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Collagen application reduces complication rates of mid-substance ACL tears treated with dynamic intraligamentary stabilization

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Abstract
Purpose Dynamic intraligamentary stabilization was recently proposed as an option for the treatment of acute ACL ruptures. The aim of this study was to investigate the feasibility of the procedure in mid-substance ACL ruptures and examine whether the additional application of a bilayer collagen I/III membrane would provide for a superior outcome.
Methods The study group consisted of patients presenting with a mid-substance ACL rupture undergoing dynamic intraligamentary stabilization using the Ligamys™ device along with application of a collagen I/III membrane to the surface of the ACL (group A, $n = 23$). The control group comprised a matched series of patients presenting with a mid-substance ACL rupture also treated by dynamic intraligamentary stabilization Ligamys™ repair, however, without additional collagen application (group B, $n = 33$). Patients were evaluated preoperatively and at 24-month follow-up for stability as well as Tegner and Lysholm scores. Knee laxity was measured as a difference in anterior translation (ΔAP) and pivot shift. Any events occurring during the follow-up period of 24 months were documented. Logistic regression of complications was performed, and adjustment undertaken where necessary.
Results A high total complication rate of 78.8 % was noted in group B, compared to group A (8.7 %) ($p = 0.002$). The addition of a collagen membrane was the only independent prognostic factor associated with reduced complications (OR 8.0, CI 2.0–32.2, $p = 0.003$, for collagen-free treatment). In group B, 6 patients suffered a re-rupture with subsequent instability requiring secondary hamstring reconstruction surgery, and 11 developed extension loss requiring arthroscopic debridement, whilst in group A, 2 patients required arthroscopic debridement for loss of exension, with no further encountered complication. Median Lysholm score was significantly higher in group A compared to group B (median 100 range 93–100 vs median 95 range 60–100, $p = 0.03$) at final follow-up.
Conclusions A high complication rate following ACL Ligamys™ repair of mid-substance ruptures was noted. Application of a collagen membrane to the surface of the ACL resulted in a reduced incidence of extension deficit and re-ruptures. The results indicate that solitary ACL Ligamys™ repair does not present an appropriate treatment modality for mid-substance ACL ruptures. Collage application proved to provide healing benefits with superior clinical outcome after ACL repair.
Level of evidence Case control study, Level III.

Keywords Dynamic intraligamentary stabilization · DIS · Ligamys · ACL · Knee · ACL reconstruction

Introduction

Tear of the anterior cruciate ligament (ACL) represents one of the most common sport-related injuries, occupying a large area in the field of sports traumatology and knee research [1, 8, 14, 15, 25].

Early attempts of restoring stability in ACL injured knees were based on suture fixation of the ACL remnants;

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these techniques soon showed high failure rates, resulting in a shift of practice towards reconstructive techniques [4, 6, 24, 28, 30].

The evident success of ACL graft reconstruction was, however, accompanied by a continued interest in understanding the problematic issues of intrinsic ACL healing [20, 33]. Findings of resulting investigations proposed several underlying pathophysiological causes mainly including the gliding translational movements of the traumatized joint, leading to an increased distance between the ruptured stumps of the ACL [2, 29]. The result of the gap between the ACL remnants prevents the formation of a fibrin blood clot "biological scaffold" [23]. It has additionally been shown that any applied form of rigid fixation to approximate the ACL stumps, including suture fixation, undergoes cyclic loading during natural motion of the knee joint, leading to its failure [10].

Dynamic intraligamentary stabilization (DIS) was recently introduced as a treatment option for acute ACL ruptures [3, 9]. The philosophy of the procedure is based on replacing the rigid form of suture fixation by a dynamic fixation device consisting of an internal dynamic screw-spring mechanism and a braided polyethylene anchoring wire, providing continuous dynamic stability in every degree of motion during the healing period [3, 9–11].

To locally enhance the biological healing potential of the ACL, several techniques have been proposed including collagen membranes and bio-absorbable scaffolds for growth factors application and micro-fracturing techniques [13, 16, 21, 22, 31]. It has also been recently shown that a collagen I/III 3D scaffold provides a suitable architecture for adherence and proliferation of ACL ligamentocytes [7].

Several reports of the early results of ACL repair using the Ligamys™ device have recently been published [3, 9]. The feasibility of the procedure for mid-substance ACL ruptures has not yet been solely examined. The purpose of this study was to investigate the early outcome of Ligamys™ repair for mid-substance ACL ruptures, and furthermore, to determine whether the additional application of a collagen I/III membrane would provide for a superior outcome.

It was hypothesized that the complication rate following Ligamys™ repair of mid-substance ACL ruptures is high, and that a superior outcome could be achieved by the intraoperative additional application of a collagen I/III membrane to the ACL surface.

Materials and methods

Inclusion criteria were as follows: radiological and intraoperative confirmation of a mid-substance ACL rupture [19], eligibility for DIS as previously described [3, 9], no further ligamentous knee injury, no chondral damage graded ≥II according to Outerbridge, no malalignment requiring surgical correction and patient consent. Of the 192 patients with an acute ACL rupture treated between March 2011 and April 2013, 23 patients with a mid-substance rupture were randomly assigned to receive DIS with the additional application of a collagen I/III membrane (Chondrogide, Geistlich Pharma AG, Wolhusen, Switzerland) to the surface of the ACL comprising the study group (group A). A matched control group was selected from the pool of patients who were treated with DIS without application of a collagen membrane (group B), Fig. 1. Matching was performed on the initial basis of fulfilling the inclusion criteria for group A, as well as the matching criteria: age, pre-injury Tegner score, presence and location of meniscal lesions and gender. A propensity score from the co-variables mentioned above was generated for each patient in both groups using the established method proposed by Rosenbaum and Rubin to ensure that both groups only differed regarding the application of a collagen patch [27]. Propensity scores were then stratified into ranges, which were matched between both groups yielding a maximum of 33 matched patients (group B) not differing in any of the matching criteria, Table 1.

All patients were evaluated preoperatively and at final follow-up for Tegner and Lysholm scores [32]. Knee laxity was measured as a difference in anterior translation (ΔAP) at 20° flexion with the aid of the KT-1000 knee arthrometer, and pivot shift documented to determine instability (grade ≥II considered positive). Events occurring during the follow-up period of 24 months were registered. If patients

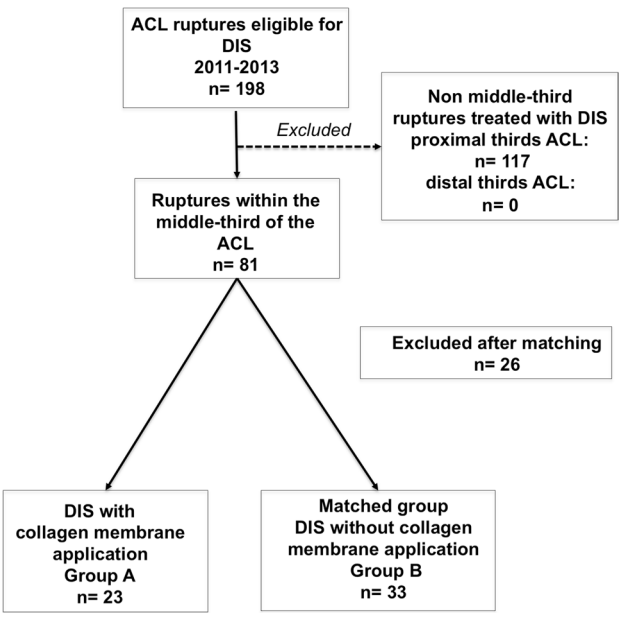

Fig. 1 Flowchart showing the process of patient inclusion in groups A (DIS and collagen membrane) and B (DIS Collagen-free)

Table 1 Preoperative comparison between both groups A (Ligamys™ repair plus collagen membrane) and B (Ligamys™ Collagen-free repair) based on gender, injured limb and age, pre-injury Tegner score and meniscal lesion

	Group A ($n = 23$)	Group B ($n = 33$)	p value
Male gender	15	24	0.38
Right leg	13	15	0.29
Age	30 ± 11	27 ± 10	0.24
Tegner score	7 (4–8)	7.5 (4–7)	0.79
Lysholm	100 (97–100)	100 (96–100)	0.94
ΔAP translation (mm)	4.7 (±1.3)	4.4 (±1.7)	0.63
Meniscal injury	17	25	0.89
Medial meniscus	12	19	0.69
Lateral meniscus	4	7	0.68
Follow-up (months)	24	24	

were to undergo ACL reconstruction during the follow-up period, scores and ΔAP immediately before the revision procedure were considered. Extension deficit was defined as >5° difference to the healthy knee measured with a goniometer with a subjective complaint. A traumatic re-rupture was defined as a history of a traumatic event with an associated positive pivot shift and ΔAP >3 mm as well as MRI confirmation.

Surgical technique

All procedures were performed under either spinal or general anaesthesia. Patients were placed in supine position with the knee positioned in a dynamic leg holder. A tourniquet was used in all cases.

DIS repair: A detailed describtion of the procedure has previously been published [3]. In brief, the tibial portion of the ACL was reduced to the femoral footprint, and the femoral portion to the tibial footprint, both secured by means of trans-osseous fixation (Fig. 2). The knee was then stabilized with a strong polyethylene cord anchored in the proximal tibia to a spring-screw implant (Ligamys™, Mathys Ltd., Bettlach, Switzerland).

Collagen application: The collagen I/III membrane (Chondrogide, Geistlich Pharma AG, Wolhusen, Switzerland) was cut in an oval shape, and 3 PDS 3.0 sutures were placed at the proximal, distal–medial and distal–lateral corners of the membrane. The membrane was then applied to the anterior surface of the ACL, at the rupture side, and secured by means of trans-osseous fixation, while the two distal patch sutures exited, through a 2.4-mm k-wire, at the anteromedial and anterolateral surfaces of the proximal tibia, respectively, where they were sutured together with the sutures of the proximal stump over a bony bridge (Fig. 3).

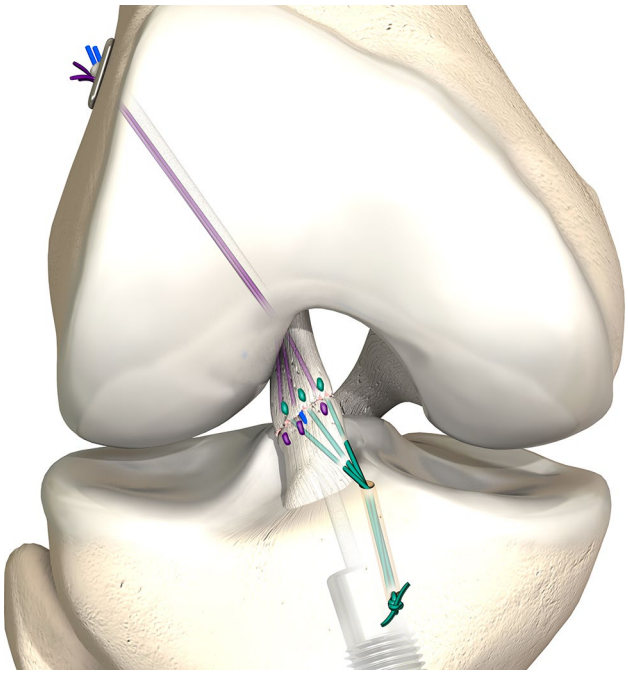

Fig. 2 Illustration of proximal and distal stump fixation and DIS. The *purple sutures* are place in the distal ACL stump, which is then pulled proximally through the femur; the *green sutures* are placed in the proximal stump and pulled distally through the proximal tibia. Final stabilization is performed using the Ligamys™ implant in the proximal tibia where the white polyethylene braid is fixed and pretension applied

Management of other lesions: The peripheral meniscal tears were sutured in acute cases. Other types of tears or chronic meniscal lesions were submitted to partial meniscectomy.

Statistical analysis

The primary question was based on the initial assumption that a reduction in complication rates is achieved with the application of a collagen membrane.

The power of this study was calculated post-hoc from the difference in complication rates between groups, effect size and group size at a $p = 0.05$. Based on the difference in total complication rates between both groups A and B (8.7 and 78.8 %, respectively), an effect size of 1.36 was calculated resulting in a power of 0.99, at $p = 0.05$.

Data were presented either as mean ± standard deviation, median (range) or percentage. Comparison between means was made using the unpaired Student's t test. Pearson's Chi-squared test was applied for categorical data. Univariate binary regression was performed to determine predictors of complications, and subsequent adjustment was made based on a multivariate model. A p value <0.05 was considered statistically significant.

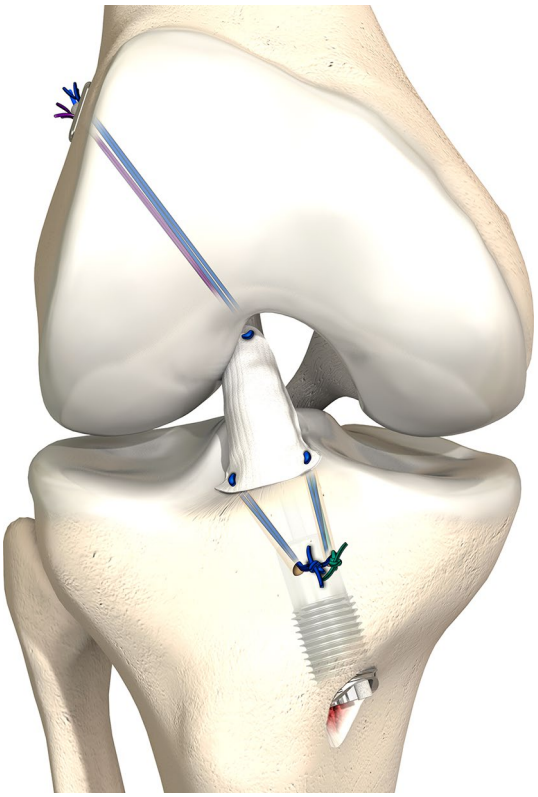

Fig. 3 Illustration after ACL coverage using the collagen membrane (group A). The membrane is applied to the anterior aspect of the ACL and secured in place by three sutures, one proximal and two distal, by mean of trans-osseous fixation

Table 2 Differences in complication rates between groups A (Ligamys™ repair plus collagen membrane) and B (Ligamys™ repair without collagen membrane)

	Group A ($n = 23$)	Group B ($n = 33$)	p value
Extension deficit	2	11	0.03
Pivoting	0	6	0.03
Re-rupture	0	6	0.03
Patients with complications	2	18	0.002

Extension deficit: defined as >5° symptomatic difference between both knees. Pivot shift: a clunk or gross pivot

Group A: collagen patch group. Group B: no collagen patch application. n.s: not significant. p value based on Chi-squared test

Results

Group A (Ligamys™ repair alongside collagen I/III membrane application) was comprised of 23 patients, and group B (primary Ligamys™ Collagen-free repair) of 33 (Table 1).

Table 3 Logistic regression showing the odds of experiencing a complication with and without collagen I/III membrane application

	OR	Lower bound	Upper bound	p value
Extension deficit				
Patch	1.0			
No patch	5.0	1.0	25.3	0.04
Pivoting				
Patch	1.0			
No patch	3.8	1.0	14.3	0.04
Re-rupture				
Patch	1.0			
No patch	6.0	1.3	27.5	0.023
Complication (total)				
Patch	1.0			
No patch	8.0	2.0	32.2	0.003

Univariate comparison revealed a higher total complication rate in group B compared to group A (group A: 8.7 %, group B: 78.8 %, $p = 0.002$, for Collagen-free treatment); these included extension deficit (group A: 8.7 %, group B: 33.3 % $p = 0.038$) and re-rupture with instability (group A: 0 %, group B: 18 %, $p = 0.03$) (Table 2).

Not applying the collagen membrane to the ACL during repair was the only independent variable predictive for the occurrence of a complication (OR 8.0, CI 2.0–32.2, $p = 0.03$). (Table 3). In a subgroup analysis of complications and after adjustment of variables, extension deficit, re-rupture and instability (positive pivot shift) showed to be influenced by collagen patch application (Table 3).

Furthermore, the collagen-free-treated group showed a significantly lower Lysholm score ($p = 0.03$). ΔAP translation and Tegner scores, however, did not significantly differ between groups (Table 4).

Overall, in the group receiving DIS with no additional patch application (group B), 4 patients suffered a traumatic re-rupture within the first and 2 within the second postoperative year (median 9 months, range 5–16) and consequently underwent ACL hamstring reconstruction, while 11 showed significant extension deficit all requiring arthroscopic debridement within the first postoperative year (median 7 months, range 3–11); the typical arthroscopic finding in these patients was a bulky mass of scar tissue extending from the ACL to the region of the notch, limiting full knee extension. Arthroscopic reduction in the scar resolved the issue instantly. In the patch-applied group (group A), 2 patients underwent arthroscopy for scar debridement within the first year, with no further encountered complication.

Table 4 Score values and Δ anterior-posterior translation at final follow-up 24 months postoperatively

	Patch	Median	Range	*p* value
Tegner score	Group A	6	4;10	ns
	Group B	5	4;9	
Lysholm score	Group A	100	93;100	0.03
	Group B	95	60;100	
ΔAP translation (mm)	Group A	1.0	−1;3	ns
	Group B	1.0	−2;5	

Patients suffering a traumatic re-rupture had the last measure before ACL reconstruction included. A (Ligamys™ repair plus collagen membrane) and B (Ligamys™ Collagen-free repair). *ns* not significant. Range (minimum;maximum). *p* value based on Mann–Whitney *U* test

Discussion

The most important finding of the present study was that ACL Ligamys™ repair of mid-substance ACL ruptures is associated with a high complication rate of 78.8 %, predominantly resulting from hypertrophic scar formation causing symptomatic extension deficit, as well as insufficient restoration of stability. The application of the collagen I/III membrane allowed for a significant drop in complication rates to 8.7 %.

DIS was generally proposed as a promising option for the treatment of acute ACL ruptures [3, 9]. The majority of ACL ruptures described in previous reports were proximal [3, 9]. Based on the results of this study, careful patient selection and caution is necessary when considering DIS candidates, as healing response appears to differ depending on the location of the tear.

Fleming et al. [5] reported that intraarticular augmentation using collagen patches enhances healing potential and improves biomechanical properties of ACL grafts in animal models.

It seems reasonable to assume that the collagen membrane acts as a scaffold, preventing inflammatory cells from diffusing, thus forming an amorphous scar tissue mass. Additionally, collagen type I has been shown to induce down-modulation of inflammation inhibiting proinflammatory cytokine expression of IL-1β & TNF-α and inducing upregulation of IL-10, an anti-inflammatory cytokine. Furuzawa-Carballeda et al. reported that polymerized type I collagen down-regulates inflammation and improves clinical outcomes in patients with symptomatic knee osteoarthritis following arthroscopic lavage. The results of this study do indicate a significantly lowered complication rate with the application of a collagen membrane in mid-substance ACL tears, treated with ligament preserving DIS repair. Extension loss and re-rupture were the two mainly encountered complications, which were successfully addressed by application of the collagen membrane, supporting the argument that a collagen scaffold would allow for a more organized healing process, possibly due to local immunomodulatory capabilities and the fibre architecture that assist the healing process and avoid excess scar tissue formation [17, 18, 26].

There are several limitations to this study needing emphasis; one is the non-randomized study design, due to which quasi-randomization with a matched control group was performed. Second limitation is the size of the study group; a larger sample size might have allowed for detection of smaller differences between groups. Furthermore, the 24-month follow-up period of the study is too short to draw major conclusions about clinical outcome; however, early complications can still be emphasized.

ACL DIS repair using the Ligamys™ device has been recently introduced as a procedure for the treatment of acute ACL ruptures with growing interest, and initial experiences have been published [3, 9, 12]. Based on the results and due to the preliminary published experience with Ligamys™ repair, the indications should be confined to proximal ACL ruptures, until biological options become better established.

Conclusions

The results of this study illustrate a high complication rate following primary DIS Ligamys™ repair of mid-substance ACL ruptures, therefore disapproving the procedure for these rupture locations. The results further indicate that collagen I/III provides for improved clinical outcome when applied to the surface of the ACL during repair, demonstrating a beneficial role in ACL healing.

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