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ORIGINAL STUDY

Cost effectiveness of two-stage algorithm (prolotherapy injections prior to total knee arthroplasty) in the management of advanced stage knee osteoarthritis in the geriatric population

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The aim of the present study was to evaluate the cost effectiveness of prolotherapy injections (PrT) combined with rehabilitation protocol (RP) prior to total knee arthroplasty (TKA)) in the management of knee osteoarthritis in the geriatric population.

Patients were divided into two groups as two-stage algorithm (PrT combined with RP prior to TKA), (Group A, n=98) and one-stage (TKA),(Group B, n=99). Clinical effectiveness was evaluated via Visual Analog Scale (VAS), The Western Ontario and McMaster Universities Arthritis Index (WOMAC) at baseline and 3-, 6-, 12-, and 18-month follow-ups. Cost–utility per quality-adjusted life years (QALY) and Incremental cost-effectiveness ratios (ICERs) of each group were calculated.

Patients in both group had better outcomes in terms of pain relief and knee functions at 18-month follow-ups ($p<0.001$). Group A had better WOMAC and VAS scores at three- and six-month follow-ups compared to Group B, while Group B had better scores at 12-month follow-ups. Both scores were not significantly different at 18-month follow-ups. Group A had the most favorable cost/QALY gain ratio ($2,968.26/QALY) compared to Group B ($5,785.52/QALY).

Both methods are efficacious and safe in treating knee osteoarthritis. However, two-stage treatment (PrT combined with RP prior to TKA) offers advantages of less cost and higher cost-effectiveness.

Keywords : Total knee arthroplasty ; prolotherapy ; cost-effectiveness ; knee ; osteoarthritis.

INTRODUCTION

Gonarthrosis is an important ailment involving knee joint and leading to pain and gait disturbance. It is a common health problem which causes pain, dysfunction and reduction in life quality. Conservative methods are preferred for its treatment, but surgical methods are employed in refractory patients *(37)*. Total knee arthroplasty (TKA) is a successful method frequently used for the treatment of gonarthrosis *(12,21)*. Total knee arthroplasty is one of major surgeries of orthopedics and has higher complication risks compared to minor surgeries *(2,18,33)*. Average life of prostheses is about 10-15 years due to factors such as prosthesis wearing, loosening, and patient related factors *(5,9)*. Previously used in older age patients and patients with advanced stage, this method has been used for younger, active and early stage patients *(34)*.

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Less invasive proliferative injection methods and rehabilitation protocols have also been used successfully in gonarthrosis treatment. In studies dealing with these methods, lower complication rates and success rates similar to prosthesis have been reported *(26).* Prolotherapy (PrT) is a regenerative injection method successfully used in knee osteoarthritis. In healing process of prolotherapy, high glucose level in extracellular matrix after injection leads to acute inflammation. This acute inflammatory response, in turn, leads to fibroblast proliferation and collagen synthesis, resulting in tissue healing and regeneration *(28).* Prolotherapy has been used for knee osteoarthritis and similar indications for a longer time, and there are many studies reporting evidence for success of the method *(1,10,16,26,27).*

No study has been found in literature dealing with cost-effectiveness analysis of rehabilitation combined with proliferative injection methods and TKA in treatment of advanced stage osteoarthritis. In the present study, one patient group was treated with PrT method whose efficiency has been approved for this condition as a two-stage treatment algorithm (first, PrT combined with regular exercise program and then TKA in patients with low satisfaction) and another patient group was treated with TKA. In follow-up examinations of at least 18 months, the two groups were compared for cost effectiveness analysis and functional evaluations. Our hypothesis was that PrT prior to TKA could reduce the cost/QALY gain ratio in the geriatric population. A successful implementation of PrT injections could provide a different approach for physicians, diminish number of patients who undergo surgery and decrease related complications, and most of all, increase the number of treatment options for physicians. Enormous contributions could be made to world economy considering the great size of patient population with this condition.

The aim of the present study was to compare the cost and effectiveness of two stage treatment algorithm (PrT combined with exercise program prior to TKA) and one-stage treatment algorithm (TKA) for gonarthrosis in the geriatric population.

METHODS

A retrospective cohort study with two equal groups was performed to assess the cost effectiveness of two-stage (prolotherapy combined with physical rehabilitation program prior to total knee arthroplasty) and one-stage (total knee arthroplasty) algorithm for treatment of advanced stage knee osteoarthritis. Study protocols were approved by The Local Ethics Committee. Each patient enrolled in the study signed an informed consent form.

Patients diagnosed III and IV levels of knee osteoarthritis according to Kellgren-Lawrence who had at least six months of symptoms resistant to at least three months of conservative methods (lifestyle modification, weight reduction, regular exercise, physiotherapy, non-steroidal anti-inflammatory drugs, intraarticular injection methods) were included in the study. Age of the patients varied between 65 and 90. Patients with rheumatic diseases, immune diseases or other systemic inflammatory diseases, patients with active infection, osteomyelitis or history of chronic infection around knee joint, patients who had undergone previous operation on knee, patients who had bleeding tendency (hereditary or acquired) and pregnant patients were excluded from the study.

In January 2016-January 2017 period, a total of 197 patients who had chronic knee osteoarthritis refractory to three months of conservative methods were included in the present study. 98 patients received PrT combined with RP prior to TKA while a similar group receiving TKA was identified during the same period. Groups were matched by age, gender and osteoarthritis severity.

The patients in Group A primarily received physical rehabilitation program combined with prolotherapy. These patients received a maximum six rounds of injections. Injections were stopped if the VAS score reduced to quarter of pre-injection level. Treatment protocol was stopped in patients who were extremely satisfied, satisfied or neutral after the injections, and they were monitored for at least 18 months. Other patients who were extremely dissatisfied and dissatisfied after six prolotherapy injections underwent total knee arthroplasty. Satisfaction of the patients was assessed using a 5-point

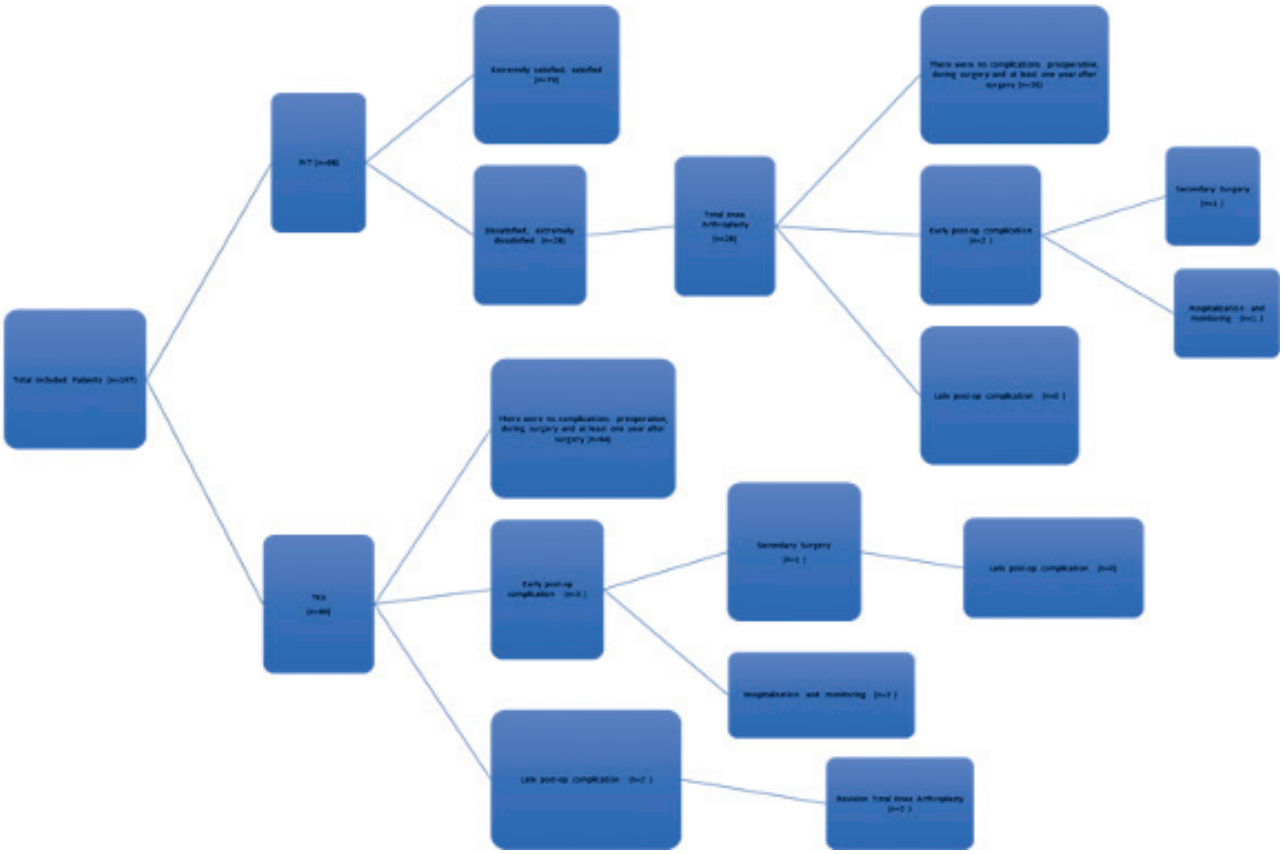

Figure 1. — Flowchart of the Study

Likert scale (extremely satisfied, satisfied, neutral, dissatisfied, extremely dissatisfied) based on patient responses *(13).* Early and late post-operative complications were treated and recorded. If a specific patient underwent secondary surgery, he/she was monitored for at least 18 months (Figure 1).

In Group B, all patients underwent total knee arthroplasty. Early and late post-operative complications were treated and recorded. If a specific patient underwent secondary surgery, he/she was monitored for at least 18 months in this group, too.

One researcher, (S.A.), performed all injection procedures. The injections were performed while the patients were in supine position and knee was flexed. Ultrasonography was used to identify location and depth of injections under aseptic conditions. Injections were carried out based on the following procedure using 27G needles : 4 mL of 25% dextrose solution was slowly infiltrated on lateral aspect of knee next to the patella, while patella was being mildly subluxated. Eight ml dextrose solution (a mixture containing 7.2 ml of 15% dextrose and 0.8 ml lidocaine) was injected to pes anserinus, tuberositas tibia, medial collateral ligament, lateral collateral ligament & biceps femoris tendon, coronary ligaments, medial patellar retinaculum, rectus femoris and patellar tendon (Figure 2). The patients were instructed to rest injected knee for three days, to refrain from heavy daily activities and to apply hot water bags for 20 minutes every two hours. Anti-inflammatory drugs were prohibited except for acetaminophen, which could be used maximum four times a day and 500 mg, if pain became unbearable.

Five days after injections, patients received a standard physiotherapy protocol described by O'Reilly et al. *(23).* This protocol included three

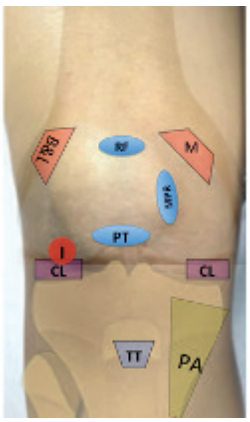

Figure 2. — The injection Points ; I : Intra-articular, P : Pes Anserinus, TT : Tuberositas Tibia, M : Medial Collateral Ligament : B&L : Lateral Collateral Ligament & Biceps Femoris Tendon, CL : Coroner Ligaments (Meniscus stabilizers), MPL : Medial Patellar Retinaculum, RF : Rectus Femoris, PT : Patellar Tendon.

sessions of about 30 minutes per resultsweek for two weeks and was carried out by the same physiotherapist. A gradual exercise program was implemented. Isometric quadriceps contraction was held in full extension for five seconds while subject was sitting on the floor with back supported and legs extended. A rolled-up towel was put under one knee and quadriceps were contracted by pushing into the floor towards towel. Then for five seconds, isotonic quadriceps contraction was held in mid flexion while patient was sitting in a chair, lifting lower leg to partially extended position and holding. Isotonic hamstring contraction was performed in a way that subject lied on front or side and bent knee pulling the foot towards body. Resistance band was used for five seconds for isotonic quadriceps contraction (exercise 2). Lastly, a dynamic stepping exercise was performed by walking up and down one step. Exercises were carried out in the abovementioned order and increased up to 20 repetitions for each leg. A home exercise program was also recommended for the patients with the same exercises three times a day for other days. Injection was terminated if the pain score reduced to at least a quarter of pre-injection level. The patients received a maximum of six rounds of injections, or they could terminate the treatment.

All patients were operated by a single surgeon (DG) using the medial parapatellar approach. All implants were fixed with cement. Fixed Posterior Cruciate Ligament-substituting knee prosthesis was used for all patients. A compressive dressing was applied after surgery, and the knee was immobilized for 24 hours. Then, a continuous passive-motion machine was used for knees. The drain and compressive dressing were taken off on the second day after operation. All patients were encouraged to walk using crutches or a walker. They started active and passive ROM exercises. The knee ROM exercises and weight bearing were increased in a gradual manner.

RESULTS

In group A, patient satisfaction after the injections was assessed using a 5-point Likert scale (extremely satisfied, satisfied, neutral, dissatisfied, extremely dissatisfied) based on responses of patients. In group A and B, pain was evaluated using a visual analog scale where the intensity of pain varied from 0 (no pain) to 10 (severe pain). The Western Ontario and McMaster Universities Arthritis Index (WOMAC), a commonly used 24-item method for evaluation of knee osteoarthritis, was employed to assess pain, stiffness and physical function. Follow-up examinations of the patients were performed independently by one of the coauthors at baseline, 3, 6, 12 and 18 months after the treatment.

Social and health service use : The costs related to knee osteoarthritis included hospital care costs. The cost of the prolotherapy included the costs of the solution, a knee injection cost, a doctor's visit cost for each injection and physical therapy costs. The cost of surgery during the waiting time and after the surgery included outpatient visits (doctor, nurse and chiropodist) while the costs of the surgery consisted of radiology, laboratory, hospital and rehabilitation services. Cost data estimated by Losina et al. *(18)* who calculated the cost of treatment in a conservative manner was used for conventional care. Treatment costs cost for 1.5 years were calculated by multiplying the cost of treatment by 1.5.

Medication use : Costs of all medications used for the patients for knee osteoarthritis after they were included in the study were calculated. These

costs were calculated using the data obtained from patients about name and dosage of the medication used for OA.

Values were expressed as mean ± SD. Two-way Repeated Measures ANOVA was used for time comparison of group effects. Analyses were conducted using a commercial software (IBM SPSS Statistics 19, SPSS Inc., an IBM Co., Somers, NY). $p<0.05$ was considered statistically significant.

Cost per quality-adjusted life years (QALY) was calculated as a measure of cost–utility ratio. To determine 18 months UALY gain, utility score at 18-month follow-up was subtracted from baseline utility score. Incremental cost-effectiveness ratios (ICERs) was used to evaluate the cost effectiveness of the treatments. ICERs were calculated based on the formula : (CB - CA) / (QB - QA), where CB and CA are the cost of treatment B and treatment A, respectively, and QB and QA are the QALY gained for treatment B and treatment A, respectively. The ICERs of group A and B were calculated as relative to conventional care. Threshold willingness to pay was considered $50,000/QALY, which is the cost-effective ratio of conservative treatments used in most studies, was used *(20),* since it is the most conservative estimate.

Demographic features of patients in Group A and B were similar (Table 1). The patients in the study were monitored with follow-ups for at least 18 months. Initial average WOMAC and VAS scores of Group A and B were not different (p=0.112 and 0.101, respectively) (Table 2).

Seventy patients in Group A benefited from injection treatment and were monitored without performing an extra procedure. TKA was applied on a total of 28 patients who were not satisfied with the protocol (dissatisfied : n=16, extremely dissatisfied : n=12). Infection developed in one

Table 1. — General characteristics of study groups

	Total	Group		p
		A	B	
GENDER *(Male/Female)*	45(22.8)/ 152(77.2)	25(25.5)/ 73(74.5)	20(20.2)/ 79(79.8)	0.375
SIDE *(Right/Left)*	97(49.2)/ 100(50.8)	47(48)/ 51(52)	50(50.5)/ 49(49.5)	0.721
STAGE *(3/4)*	43(21.8)/ 154(78.2)	24(24.5)/ 74(75.5)	19(19.2)/ 80(80.8)	0.368
AGE	68.54±4.44	68.11±4.37	68.98±4.47	0.085
DURATION OF COMPLAINT	8.17±3.10	8.04±2.97	8.29±3.23	0.569

Data are shown as mean ± standard deviation / Median / Minimum-Maximum *or frequency, percentage p: Independent samples t test or chi-square test were used.*

Table 2. — VAS and WOMAC scores of two patient groups

Variables	GROUP		p^1
	A	B	
VAS_0	7.34±1.23 (a)	7.58±0.76 (a)	0.101
VAS_3AY	4.78±2.44 (b)	5.82±0.9 (b)	<0.001
VAS_6AY	2.85±2.21 (c)	3.61±1.19 (c)	0.003
VAS_12AY	1.96±1.57 (d)	1.42±1.41 (d)	0.013
VAS_18AY	1.61±1.68 (d)	1.34±1.42 (d)	0.227
p^2	<0.001	<0.001	
WOMAC_0	73.12±6.28 (a)	74.67±7.26 (a)	0.112
WOMAC_3AY	56.96±14.91 (b)	61.79±7.57 (b)	0.005
WOMAC_6AY	42.17±16.68 (c)	46.35±8.17 (c)	0.026
WOMAC_12AY	30.38±12.74 (d)	25.22±9.94 (d)	0.002
WOMAC_18AY	27.11±11.5(e)	24.32±9.74 (d)	0.068
p^2	<0.001	<0.001	
TOTAL_COST	2,128.16±2,886.96	6,291,47±1,394,36	<0.001

p^1: Between-subject comparison, p^2: Within-subject comparison, (abcde): In same column, different letters indicate statistically significant difference.

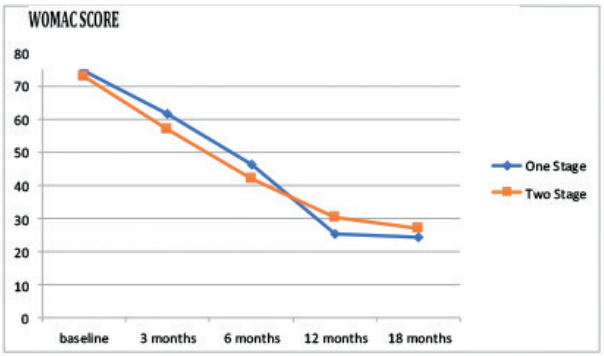

Figure 3. — WOMAC Score Changes of Groups.

of the patients who had TKA. This patient was given antibiotics treatment for a two-week hospital stay period and fully recovered. Insert dislocation occurred in one patient. Insert was replaced and lateral release was performed. Drainage from wound site and infection were observed in two patients in Group B. These patients were recovered after two weeks of antibiotics treatment as in-patients. Insert dislocation occurred in one patient due to falling. Insert was replaced and soft tissue procedures were performed on this patient. Revision knee prosthesis surgery was carried out for two patients who had prosthesis loosening (Figure 1). Intra-group statistical analyses showed significant improvements (P<0.001) in Group A and B for WOMAC and VAS scores compared to baseline. When the two groups were compared, VAS scores in the third and sixth month follow-ups (p<0.001 and p=0.003, respectively) and WOMAC scores in the third and sixth month follow-ups (0.005, 0.026, respectively) were significantly better in Group A while both scores were significantly better in Group B in the twelfth month follow-ups (p=0.013 and 0.002, respectively). No difference was observed between Group A and B for VAS and WOMAC scores in the eighteenth month follow-ups (p =0.227 and 0.068, respectively) (Table 2, Figure 3).

Table 3. — Utility Scores of Groups

	Baseline utility score	18 months utility score	QALY gained/ 18 months year
GROUP A	0.436	0.733	0.297
GROUP B	0.419	0.738	0.319

QALY : Quality-adjusted life years

Utility scores of Group A was 0.436 QALY before the treatment and improved to 0.733 QALY post-treatment, meaning an average increase of 0.297 QALY. Utility scores of Group B increased from 0.419 QALY before the treatment to 0.738 QALY after the treatment, and the increase was 0.319 QALY. The estimated cost for an 18-month of conventional care (including NSAIDS, physiotherapy, ambulatory aids and acetaminophen) was $964.50. Considering a utility score of 0.09 QALY gained, cost of 1 QALY gained was $10,716.67. Group A with a cost of $2,968.26/QALY was more cost-effective within a willingness-to-pay threshold of $50,000/QALY compared to Group B ($14,756.87/QALY) (Table 3 and 4).

DISCUSSION

Knee osteoarthritis is a debilitating condition which can decrease patient's satisfaction and comfort considerably. Treatment strategies differ from clinic to clinic and optimal treatment algorithm continues to be debated *(3,4,5,27)*. One- and two-stage algorithms for the treatment of this condition were compared in the present study. It was observed that both treatment modalities were clinically effective.

Table 4. — Cost-utility ratios for the groups

	Cost per 18 months (USD)[a]	QALLY Gained Per 18 months	Cost per QALY gained (USD) [b]	ICER vs. Conventional care (/QALY)[c]
GROUP A	$468.72	0.297	$1,578.18	$2,968.26
GROUP B	$1,385.68	0.319	$4,343.82	$14,756.87

QALY : quality-adjusted life years; ICERs: Incremental cost-effectiveness ratios. a Cost per 18 months including average cost of the treatments. b Cost per QALY gained determined by the formula : (Cost per 18 months)/(QALY gained per 18 months). c ICER vs. conventional care determined by the formula (Cost per 18 months of groups-cost per 18 months conventional care)/(QALY gained per 18 months of groups-QALY gained per 18 months conventional care) for each groups.

However, two-stage algorithm offered advantages of less cost and higher cost-efficiency.

Proliferative injection methods (prolotherapy, platelet-rich plasma, hyaluronic acid etc.) have been successfully used for the treatment of degenerative problems *(16,36).* There are many studies in literature with substantial evidence for the success of these methods *(16,27,36)*. Prolotherapy is one of these methods and high clinical success and low complication rates in knee osteoarthritis have been reported with this method *(1,25,26).* Robago et al. *(27)* compared intra- and peri-articular prolotherapy injections where saline injection was used with exercise group in a three-arm, blinded randomized controlled study and reported that prolotherapy treatment resulted in better clinical outcomes compared to saline injections and at-home exercises. Sit et al. *(31)* evaluated prolotherapy injections in the treatment of knee osteoarthritis in a triple-blinded randomized controlled trial and obtained successful results after one year of follow-ups. In another study, Robago et al. *(26)* investigated long-term effects of prolotherapy and found that clinical efficacy of prolotherapy continues increasingly in a 2.5 year period. Similar to the study by Robago et al., intra- and peri-articular injections were carried out for our patients in the present study. Clinical outcomes of the patients were similar to those in other studies using the same method. Significant improvements were obtained in WOMAC and pain scores compared to pre-surgery level. In addition, success of the treatment was not different from the other group.

Unlike other methods, prolotherapy can be performed intra-articularly or periarticularly. Thus, proliferation and healing can be achieved in intra- and peri-articular structures, increasing the stability of knee and its motility. In this context, Topol et al. *(35)* studied inside the joint arthroscopically after prolotherapy injections they performed. They studied cartilage structures in biopsy specimens, and observed activation in cartilage structures, development of cartilage along with variable cellular organization, fiber parallelism and cartilage typing patterns consistent with fibro- and hyaline-like cartilage. In rat models, increased inflammatory reaction and significant enlargement in ligament or cartilage structures were observed at injection sites after prolotherapy *(14,15).* Based on magnetic resonance imaging, Rabago at al. *(25)* found that prolotherapy injections increased cartilage volume stability. In the present study, pain and WOMAC scores were parallel to each other both in prolotherapy and TKA groups. This finding implied that prolotherapy methods not only relieved pain of patients, but also improved knee functions.

There is an established conviction that proliferative injection methods should be performed for young or early-stage patients with knee osteoarthritis, while total knee arthroplasty is more effective in advanced age patients. Kon et al. *(17)* investigated the effect of platelet-rich plasma (PRP) and hyaluronic acid on the success of knee osteoarthritis. They found better outcomes with both treatment approaches in active young patients and in early stage osteoarthritis compared to patients older than 50 years and patients with advanced stage osteoarthritis. In their randomized, double-blinded study, Jubert et al. *(16)* found that PRP provided significant improvement in patients with advanced stage knee osteoarthritis, which was superior to control treatment of corticosteroid injection. In the same study, PRP was not better than corticosteroid use in patients older than 67 years old and in patients with advanced stage of the condition. Uçar et al. *(36)* carried out a randomized prospective study and found that VAS and WOMAC values were statistically lower than pre-injection values in middle-aged patients (younger than 65 years of age) who had hyaluronic acid injection. On the other hand, no significant changes were observed in patients older than 65 years at 12-month follow-ups. No comparison was made in previous prolotherapy studies for age and stage of the condition. In the present study, no difference was found between old and young patients and between stage 3 and stage 4 patients for the success of the treatment. Results of the present study revealed that two-stage algorithm could be used in patients without serious defects and instability irrespective of age of the patients and stage of the condition.

Prolotherapy injections were combined with rehabilitation program in the present study. Since prolotherapy method allows healing of not only

structures inside the knee but also peripheral knee support structures and connective structures, strengthening and rehabilitation via exercise programs of these structures healed and rejuvenated by prolotherapy are crucial for the success of treatment method. In parallel to our findings, a multidisciplinary approach combining prolotherapy and exercise programs were adopted for patients in prolotherapy studies. It has been known that appropriate rehabilitation programs could help substantially in treatment of osteoarthritis patients. Rehabilitation and home exercise program used in the present study was used in some earlier studies and has been found useful in treatment of knee osteoarthritis. Our results indicated that this rehabilitation program made a major contribution to the success of two-stage algorithm presented in our study and that combining injection method with rehabilitation program improved the success rate and resulted in a clinical success rate comparable to TKA.

Total knee arthroplasty is a method used successfully in knee osteoarthritis with an 80-90% standing rate and high clinical success even in 10-15 years of follow-ups *(9,12,20).* Bistolfi et al. *(4)* evaluated two different TKA methods (Fixed and Mobile-Bearing) and mentioned that minimum 85% of patients in both groups reported being ''satisfied'' or ''enthusiastic'' at an average 116 months of follow-up periods. Nevertheless, despite many studies carried out lifetime of prostheses cannot go beyond 10-15 years due to factors such as polyethylene wearing, osteolysis and patients themselves *(5,9).* In a more recent study, Pitta et al. *(24)* monitored 16,083 patients for whom they performed TKA using modern prostheses and improved techniques for at least five years. They found that 417 patients needed revisions, and many of them were due to polyethylene wearing which has not been remedied yet. Dion et al. *(8)* reported that even in patients for whom highly cross-linked polyethylene, developed specifically to prevent wearing, was used wearing and osteolysis were still the most common reasons for failure of prostheses.

Previously used in elder patient and in patients with more advanced stage, this method is now used in younger and active patients *(34).* Some authors found no difference between young and old patients for functional outcome, but some others reported lower lifetime of prostheses in younger patients because of their more active lives. Aujla et al. *(3)* reported 85.5% success rate for TKA in 1,283 patients who were 55 years old and younger. They also found that 5.4% of the patients underwent revision in an average of 10.8 months and that 98.2% of the revisions were due to aseptic loosening. Lizaur-Utrilla et al. *(19)* compared patients older and younger than 55 years of age for the outcomes of TKA for osteoarthritis. Using 10-year follow-ups, they found similar clinical outcomes, revision and complication rates in older and younger patients. Shah et al. *(30)* found higher peri-prosthetic infection and mechanic loosening in patients younger than 65 years of age and pointed to twice higher obesity frequency in these patients as the most frequent culprit. Besides, younger patients had less severe radiographic disease and reported lower outcome scores than older patients undergoing total knee arthroplasty. Goh et al. *(11)* performed TKA in 114 patients who were younger than 50 years of age and found that 88.8% of them were satisfied with the results and 86.6% of them mentioned that the treatment fulfilled their expectations. However, the authors also reported that 97.8% of the patients went for a revision in an average of 7 years (range 3-16 years). After all, a second operation is needed for these patients after an average of 10 years. Because of advanced age of the patients needing the second operation, additional morbidity and anesthesia risks are higher *(7).* Due to previous prosthesis surgery, soft tissue support is poor and bone stock is less. As a result of these problems, success of revision surgeries has been shown to be lower than the primary ones *(29).* Mortazavi et al. *(22)* evaluated a total of 499 total knee arthroplasty revisions and stated a failure rate of 18.3% at an average follow-up period of 64.8 months. Early period failure rate (less than two years) was 83%. In the present study, despite turning back to prosthesis in 29% of the patients, prolotherapy injection supported with planned rehabilitation programs provided satisfactory outcomes in 71% of the patients without the need for surgery at follow-up periods of at least 18 months. Nevertheless, 18-month follow-

ups are not enough to show long term effects of this treatment modality, success rate and surgery requirement. Therefore, additional studies with longer follow-ups are needed. We suggest that two-stage algorithm could lower the need for surgery in most of younger patients who do not have serious deformity and instability, and thus reduce number of revision surgeries and surgery-related complication rates.

Incidence of knee osteoarthritis have recently been on increase. As parallel to this increase, numbers of patients treated with various conservative methods and patients who undergo surgery increase, constituting a significant part of health care expenditures. Therefore, many cost studies were carried out on knee osteoarthritis. Stan et al. *(34)* carried out cost-efficiency analysis on three patients for whom they performed a) conservative treatment (standard rehabilitation program), b) total knee arthroplasty after high-tibial osteotomy and c) primary total knee arthroplasty. Although they found similar clinical outcomes in TKA and TKA after HTO, cost was significantly lower in patients who had TKA only, and TKA was more cost-effective than TKA after HTO. Conservative treatment performed in late stages, on the other hand, was the method with the lowest clinical efficiency and cost-effectiveness. Dakin et al. *(6)* compared the cost-effectiveness of primary TKA and conservative treatment and concluded that TKA is highly cost-effective compared to conservative method. In the present study, the most successful method of the previous studies (TKA) was used for comparison. Other study group comprised a successful injection treatment in combination with a rehabilitation program. With this algorithm, 71 patients were treated without need for surgery. Twenty-nine of the patients were operated because they were not satisfied with the outcome. The clinical results of the two groups were similar after an average 18 months of follow-up periods. Only rehabilitation program was used for comparison in previous cost analysis studies. In the present study, rehabilitation program was combined with a regenerative injection method whose efficiency in knee osteoarthritis has been confirmed. Based on 18-month follow-up evaluations, more cost-effective outcomes were observed in patients who had TKA during their first admission. Thus, multidisciplinary approach seemed beneficial for osteoarthritic patients. Many patients may benefit from regenerative methods in combination with proper rehabilitation programs.

Some authors reported that conservative treatment in knee osteoarthritis failed to successfully correct abnormal joint loading, resulting in continued disease progression. They mentioned that knee osteoarthritis patients would eventually experience disease progression and undergo TKA with the same frequency and at the same rate as if conservative methods had not been employed *(34).* Furthermore, some authors argued that due to disease progression, success of TKA was low in patients for whom conservative treatment was used at early stages *(34).* Findings of the present study supported this conclusion. Based on 18-month follow-ups, significant improvement was obtained not only in pain levels but also in knee functions of the patients. There was no difference for knee functions between the two groups at the last follow-ups. When 29 patients who had TKA because of their dissatisfaction with prolotherapy and 99 patients who had direct TKA were compared, clinical outcomes were not different at the last follow-ups. It has been known that success rate of knee arthroplasty is higher in patients who perform regular exercises before arthroplasty *(32).* Regular exercises were made habitual in patients who received two-stage treatment. We argue that this practice made a positive effect on patients who underwent surgery after failed injections. In addition, ligamentous imbalance was mentioned to be one of the reasons lowering the life of arthroplasty *(34).* Rehabilitation program combined with prolotherapy regulates ligament balance of knee and posture of patients. Thus, loosening could be decreased in patients who had knee arthroplasty after prolotherapy.

Two-stage algorithm group had better outcomes for WOMAC and VAS scores at three- and six-month follow-ups, whereas at 12-month follow-ups clinical outcomes and pain scores were better in one-stage group (Figure 3). Based on 18-month follow-ups, on the other hand, success of the two approaches were similar. These findings mean that prolotherapy method provided a fast clinical

improvement in patients right after the start of treatment, while total knee arthroplasty resulted in satisfactory outcomes in six months after increasing patient satisfaction and healing of surgery related tissues. Effects of the treatment modalities after a year, on the other hand, were similar.

In conclusion, findings of the present study indicated that peri- and intra-articular prolotherapy injections combined with regular rehabilitation programs could provide significant improvement in outcomes in knee osteoarthritis, decrease the number of patients undergoing knee arthroplasty, and thus lower treatment costs because of similar clinical outcomes of these methods with direct TKA practice in geriatric population.

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