification. According to the LP classification, 1 patient with type B was also classified as Stulberg 4. Body mass index of this patient was >30 kg/m² at the last follow-up visit.

Twenty-nine families (82.8%) described the treatment protocol as "easy" in terms of applicability, 4 (10.3%) as "moderate," and 2 (6.2%) as "difficult."

Discussion

In this study, we presented clinical and radiological results of patients with LCPD who received conservative treatments without using a brace. Patients' demographic characteristics were consistent with the current literature. In total, 82.1% of patients had good and fair radiological results and 17% had poor radiological results. Up to 2000s, several treatment methods including surgical interventions, splints, and orthoses had been used for the treatment of LCPD. However, these methods were not as successful as expected. Since the 2000s, conservative treatments have started to be used more frequently for LCPD; however, casting and classical brace treatments have been mostly abandoned due to the need for serious patient compliance and physical and psychological difficulties in daily practice with their application. Currently, more functional braces are being used for limited periods. Although surgical procedures are being performed in certain patient groups, no consensus exists on the better and ideal choice of surgical treatment for patients. However, better results had been reported with surgical treatment in patients above age 8 with B and B/C hips and good results in patients with LP A and B regardless of the treatment.

When comparing our findings with the current literature, brace and splint treatments have no superiority over the algorithm we applied. Indeed, the use of braces and splints requires critical patient compliance; furthermore, their use is difficult for patients older than 5 and may cause physiological and psychological adjustment problems. Similar to previous literature, we reported that the disease had a significantly more aggressive course radiologically among patients whose conditions started after the age of 8 years; 4 of our 10 patients in this group were eventually classified as Stulberg 4 and 5 ($P = .041$). Furthermore, a significant correlation was found between the LP and Stulberg classification ($P < .001$). There was impairment in internal rotation, and abduction especially in those who had the disease after the age of 8 years in line with the literature. However, in our series, unlike the literature, not all patients with LP B/C or C-type hips ($P < .1$) but only 6 of the 19 hips were classified as Stulberg 4 or 5. Also, there was no significant difference between the ages of LP A, B and B/C, C patients. Also, Aksoy et al had reported similar results in their study comparing radiological and clinical results of patients treated with and without a brace. This may be attributed to good prognostic factors of an unknown cause or treatment success of our algorithm, but it is impossible to determine this with available data. In addition, of all families that we asked to subjectively evaluate our treatment algorithm, 29 (82.8%) evaluated the treatment protocol as "easy," 4 (12.3%) as "moderate," and 2 (6.2%) as "difficult." These results indicate the high compliance of our treatment algorithm.

Active physical rehabilitation therapy has been shown to be superior to the observational treatment by the means of increasing the joint muscle strength. However, a standardized conservative treatment algorithm including physical rehabilitation therapy has not yet been reported. The primary aim of our treatment algorithm was to prevent the formation of contractures in the muscles around the hip and in the adductor group, preventing the development of hinge abduction by compressing the femoral head laterally to the acetabular edge, and thus, preventing the collapse of the femoral head. It also aimed to reduce the intra-articular pressure by helping the muscle lengths grow sufficiently by applying intermittent manual
traction.4 The timing of initiation of physiotherapy in LCPD is not a well-described issue in the literature, and general consensus is that the earlier the treatment is started, the better the prognosis.19,20 Because most of these children already present with a history of intermittent limp and/or thigh or knee pain of varying duration which is a sign of synovitis and soft tissue contracture. In our study in line with current concepts, we started the physiotherapy as soon as possible in the fragmentation phase to prevent possible soft tissue contractures. The only exception for early initiation of the physiotherapy is the patients with hinge abduction which is a finding that manifests in late phases of the disease. Maintenance of hip congruence is crucial. Therefore, in these patients, achievement of congruence with surgical release of medial contractures or other surgical interventions including femoral and/or pelvic osteotomies has been reported to possess better clinical and radiological results.4 Although physeal lateralization was evident in 19 of our hips, a hinged abduction did not develop in any of the cases. Thus, surgical intervention was not performed for any of the hips including the Stulberg type 3, 4, and 5 hips in our series. An acceptable amount of hip ROM and good HHS scores could be achieved with conservative means. Nevertheless, surgical treatment must be reserved for the patients developing hinge abduction during follow-ups with conservative treatment modalities as recommended by Herring et al.4

Although the causes of LCPD are largely unclear, the basis of its pathology includes interrupted blood supply to the femoral head or dysfunctional venous drainage due to hypercoagulation.2 Therefore, ASA was administered to patients in the early stages (during the fragmentation stage) and NSAIDs were used to relieve pain secondary to intra-articular synovitis (during the fragmentation stage) and reduce the intra-articular pressure.2 Acetylsalicylic acid is generally prescribed for its analgesic and anti-inflammatory effects for children with Kawasaki disease and rheumatic fever. However, it is also used for its antiplatelet effects in acute ischemic stroke, prosthetic heart valve, shunts, transcatheter atrial septal defect, ventricular septal defect, and after ventricular assist device placement in children as well.21,22 Although it can be used for its anticoagulant effects in various conditions for children older than 3 years old, literature lacks

Table 3. Correlations between Stulberg classification and clinical findings

|               | Stulberg class I-II-III | Median | Stulberg class IV-V | Median | \( P \) |
|---------------|-------------------------|--------|---------------------|--------|--------|
| Age           | 6.3 ± 2.3               | 6.0    | 9.3 ± 3.2           | 10.0   | 0.041* |
| Gender        | Female                  | 4 (12.5%) | 0 (0.0%)         |        | 1.000c |
|               | Male                    | 28 (87.5%) | 7 (100.0%)       |        |        |
| Harris hip scores | 90.5 ± 3.3            | 93.5   | 84.6 ± 8.1         | 86.7   | 0.028**|
| Distance walked | 6 blocks              | 5 (15.6%) | 4 (57.1%)         |        | 0.837c |
| Pain          | (−)                     | 18 (56.3%) | 2 (28.6%)        |        | 0.184c |
| Limping       | (−)                     | 29 (90.6%) | 5 (71.4%)        |        | 0.213c |
|               | (+)                     | 3 (9.4%)  | 2 (28.6%)         |        |        |
| Stair climbing | Without railing         | 1 (3.1%)  | 0 (0.0%)          |        | 1.000c |
|               | With railing            | 31 (96.9%) | 7 (100.0%)       |        |        |
| Limb length discrepancy | (−)                 | 27 (84.4%) | 2 (28.6%)       |        | 0.007c |
|               | (+)                     | 5 (15.6%)  | 5 (71.4%)        |        |        |
| Loss of internal rotation | (−)                 | 24 (75.0%) | 0 (0.0%)        |        | 0.000c |
|               | (+)                     | 8 (25.0%)  | 7 (100.0%)       |        |        |
| Loss of abduction | (−)                  | 28 (87.5%) | 2 (28.6%)       |        | 0.004c |
|               | (+)                     | 4 (12.5%)  | 5 (71.4%)        |        |        |

*Mean–Whitney U test; **, chi-square test [Fischer’s test]; SD, standard deviation; n, number; (−), do not exist; (+), exist.

Bold \( P \) values represents statistical significance.
about its use in LCPD and there is no previous clinical evidence that ASA is effective for the prevention of coagulation in LCPD. Since it is known that the use of ASA is associated with Reye’s syndrome, especially during viral diseases, it should be noted that it should be used in suitable patients. In our series, we did not encounter any drug-related complications in any of our patients, as this rule and the rules of use of drugs were followed.

In general, most current studies evaluated LCPD mid-term results radiologically. Studies that examined this patient group clinically were very limited, and in those studies, it was concluded that even if the radiological conditions of patients were generally poor, patients had better clinical outcomes. In the presence of intra-articular or extra-articular pathology in the hip joint, the hip ROM is the first affected. Thus, hip abductor muscle strengths, lower extremity alignments, limb length discrepancy, the extent of ROM, limping, femoroacetabular impingement, and instability are clinical findings that should be evaluated for LCPD. In a meta-analysis of 23 studies, Nguyen et al concluded that a standardized system should be developed for staging clinical and functional results to examine the long-term results and efficacy of treatments for LCPD. In our study, we used the modified HHS system to evaluate clinical results. When the relationships between age and LP classification and HHS subheadings (“pain, activity, and function”) were examined, no significant differences were found in terms of pain and activity between poor and other Stulberg types. Furthermore, there was no relationship between the age at disease onset and “pain and activity” factors. When the correlation between HHS and Stulberg classification was considered separately for each Stulberg class, there were no statistically significant differences, especially between groups 1, 2, 3, and 4. However, when we analyzed the Stulberg classification as “good,” “fair,” (1, 2, 3) and “poor” (4 and 5), there was a significant correlation between the HHS and Stulberg classification, which generally originates from functional limitations rather than pain and activity; the subgroups of HHS. Thus, clinical differences were mostly seen in abduction loss, internal rotation loss, limb length discrepancy, and walking distance. Larson et al examined mid-term functional and radiological results of 58 previously reported hips treated with a brace or conservative methods and concluded that functional results in the third decade of the life of patients were worse than they were supposed to be.

The most powerful aspect of our study was that the treatment algorithm included a mean follow-up period of 13.7 years. In addition, the clinical results of our patients were discussed in detail and included more than radiological results. This study also has some limitations that should be addressed. First, not all factors (i.e., body mass index, trauma, smoking) that could potentially affect the prognosis of patients with LCPD were evaluated. Second, our study was not a prospective randomized trial. Multicenter, prospective, randomized comparative studies with more patients are required to determine if surgical or conservative algorithms are more appropriate for treating LCPD.

Our results revealed that our algorithm can be applied for patients over the age of 8 and with B/C and C LP, as our results are comparable with the literature and there is no exact evidence reported that surgery provides better clinical and radiological results in this group. In general, these patients have good clinical outcomes during mid-term follow-ups, as revealed in our study. However, when they are evaluated in terms of the ROM, limb length discrepancy, and walking distance, the functional results of these patients may not be as good as they seem. In future, different clinical classification systems should be established to evaluate patients with LCPD at mid-term stage.

| Table 4. Correlations Between Lateral Pillar Classification and Clinical Findings |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| | Lateral Pillar Class A-B | Lateral Pillar Class B/C-C | P |
| | Mean ± SD/n (%) | Median | Mean ± SD/n (%) | Median |
| --- | --- | --- | --- | --- |
| Age | 6.5 ± 2.6 | 6.0 | 7.3 ± 2.7 | 7.0 | 0.368* |
| Gender | Female | 1 (5.0%) | 3 (15.8%) | 0.342* |
| | Male | 19 (95.0%) | 16 (84.2%) | 0.477* |
| Harris hip scores | 90.3 ± 5.4 | 91.6 | 88.5 ± 6.9 | 90.0 | 0.560* |
| Distance walked | 6 blocks | 2 (10.0%) | 7 (36.8%) | 0.047* |
| | Unlimited | 18 (90.0%) | 12 (63.2%) | 0.118* |
| Pain | (−) | 10 (50.0%) | 10 (52.6%) | 0.069* |
| | (+) | 10 (50.0%) | 9 (47.4%) | 0.589* |
| Limping | (−) | 18 (90.0%) | 16 (84.2%) | 1.000* |
| | (+) | 2 (10.0%) | 3 (15.8%) | 0.265* |
| Stair climbing | Without railing | 1 (5.0%) | 0 (0.0%) | 0.047* |
| | With railing | 19 (95.0%) | 19 (100.0%) | 0.047* |
| Limb length discrepancy | (−) | 17 (85.0%) | 12 (63.2%) | 0.047* |
| | (+) | 3 (15.0%) | 7 (36.8%) | 0.265* |
| Loss of internal rotation | (−) | 14 (70.0%) | 10 (52.6%) | 0.265* |
| | (+) | 6 (30.0%) | 9 (47.4%) | 0.047* |
| Loss of abduction | (−) | 18 (90.0%) | 12 (63.2%) | 0.047* |
| | (+) | 2 (10.0%) | 7 (36.8%) | 0.047* |

*Mean-Whitney U test; χ², chi-square test (Fisher's test); SD, standard deviation; n, number; (−), do not exist; (+), exist.

Ethics Committee Approval: Ethical committee approval was received from the Clinical Research Ethics Committee of Istanbul Medeniyet University, Göztepe Training and Research Hospital (ID: 2013-KAEK-64-2013/0047).

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