Effects of arthroscopic anterior cruciate ligament reconstruction combined with sodium hyaluronate on knee function and inflammatory markers in anterior cruciate ligament injury patients with or without knee osteoarthritis

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Abstract

Background. Anterior cruciate ligament injury (ACLI) is a common sports injury of the knee joint, and ACLI patients often develop early knee osteoarthritis (KOA) after surgery. This may be due to the activation of a post-surgical inflammatory response.

Objectives. To investigate the treatment efficacy of arthroscopic anterior cruciate ligament reconstruction (AACLR) combined with sodium hyaluronate (SH) in ACLI patients with and without KOA.

Materials and methods. This prospective cohort study included 226 ACLI patients with or without KOA who were admitted between July 2015 and December 2018 into The Second Xiangya Hospital, Changsha, China. All patients received AACLR surgery combined with 50 mg SH. Serum levels of inflammatory markers were evaluated with enzyme-linked immunosorbent assay (ELISA), and knees were assessed using the Lysholm Knee Score and the International Knee Documentation Committee Knee Evaluation Form (IKDC). The range of motion of the knee joint was also measured.

Results. The mean disease course was 73.39 ±30.90 months for ACLI patients with KOA, which was significantly longer than for those without KOA (3.74 ±1.70 months). Also, surgery duration was remarkably longer for patients with KOA than it was for those without this disease. The Lysholm Knee Score and IKDC score, as well as the range of knee joint motion were significantly improved in all patients after treatment compared to baseline. However, no significant differences were found between the groups. One day, 3 days and 7 days after surgery, significantly higher inflammatory marker levels were found in the patients with KOA than in those without KOA.

Conclusions. The AACLR combined with SH was efficacious as it improved knee function and inflammation in all patients, while patients without KOA exhibited a more rapid recovery from the post-surgical inflammatory response.

Key words: inflammatory markers, knee osteoarthritis, sodium hyaluronate, anterior cruciate ligament injury, arthroscopic anterior cruciate ligament reconstruction

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Background

Anterior cruciate ligament injury (ACLI) is a common sports injury of the knee joint, and is also a frequent result of falls, traffic accidents and excessive knee flexion.[1,2] Incidence of ACLI in the USA is reported to be more than 120,000 cases per year.[3] Reconstruction surgery is currently the preferred treatment method for ACLI,[4,5] with arthroscopic anterior cruciate ligament reconstruction (AACLR) widely used in this regard.[6] Furthermore, the number of patients receiving AACLR gradually increased between 2004 and 2009.[7] Despite the methods available for the treatment of ACLI, patients often develop early knee osteoarthritis (KOA) after surgery, which may be due to the activation of an inflammatory response.[8,9] Nonetheless, ACLI patients may still develop KOA if they do not receive treatment for their injury promptly.[10]

Besides AACLR, the use of sodium hyaluronate (SH) is a clinical option for many injuries, including spinal cord injury[11] and partial-thickness rotator cuff tears.[12] However, the application of SH to ACLI is not fully understood. Moreover, studies on the use of AACLR and SH in ACLI patients with KOA, as well as their effects on inflammatory mediators are inadequate.

Objectives

The current study aimed to investigate the effects of AACLR combined with SH in the treatment of ACLI patients with or without KOA, with a particular focus on dynamic changes of inflammatory markers. This research may provide more clinical evidence for the application of AACLR and SH in ACLI patients with KOA.

Materials and methods

Patients

This prospective cohort study included 226 patients with ACLI who were admitted between July 2015 and December 2018 into The Second Xiangya Hospital, Changsha, China. All enrolled patients were divided into ACLI combined with KOA (ACLI/KOA) group and ACLI without KOA (ACLI) group, according to each patient's diagnosis. A diagnosis of ACLI was confirmed using X-ray and magnetic resonance imaging (MRI), in addition to arthroscopic assessment during surgery. The KOA was diagnosed according to the 2019 guidelines for the diagnosis and treatment of osteoarthritis (OA) published by the Chinese Medical Association of Orthopedic Surgeons.[13] Inclusion criteria included: 1) meeting the diagnosis criteria for ACLI and KOA; 2) a complete rupture of the anterior cruciate ligament; 3) no treatment, painkillers or anti-inflammatory drugs in the 3 months before the study; and 4) unilateral ACLI. The following exclusion criteria were applied: 1) central or ipsilateral lower extremity nerve injury, varus or valgus deformity of the knee joint, or fracture and/or open injury of the lower extremities; 2) bilateral ACLI; 3) inflammatory diseases such as ankylosing spondylitis or system inflammation such as severe pneumonia. For ACLI patients without KOA, the inclusion and exclusion criteria were the same as for those without ACLI/KOA, except for a diagnosis of KOA.

Written informed consent was obtained from all patients and the study was approved by the ethics committee of the Second Xiangya Hospital and Central South University, Changsha, China (approval No. CSU2015048). Institutional Review Board (IRB) approval was also obtained and the study adhered to the tenets of declaration of Helsinki.

Treatment strategy

Sample size calculation was performed using the following formula (Equation 1):

$$\frac{[(t\alpha + t\beta)s]^2}{\delta}$$

where α – significant level, β – error probability, δ – effective difference, and s – overall standard deviation.

Lysholm Knee Score after 1 week was used as the main study outcome, with an increase of at least 6 considered to be effective. From previous experience of the authors, the mean Lysholm Knee Score is approx. 30–50 ±8 in such patients before surgery. It was estimated based on our clinical experience that 1 week after surgery the score would be approx. 40–60 ±8. Thus, the following values were used to calculate the sample size: $\delta = 6$, $s = 8$, $\alpha = 0.05$, and $\beta = 0.10$. As a result of these calculations, the minimum sample size for the study was 113 patients per group.

All patients were consecutively enrolled in the study and underwent the Lachman test and routine pre-operation examination. This included whole blood tests, routine stool and urine tests, coagulation function tests, liver and kidney function tests, etc. All surgeries were conducted by the same team of surgeons.

All patients received AACLR in combination with SH. For the AACLR surgery, ACLI/KOA patients received combined spinal epidural anesthesia using 5% levobupivacaine (3 mL). A pneumatic tourniquet was prepared and the pressure was maintained at 60 kPa. The arthroscope (Smith & Nephew, Inc. Endoscopy Division, London, UK) was inserted from an infrapatellar medial to lateral approach, and the anatomical structures of the meniscus, cartilage and anterior and posterior cruciate ligament of the knee joint were assessed. The joint cavity was cleaned and the injured meniscus was repaired. If there was hyperplasia and stenosis of the intercondylar fossa, it was expanded and the hyperplastic synovium was excised. Autologous ipsilateral semitendinosus and gracilis tendon were used for transplantation. Briefly, a 3 cm incision was made 2 cm from

the medial tibial tubercle, and the semitendinosus and gracilis tendons were partly resected. The muscle tissues attached to tendons at both ends were removed and both ends of the tendon were knitted and sutured with antibacterial microthread. Then, the broken end of the anterior cruciate ligament was excised and a plasma knife was used to cauterize the center of the anterior cruciate ligament between the tibia and femur. After bending the knee to 90°, a tibial canal locator was introduced under arthroscopic guidance, and a guide needle was inserted into the joint through the medial incision of the tibial tubercle. The locator was removed and a tibial canal was created using a tibial hollow drill. A femoral canal was then created using the same method. The tendon bundle was inserted into the loop of an endobutton plate and the grafts were pulled into the tibia and femur canals, using the traction line. After the endobutton plate was turned over and fixed to the surface of the bone cortex through the canal, the fixed traction line was tightened. The knee joint was repeatedly flexed and extended 30 times under the tension of the tendon bundle to ensure that the tendon bundle had no entrapment or impact. The tibial end of the tendon bundle was fixed with screws at the outer opening of the tibial canal under the guidance of the guide needle. After satisfactory fixation, the articular cavity was washed thoroughly and the skin was sutured layer by layer. The affected limb was then dressed and bandaged.

All ACLI patients without KOA (ACLI group) underwent the surgery using the same method except for the expansion of the intercondylar fossa and excision of the hyperplastic synovium. All patients had 50 mg SH (2.5 mL/25 mg; Shandong Boshilun Furida Pharmaceutical Company Ltd., Shangdong, China) injected into the knee joint cavity immediately after the wound was sutured.

After surgery, the affected limbs of all patients were raised and bandaged with an elastic bandage. All patients received an ice compress to the affected area for 30 min every 2 h for the 1st day. Celecoxib (0.4 g each time) (Pfizer Pharmaceuticals LLC, New York, USA) was used if pain affected sleeping.

During the first 3 days following surgery, patients were asked to perform static contraction of the quadriceps femoris muscle. After the first 3 days post surgery, patients were asked to do quadriceps training. From 3 weeks following surgery, patients could attempt to walk on crutches, and after 2 months, they could attempt to walk normally and perform knee hyperextension and squat training. Athletic sports could be undertaken approx. 6–8 months after surgery.

Evaluation of inflammatory mediators

Blood samples were collected from all patients before surgery, as well as 1 day, 3 days, 7 days, 1 month, 2 months, and 3 months post surgery. Serum levels of the inflammatory markers – C-reactive protein (CRP), interleukin (IL)-1β, IL-6, IL-10, and tumor necrosis factor alpha (TNF-α) – were measured with enzyme-linked immunosorbent assay (ELISA) using commercially available kits (all from Abcam, Cambridge, UK).

Data collection and measurement

Patients' demographic data including age, gender and body mass index (BMI) were recorded. Clinical characteristics including disease course, injury side, intraoperative indices of surgery duration, and postoperative complications, were collected. The Lysholm Knee Score and the International Knee Documentation Committee Knee Evaluation Form (IKDC) were examined before surgery and 1 month, 3 months and 6 months following surgery. The range of motion of the knee joint (the angle between the new position of the distal bone and the proximal end when the distal end of the joint moved towards or away from the proximal end) was evaluated before and 6 months after surgery.

Statistical analyses

All continuous data were normally distributed, which was confirmed using Kolmogorov–Smirnov analysis (results shown in Supplementary Table 1: https://doi.org/10.5281/zenodo.7120784). Continuous data were expressed as mean ± standard deviation (M ±SD). Comparisons between the 2 groups were conducted using an unpaired t-test. For comparison of data before and after treatment, a paired t-test was used. Rates were compared using χ^2 test. All analyses were performed using GraphPad Prism v. 6.0 (GraphPad Software, San Diego, USA) and SPSS v. 18.0. (SPSS Inc., Chicago, USA), with a statistical difference considered as $p < 0.05$.

Results

Basic characteristics and intraoperative indices of all patients

The basic characteristics of all patients are shown in Table 1. The mean disease course was 73.39 ±30.90 months for the ACLI/KOA group, which was significantly longer than the 3.74 ±1.70 months for the ACLI group ($p < 0.05$). Furthermore, surgery duration was remarkably longer for the ACLI/KOA group than it was for the ACLI group ($p < 0.05$). No significant differences were found for other indices.

Comparison of Lysholm Knee Score, IKDC score and the range of knee joint motion between groups

The Lysholm Knee Score, IKDC score and the range of knee joint motion were compared between the 2 groups.

Table 1. Basic characteristics and intraoperative indices of all patients

Variables	ACLI/KOA (n = 113)	ACLI (n = 113)	t or χ^2	p-value
Age [years]	35.23 ±10.97	36.76 ±10.40	–1.083	0.280
Sex, female (%)	41 (36.28)	39 (34.51)	0.069	0.793
BMI [kg/m^2]	24.20 ±2.94	24.19 ±3.01	0.022	0.982
Disease course (ACLI) [months]	73.39 ±30.90	3.74 ±1.70	23.921	<0.001
Injury side, n (%)			0.142	0.707
left	53 (46.90)	56 (49.56)	–	–
right	60 (53.10)	57 (50.44)	–	–
Surgery duration [min]	129.28 ±11.78	121.55 ±11.06	5.088	<0.001

Comparison was made with unpaired t-test between ACLI/KOA and ACLI group for continuous data on age, body mass index (BMI), disease course and surgery duration. Rates (sex and injury side) were analyzed using χ^2 test. ACLI – anterior cruciate ligament injury; KOA – knee osteoarthritis; SH – sodium hyaluronate; AACLR – arthroscopic anterior cruciate ligament reconstruction.

Table 2. Comparison of Lysholm Knee Score, International Knee Documentation Committee Knee Evaluation Form (IKDC) score and the range of motion of knee joint among different groups

Variables		ACLI/KOA (n = 113)	ACLI (n = 113)	t	p-value
Lysholm Knee Score	before	42.74 ±6.68	41.47 ±6.35	1.467	0.143
	1 month	55.30 ±5.80*	55.57 ±5.62*	–0.359	0.720
	3 months	64.16 ±6.09*	64.55 ±5.67*	–0.508	0.611
	6 months	88.82 ±3.54*	89.13 ±3.55*	–0.657	0.511
IKDC score	before	43.01 ±7.02	42.44 ±7.24	0.603	0.547
	1 months	52.48 ±7.37*	53.19 ±7.32*	–0.731	0.465
	3 months	62.07 ±6.68*	62.04 ±7.20*	0.028	0.977
	6 months	89.57 ±4.12*	89.53 ±3.94*	0.070	0.944
Knee joint motion [°]	before	65.27 ±5.86	65.53 ±6.00	–0.325	0.745
	6 months	115.40 ±8.55*	115.24 ±8.63*	0.136	0.892

Comparison was made with unpaired t-test between ACLI/KOA and ACLI group. *p < 0.05 compared with the baseline using paired t-test. ACLI – anterior cruciate ligament injury; KOA – knee osteoarthritis; SH – sodium hyaluronate; AACLR – arthroscopic anterior cruciate ligament reconstruction.

No significant differences were found between the groups before the study, while all 3 scores significantly improved after 6 months in both groups compared to baseline scores ($p < 0.05$, Table 2). However, no significant differences were found between the ACLI/KOA and ACLI groups after surgery.

Dynamic changes of inflammatory markers in different groups

To further investigate the effects of different surgery methods, dynamic changes in inflammatory markers were evaluated. As shown in Fig. 1, before surgery, the levels of pro-inflammatory markers (CRP, IL-1β, IL-6, and TNF-α), as well as levels of anti-inflammatory IL-10, were higher in ACLI/KOA patients compared to the ACLI patients ($p < 0.05$). After treatment, significant differences were found 1 day, 3 days and 7 days after surgery, with markedly higher inflammatory markers found in ACLI/KOA patients compared to those without KOA ($p < 0.05$).

Postoperative complications

Postoperative complications were compared between the 2 groups. There was 1 case of incision infection in the ACLI/KOA group and no complications were found in the ACLI group (Table 3).

Table 3. Postoperative complications in different groups

Variables, n (%)	ACLI/KOA (n = 113)	ACLI (n = 113)
Incision infection	0 (0)	0 (0)
Intra-articular infection	0 (0)	1 (0.88)

ACLI – anterior cruciate ligament injury; KOA – knee osteoarthritis; SH – sodium hyaluronate; AACLR – arthroscopic anterior cruciate ligament reconstruction.

Discussion

Despite several studies on the application of AACLR in the treatment of ACLI, few have focused on the effects of AACLR on ACLI patients with KOA. In the present

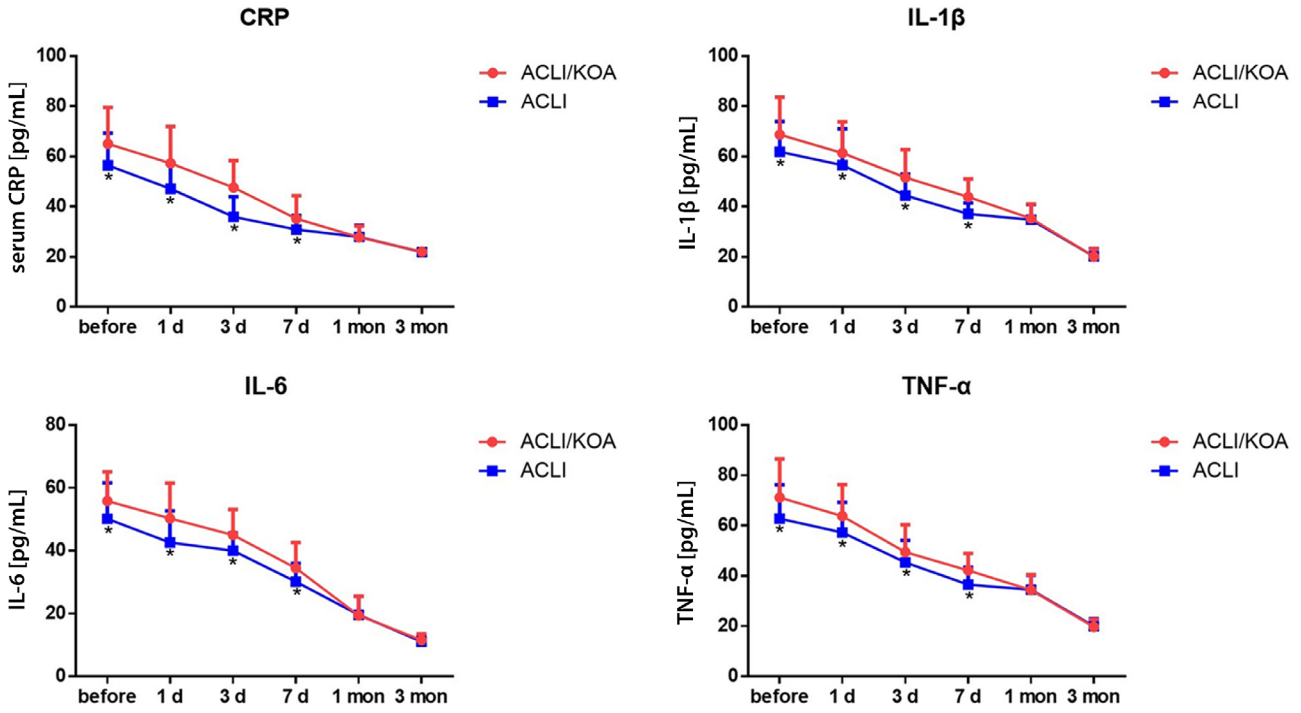

Fig. 1. Dynamic changes in the inflammatory markers C-reactive protein (CRP), interleukin (IL)-1β, IL-6, and tumor necrosis factor alpha (TNF-α) in both groups. A comparison between the 2 groups was conducted using an unpaired t-test. Data are expressed as mean ± standard deviation (M ±SD)

* $p < 0.05$ compared to anterior cruciate ligament injury/knee osteoarthritis (ACLI/KOA) group.

study, it was demonstrated that AACLR combined with SH was efficacious in ACLI/KOA patients. Indeed, there were improvements in the recovery of knee function and inflammatory markers. Meanwhile, ACLI patients without KOA experienced a more rapid recovery from the inflammatory response than ACLI/KOA patients.

Some studies have demonstrated a relationship between chronic ACLI and KOA. Generally, ACLI patients have a higher risk of developing KOA, even after reconstruction surgery. In a meta-analysis, Lie et al. demonstrated that 10 years after ACLI, patients may develop KOA, and that meniscectomy might be a risk factor.[14] In another study, it was found that adults developed OA earlier than adolescents 5 and 10 years after ACLI reconstruction surgery.[15] The activation of inflammation is one of the key factors in KOA development, and inflammatory markers were found to be elevated in KOA patients. In ACLI patients, it was found that levels of matrix metalloproteinase-13 (MMP-13), IL-6, IL-1β, and caspase-3 were all significantly upregulated in chondrocytes, especially in patients who had not undergone reconstruction surgery.[16] A systematic review showed that ACL patients without reconstruction had elevated collagen turnover, and the overall inflammatory cytokine response in synovial fluid increased in ACL patients who had reconstruction surgery.[17] However, recent research demonstrated that 5 years after the injury, inflammatory biomarkers could not predict the incidence of KOA, which indicated that the correlation between inflammatory biomarkers and KOA was weak in the long term following reconstruction surgery in ACLI patients.[18] Despite the findings of these studies, the dynamic changes in inflammatory markers in ACLI patients with KOA are not clear, especially in the short term. In the current study, ACLI/KOA patients had higher levels of inflammatory markers than ACLI patients without KOA, which may be due to the influence of KOA. It was also found that AACLR combined with SH was efficacious, as it reduced the inflammatory response in ACLI patients regardless of a diagnosis of KOA.

The application of AACLR to ACLI has been reported in several investigations. Trung et al. demonstrated that ACL reconstruction using the anterior half of the peroneus longus muscle improved knee function in ACLI patients.[19] Another study found that simultaneous AACLR and posterior cruciate ligament reconstruction with hamstring tendon autograft significantly enhanced knee function, with a 90% satisfaction rate found in patients.[20]

The SH has been reported to improve the formation of nascent neural networks in spinal cord injury,[8] while another study demonstrated that both SH and MD-Knee were effective in the treatment of KOA.[21] Furthermore, intra-articular injection of SH into the ankle was reported to provide pain relief and to delay the need for surgery in patients with OA of the ankle.[22] However, very little research has investigated the application of SH in the treatment of ACLI. In the current study, it was found that AACLR combined with SH was efficacious in both ACLI/KOA and ACLI, which is consistent with the results of previous studies.

Limitations

Limitations include the small sample size, the limited number of tested inflammatory factors and short follow-up period. Further studies that address these limitations will provide deeper insight into the use of AACLR combined with SH in patients who have ACLI with or without KOA.

Conclusions

This prospective cohort study demonstrated the efficacy of AACLR in combination with SH in patients with ACLI with or without KOA. Results showed that the described approach enhanced the recovery of knee function and reduced the inflammatory response in both groups. Furthermore, ACLI patients without KOA recovered more rapidly from the inflammatory response.

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