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ORIGINAL ARTICLE

Pre-operative Joint Inflammation has no Bearing on Outcome of Arthroscopic Anterior Cruciate Ligament Reconstruction at 1-Year Follow-Up; a Prospective Study

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Abstract

Background To study the effect of pre-operative joint inflammation on clinical outcome at 1 year follow-up following ACL reconstruction surgery.

Methods Male patients, aged 18–40 years, suffering from isolated ACL injury were included. All patients were randomly divided into two groups based on the type of graft used: Group A: semitendinosus gracilis graft with preserved insertions (STG-PI), Group B: bone-patellar tendon-bone graft (BPTB). Patients were categorised based on the time of presentation after injury: (a) within 6 weeks of injury, (b) between 6 and 12 weeks of injury, (c) after 12 weeks of injury. Synovial fluid levels of Interlukin-1, Interlukin-6 and TNF-α were measured in all the ACL deficient knees by taking a joint fluid sample intra-operatively.

Results The total number of patients in the study was 59; 23 in group A (STG-PI) and 36 in group B (BPTB). Mean age of patients was 26 ± 5.146 years. 14 out of 59 (23.7%) patients presented within 6 weeks of injury, 16 (27.11%) patients presented between 6 and 12 weeks after injury and 29 (49.1%) patients presented after 12 weeks of injury. IL-6 levels were significantly high in group with < 6 weeks of injury than in group with > 12 weeks since injury. IL-6 had significant correlation with VAS scores, KT 1000, Lysholm knee scores and Tegner level of activity. There was no difference in outcome (pain scores, mechanical stability, Lysholm knee score and Tegner level of activity) at 1 year follow-up when patients with different time intervals since injury were compared.

Conclusion The clinical outcome in terms of pain score, mechanical stability, functional scores and return to sporting activity is comparable, irrespective of the time since injury, at short term follow-up.

Keywords ACL reconstruction · IL-6 · Inflammation · Acute injury

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Introduction

ACL reconstruction with an autograft is the treatment of choice in patients with ACL tear. It has been previously suggested that aseptic inflammation in the joint can affect the healing process, i.e., ligamentization, which in turn may affect mechanical stability and functional outcome [1, 2]. So, understanding the process of healing of the graft and factors affecting it, and its application during the planning of surgery may immensely improve the final outcome in sportspersons suffering from these career threatening injuries and enable them to return to highest levels of sporting activity [2, 3].

The timing of ACL reconstruction surgery is a topic of debate in itself. It is thought that inflammation is more in an acutely injured knee [4, 5]. Although, a recent meta-analysis had proposed early ACL reconstruction to be the preferred approach [4], several authors hold a firm view about the need to delay surgery for 3–6 weeks as the early surgery may lead to inferior clinical outcome [1–8]. The reason for this observation has been argued to be the swelling and inflammation in an acutely injured knee [5–11]. However, it has also been observed that delaying the surgery predisposes to chondral and meniscal injuries in an ACL deficient knee [12]. Thus, the matter is far from settled.

We conducted this study at our centre with the hypothesis that inflammation in the knee joint at the time of surgery can lead to poor clinical outcome at 1 year follow-up.

Materials and Methods

The study was conducted at a tertiary care hospital from January 2015 to October 2016. The study was approved by institutional ethics committee and registered with clinical trials registry of the country. Male patients, aged 18–40 years, suffering from isolated ACL injury and consenting to participate in the study were included. Those with previous injury to same or other knee, injury due to non-sports related activities, inflammatory arthritis including Rheumatoid arthritis, Ankylosing Spondylitis etc. were excluded. All the patients with ACL injury were divided into two groups based on the type of graft used in the surgery:

Group A Semitendinosus gracilis graft with preserved insertions (STG-PI).

Group B Bone-patellar tendon-bone graft (BPTB).

Patients were allocated into the two groups based on computer generated random allocation numbers.

Patients were categorised based on the time of presentation after injury:

Within 6 weeks of injury
Between 6 and 12 weeks of injury
After 12 weeks of injury

Technique

Patient was operated under spinal anaesthesia. Patient was positioned supine with the operable leg in the hanging position. Before making arthroscopic portals, arthrocentes is was performed using 18 G needle. 2–3 ml of synovial fluid sample was obtained before pushing saline/3% glycine into the joint. Synovial fluid sample obtained was carried using standard cold chain techniques and immediately centrifuged for 5 min at the speed of 450 G to remove cells and debris. It was stored at − 60° to − 80° centigrade till final analysis for IL-1, IL-6 and TNF-α was done using ELISA (enzyme-linked immunosorbent Assays) based quantikine HS kits (Diaclone, Besancon, France, Ltd.). Levels found in ELISA kits were noted down along with complete patient profile.

Surgical Techniques

Patients in group A were operated using STG-PI [13] autograft while those in group B were operated using BPTB autograft [14].

Rehabilitation

All the patients underwent a uniform rehabilitation programme. During the first 7 days, patients underwent full range of motion at knee joint, static quadriceps exercises, straight leg raising and full weight bearing as per pain tolerance. This regimen was continued for upto 6 weeks. At 6 weeks, cycling was introduced in addition to the existing physiotherapy. At 3 months, jogging was allowed. At 6 months, patients were allowed to practise sports and undergo endurance exercises for next 2–3 months. Patients were advised to return to competitive sports after 8–9 months.

Post-operative Follow-up

All the patients were followed up for clinical outcome in terms of pain and mechanical stability and functional outcome in terms of knee scores and return back to sporting activity. Sequential follow-up was done at 1 month, 2 months, 6 months and 12 months post operatively.

Post-operative pain was measured using visual analogue scale(VAS),anterior knee laxity was assessed using KT 1000 arthrometer, functional outcome was assessed using Lysholm knee score [15] and return to sports was assessed using Tegner scale of sports activity [16].

Statistical Methods

Discrete categorical data was represented in the form of either a number or a percentage (%). Continuous data, assumed to be normally distributed, was written in the form of its mean and standard deviation and if it was skewed, it was written in the form of its median and interquartile range, as per the requirement. The normality of quantitative data was checked by measures of Kolmogorov–Smirnov tests of normality. As data for the follow-up and difference of scores was skewed, so Kruskal–Wallis test, followed by Mann–Whitney test were applied. Age was normally distributed, so data means of three groups were compared using one-way ANOVA, followed by 'Post Hoc Multiple Comparisons' test. Proportions were compared using Chi square or Fisher's exact test, depending on their applicability. To see the relationship between different variables, Spearman correlation coefficients were calculated. All the statistical tests were two sided and were performed at a significance level of $\alpha = 0.05$. The analysis was conducted using IBM SPSS STATISTICS (version 22.0).

Results

The total number of patients in the study was 59. There were 23 patients in group A (STG-PI) and 36 patients in group B (BPTB). Mean age of patients in the study was 26 ± 5.146 years. Maximum number of patients, 43 out of 59 (73%), fell in the age group of 18–29 years. 14 out of 59 (23.7%) patients presented within 6 weeks of injury, 16 (27.11%) patients presented between 6 to 12 weeks after injury and 29 (49.1%) patients presented after 12 weeks of injury.

IL-6 levels were raised in 52 (88.13%) patients, normal in 05 (8.47%) and decreased in 02 (3.38%) patients. IL-1 levels were raised in 03 (5.08%) patients, normal in 01 (1.7%) and decreased in 55 (93.22%) patients. TNF-α levels were raised in 05 (8.47%) patients and normal in 54 (91.52%) patients.

Association between time since injury and pre-operative values of interleukin-1, interleukin-6 and tumour necrosis factor-α was studied and no statistically significant difference was found (0.342, 0.65 and 0.186, respectively) (Table 1).

The difference between any two individual groups was also studied:

1. Between < 6 weeks and 6–12 weeks
2. Between < 6 weeks and > 12 weeks
3. Between 6–12 weeks and > 12 weeks

Difference in levels of IL-6 between groups (< 6 weeks and > 12 weeks) was significant (p value = 0.029). Thus, IL-6 levels were significantly high in group with < 6 weeks of injury than in group with > 12 weeks since injury.

Difference in levels of IL-6 between groups (< 6 weeks and 6–12 weeks) was not significant (p value = 0.54). Difference in levels of IL-6 between groups (6–12 weeks and > 12 weeks) was not significant (p value = 0.246). Difference in levels of IL-1 and TNF-α between all the groups was not significant (Table 2).

Table 1 Showing levels of inflammatory markers in different groups of time since injury

Time since injury	Number of patients	Inflammatory markers	Mean	Std. deviation
< 6 weeks	14	IL-1	3.6314	13.40411
		IL-6	108.7643	84.43148
		TNF-α	8.2071	30.70832
6–12 weeks	16	IL-1	0.1250	0.50000
		IL-6	55.9256	73.63711
		TNF-α	0.0000	0.00000
> 12 weeks	29	IL-1	2.2828	7.97504
		IL-6	55.3593	65.50712
		TNF-α	24.9279	127.62633

Table 2 Showing comparison of different groups of time since injury in terms of levels of inflammatory markers and respective p value

Time since injury	p value of Mann Whitney U test		
	IL-1	IL-6	Tnf α
< 6 weeks and 6–12 weeks	0.246	0.054	0.285
< 6 weeks and > 12 weeks	0.806	0.029*	0.414
6–12 weeks and > 12 weeks	0.145	0.696	0.082

*indicates significant significant results

Correlation of Inflammatory Markers with VAS

Correlation between pre-operative quantitative values of IL-1, IL-6 and TNF-α with VAS scores was studied at 1 month, 2 months, 6 months and 1 year. It was observed that IL-6 had significant correlation with VAS scores at 1 month, 2 months, 6 months and at 1 year follow-up ($p < 0.05$) (Table 3).

Correlation of Inflammatory Markers with KT 1000

Correlation between pre-operative quantitative values of IL-1, IL-6 and TNF-α with KT 1000 values (difference between affected and unaffected knee) was studied at 1 month, 2 months, 6 months and 1 year. It was observed that IL-6 had significant correlation with KT 1000 values

at 2 months, 6 months and at 1 year follow-up ($p < 0.05$) (Table 4).

Correlation of Inflammatory Markers with Lysholm Knee Score

Correlation between pre-operative quantitative values of IL-1, IL-6 and TNF-α with Lysholm knee scores was studied at 1 month, 2 months, 6 months and 1 year. It was observed that IL-6 had significant correlation with Lysholm knee scores at 2 months, 6 months and at 1 year follow-up ($p < 0.05$) (Table 5).

Correlation of Inflammatory Markers with Tegner Level of Sports Activity

Correlation between pre-operative quantitative values of IL-1, IL-6 and TNF-α with Tegner level of sports activity was studied at 1 month, 2 months, 6 months and 1 year. It was observed that IL-6 had significant correlation

Table 3 Correlation of values of IL-1, IL-6 and TNF-α pre-operatively and VAS scores at sequential follow-up

	VAS 0	Vas 1	VAS 2	Vas 6	VAS 12
IL-1					
Correlation coefficient	−0.016	0.333**	0.129	0.044	0.037
p value	0.905	0.010	0.332	0.741	0.782
IL-6					
Correlation coefficient	0.217	0.477**	0.536**	0.534**	0.364(**)
p value	0.099	0.000	0.000	0.000	0.005
TNF-α					
Correlation coefficient	−0.146	0.070	0.121	0.008	0.109
p value	0.271	0.598	0.362	0.954	0.411

**indicates highly significant results

Table 4 Correlation of values of IL-1, IL-6 and TNF-α pre-operatively and KT 1000 difference at sequential follow-up

IL-1					
Correlation coefficient	−0.038	−0.261(*)	−0.052	−0.071	0.051
p value	0.774	0.046	0.695	0.594	0.700
IL-6					
Correlation coefficient	−0.122	0.019	0.513**	0.626**	0.740**
p value	0.357	0.884	0.000	0.000	0.000
TNF-α					
Correlation coefficient	0.179	−0.092	−0.103	−0.009	0.123
p value	0.174	0.487	0.437	0.944	0.352

*indicates significant results

**indicates highly significant results

Table 5 Correlation of values of IL-1, IL-6 and TNF-α pre-operatively and Lysholm knee score at sequential follow-up

	LS 0	LS 1	LS 2	LS 6	LS 12
IL-1					
Correlation coefficient	0.157	−0.191	0.045	−0.228	−0.163
p value	0.234	0.147	0.738	0.082	0.217
IL-6					
Correlation coefficient	−0.005	−0.230	−0.317*	−0.714**	−0.436**
p value	0.972	0.079	0.015	0.000	0.001
TNF-α					
Correlation coefficient	0.103	−0.070	−0.161	−0.234	−0.148
p value	0.438	0.599	0.222	0.074	0.265

*indicates significant results

**indicates highly significant results

Table 6 Showing correlation of interleukins with Tegner activity scale

	TAS 0	TAS 1	TAS 2	TAS 6	TAS 12
IL-1					
Correlation coefficient	0.056	−0.110	0.037	−0.033	−0.129
p value	0.673	0.408	0.780	0.802	0.331
IL-6					
Correlation coefficient	−0.237	0.122	0.046	−0.052	−0.570**
p value	0.070	0.357	0.730	0.695	0.000
TNF-α					
Correlation coefficient	0.091	−0.106	−0.001	−0.060	−0.014
p value	0.494	0.426	0.992	0.653	0.919

**indicates highly significant results

with Tegner level of sports activity at 1 year follow-up (Table 6).

The two groups (group A, STGPI and group B, BPTB) were compared in terms of pre-operative factors like age, time since injury and IL-6 levels and post-operative factors like KT-1000, VAS score, Lysholm knee score and Tegner level of sports activity. The comparison was found to be statistically insignificant (Table 7).

Association between time since injury and outcome variables was studied. Comparison of VAS score between < 6 weeks and > 12 weeks since injury, at post-operative 1 month, was statistically significant. All the other variables were comparable (Tables 8, 9, 10 and 11).

None of the patients in any of the groups suffered from arthrofibrosis and hence there was no need for procedures like arthroscopic arthrolysis.

Table 7 Comparison of pre-operative and post-operative factors between group A, STGPI and group B, BPTB

S. no		STG-PI	BPTB	*p* value	Diff
1	Age (years)	26.65 ± 6.358	25.58 ± 4.245	0.441	NS
2	Time since injury	30.4% [< 6 weeks]	19.4% [< 6 weeks]	0.568	NS
3	IL-6	66.80 ± 74.63 pg/ml	69.06 ± 75.9 pg/ml	0.913	NS
4	KT 1000 difference at 1 year	1.15 ± 0.714	1.46 ± 1.3	0.752	NS
5	VAS score at 1 year	0.04 ± 0.2	0.11 ± 0.31	0.367	NS
6	Lysholmkneescore at 1 year	99.09 ± 1.8	98.5 ± 2.47	0.344	NS
7	Tegnerlevel of activity at 1 year	7.09 ± 1.6	7.19 ± 1.5	0.768	NS

Table 8 Association between time since injury and VAS

VAS	*p* value (at 1 month)	*p* value (at 6 months)	*p* value (at 12 months)
Between < 6 weeks and 6–12 weeks	0.59	0.06	0.29
Between < 6 weeks and > 12 weeks	0.04**	0.09	0.12
Between 6–12 weeks and > 12 weeks	0.33	0.86	0.89

**indicates highly significant results

Table 9 Association between time since injury and KT1000

KT1000	*p* value (at 1 month)	*p* value (at 6 months)	*p* value (at 12 months)
Between < 6 weeks and 6–12 weeks	0.89	0.88	0.53
Between < 6 weeks and > 12 weeks	0.79	0.07	0.23
Between 6–12 weeks and > 12 weeks	0.89	0.19	0.88

Table 10 Association between time since injury and Lysholm knee score

Lysholm knee score	*p* value (at 1 month)	*p* value (at 6 months)	*p* value (at 12 months)
Between < 6 weeks and 6–12 weeks	0.22	0.05	0.71
Between < 6 weeks and > 12 weeks	0.73	0.07	0.89
Between 6–12 weeks and > 12 weeks	0.45	0.81	0.84

Table 11 Association between time since injury and Tegner level of activity

Tegneractivity level	*p* value (at 1 month)	*p* value (at 6 months)	*p* value (at 12 months)
Between < 6 weeks and 6–12 weeks	0.28	0.35	0.68
Between < 6 weeks and > 12 weeks	0.89	0.89	0.59
Between 6–12 weeks and > 12 weeks	0.24	0.18	0.89

Discussion

ACL reconstruction surgery has undergone a lot of advancement over the years. Many factors have been studied which affect the final outcome after ACL surgery. Still, only 60–65% of sportspersons are able to return to sports [17, 18]. Pre-operative joint inflammation is one such factor affecting the final outcome [3, 8] that has not been studied much. In the current study, we measured synovial fluid levels of three previously well-established markers of inflammation (Interlukin-1, Interlukin-6 and TNF-α) in ACL deficient knees and compared them with clinical outcome in terms of pain, mechanical stability, functional outcome and return to sporting activity in two different types of autografts i.e., semitendinosus and gracilis graft with preserved insertions (STGPI) and bone patellar tendon bone graft (BPTB). Additionally, we studied the association between time since injury and outcome variables at sequential follow-up.

In the present study, a more recent ACL injury was associated with higher levels of IL-6 pre-operatively and patients with higher levels of IL-6 had increased pain scores, decreased mechanical stability and poorer functional outcome in terms of Lysholm knee score and Tegner level of sports activity. These findings were consistent irrespective of the type of graft used for ACL reconstruction. However, when patients with different times since injury were studied, they had comparable outcome (pain scores, mechanical stability, Lysholm knee score and Tegner level of sports activity) at 1 year follow-up. These findings might seem difficult to understand. However, there is a plausible explanation for these. Some patients in the < 6 weeks group might have tremendously high values of IL-6 and some patients in the > 12 weeks groups might have tremendously low values of IL-6 which would give a false impression of the average values of IL-6 in these groups. To counter this technical error, we compared the outcome in patients based on time since injury alone. This revealed that all the groups had comparable outcome at 1 year follow-up, irrespective of time since injury.

Many markers of inflammation have been studied in relation with acute knee injury [8, 9]. Song et al. have provided evidence of an association between poor graft health and an enhanced inflammatory and macrophage response [2]. This poor graft health translates into poorer final outcome. Hence, the timing of surgery is debatable.

In the present study, we observed a decreasing trend with time for all the inflammatory markers. The comparison of mean values of IL-6 in patients with < 6 weeks of time since injury with those presenting late > 12 weeks was statistically significant. Other studies also suggest the same, i.e., levels of interleukins fall after the acute phase of injury has passed [1].

Normal levels of cytokines in human synovial fluid are [19]:

IL-1: 5.7–14.3 pg/ml.

IL-6: 0.4–1.2 pg/ml.

TNF-α: 0–4.4 pg/ml.

IL-1, IL-6 and TNF-α have been reported to be increased in synovial fluid of patients with acute knee injury as they are considered key mediators in the acute phase of healing [9]. We observed that IL-6 levels were raised in 83.13% patients while most of the patients did not have IL-1 and TNF-α in their pre-operative synovial fluid sample and their reported value was baseline, i.e. zero, in 83.1% samples for IL-1 and 89.8% samples for TNF-α. Additionally, 93.33% patients had decreased levels of IL-1, 5.08% patients had raised levels and 1.7% had normal levels. Also, 91.52% patients had normal levels of TNF-α and 8.47% had elevated levels. These findings point towards IL-6 as the main inflammatory marker in an acute knee injury. This observation is in unison with the findings of Cuellar et al. where IL-6 was significantly elevated in painful ligamentous injury of knee whereas IL-1 and TNF-α were not. Cuellar et al. also identified three cytokines -IFN-γ, MCP-1 and MIP-1β- which had yet not been identified in isolated ACL injury in humans [8].

In the present study, levels of IL-6 had statistically significant correlation with KT 1000 differences at 2 months, 6 months and 1 year of follow-up. This further validates the point made in previous studies that the biological environment created in the tunnel with increased expression of inflammatory cytokines, TNF-α, IL-6 and IL-8, inhibits the process of ligamentization [2]. In the present study, levels of IL-6 had statistically significant correlation with VAS scores at 1 month, 2 months, 6 months and 1 year of follow-up. In the present study, levels of IL-6 had negative and statistically significant correlation with Lysholm knee scores at 2 months, 6 months and 1 year of follow-up. In the present study, levels of IL-6 had negative and statistically significant correlation with Tegner level of sports activity at 1 year of follow-up. However, on the contrary there is no difference

in outcome at 1 year follow-up (i.e., pain scores, mechanical stability, Lysholm knee score and Tegner level of activity) when patients with different time intervals since injury are compared.

It was observed that group A (STG-PI), with $n=23$, and group B (BPTB), with $n=36$, had no statistically significant difference in terms of pre-operative (age, time since injury and IL-6 levels) and post-operative factors (KT-1000 difference, VAS score, Lysholm knee score and Tegner activity scale. Thus, the type of graft used did not act as a confounding factor in the results of the study.

In this study, patients with acutely injured knee (< 6 weeks) had increased levels of interleukins (especially IL-6), representing joint inflammation, as compared to those presenting at > 12 weeks. Additionally, IL-6 had a significant correlation with mechanical stability, pain scores, functional outcome and return to sports. However, there was no difference in outcome at 1 year follow-up (pain scores, mechanical stability, Lysholm knee score and Tegner level of activity) when patients with different time intervals since injury were compared. Since, in previous studies it has been observed that delaying the timing of surgery predisposes to chondral and meniscal injuries in ACL deficient knees [12, 20–22] hence, it seems that ACL reconstruction can be performed in an acutely injured knee with ACL tear. Early ACL reconstruction has been advocated in a recent meta-analysis as well.

There are studies in literature which show increased risk of arthrofibrosis after ACL reconstruction in an acutely injured knee [6, 7, 23]. However, there is also adequate recent literature which highlights that there is no increased incidence of arthrofibrosis in knees when performing ACL reconstruction acutely [24, 25]. In the current study, none of the patients in any of the groups suffered from arthrofibrosis and hence there was no need for procedures like arthroscopic arthrolysis.

Limitations

As a limitation of this study, we did not collect synovial fluid samples post-operatively from the patients for ethical reasons. Only three markers of inflammation were studied as facilities to study these were available at our institute. It is a short-term study. It would be advisable to do a long-term study that evaluates the clinical outcome over a longer follow-up. Patient reported outcome measures could have been used.

Conclusion

The current study demonstrates that clinical outcome in terms of pain score, mechanical stability, functional scores and return to sporting activity is comparable irrespective of the time since injury. In such a scenario, it would be appropriate to perform ACL reconstruction as early as possible as the delay in surgery leads to increased risk of meniscal and chondral damage. However, the current study reflects short term results only. It would be advisable to perform a similar study with a longer follow-up.

Author Contributions RG designed the study, was the chief surgeon in all the cases, contributed in editing and proof reading the manuscript. SK contributed in writing the manuscript, data collection, did literature review on the topic, and assisted in some cases. AM: contributed in writing the manuscript, did literature review on the topic, and assisted in some cases. VB: contributed in editing and proof reading the manuscript. GDM: contributed in data collection and did literature review. JK: contributed in estimation of bio-chemical markers and statistical analysis.

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Compliance with Ethical Standards

Conflict of interest There are no financial or other relationships that might lead to a conflict of interest.

Ethical standard statement The manuscript has been read and approved by all the authors. The manuscript represents honest work.

Informed consent Informed consent was obtained from all the participants included in the study.

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