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The Effect of Limited Perioperative Nonsteroidal Anti-inflammatory Drugs on Patients Undergoing Anterior Cruciate Ligament Reconstruction

Endre Soreide,*† MD, Lars-Petter Granan,‡§ MD, PhD, Geir A. Hjorthaug,‖ MD, Birgitte Espehaug,¶ PhD, Sigbjørn Dimmen,# MD, PhD, and Lars Nordsletten,† MD, PhD
Investigation performed at Oslo University Hospital, Oslo, Norway

Background: The administration of nonsteroidal anti-inflammatory drugs (NSAIDs) to patients undergoing anterior cruciate ligament reconstruction (ACLR) is controversial because it may impair tissue healing and clinical outcomes.

Purpose: To assess the effect of NSAID administration on patients undergoing ACLR.

Study Design: Cohort study; Level of evidence, 3.

Methods: Included patients were aged >15 years and were registered in the Norwegian Knee Ligament Registry from 2008 until 2013 after the primary ACLR. Patients with insufficient data regarding administration of NSAIDs and those with associated knee ligament injuries requiring surgical treatment were excluded from this study. Graft survival was estimated using Kaplan-Meier survival curves, and hazard ratios (HRs) for revision were evaluated using Cox regression analysis. Logistic regression analysis was used to calculate the odds ratio (OR) for a Knee Injury and Osteoarthritis Outcome Score (KOOS)–quality of life (QOL) subscale score <44 at 2-year follow-up.

Results: A total of 7822 patients were included in the analysis for graft survival and assessment for risk of revision. Of these, 4144 patients were administered NSAIDs postoperatively. The mean duration of follow-up was 2.8 years (range, 0-5.9 years). Administration of NSAIDs did not influence graft survival (P = .568). Adjusted Cox regression analyses demonstrated the same finding regarding risk of revision (HR, 1.0; 95% CI, 0.8-1.3). ACLR using a bone–patellar tendon–bone autograft showed a reduced risk of revision (HR, 0.3; 95% CI, 0.1-0.8) among patients administered NSAIDs. In subgroup analyses of 3144 patients, administration of NSAIDs demonstrated a beneficial effect on the risk of a KOOS-QOL score <44 at 2-year follow-up (OR, 0.8; 95% CI, 0.6-0.9).

Conclusion: Administration of NSAIDs to patients after ACLR does not have a negative effect on graft survival, risk of revision, or risk of a KOOS-QOL score <44 at 2-year follow-up. We emphasize using caution when administering NSAIDs by keeping the duration and dosage of NSAIDs as short and low as possible to ensure sufficient pain relief while limiting unwanted exposure to any known and unknown adverse effects of these drugs.

Keywords: anterior cruciate ligament injury; anterior cruciate ligament reconstruction; anterior cruciate ligament reconstruction revision; nonsteroidal anti-inflammatory drug; Knee Injury and Osteoarthritis Outcome Score

Rupture of the anterior cruciate ligament (ACL) is a serious knee injury that occurs mainly in the physically active population.[25,35] This ligament injury causes mechanical joint instability that may lead to varying degrees of functional impairment in demanding sports and in daily living.

An anterior cruciate ligament reconstruction (ACLR) is performed to restore the mechanical stability of the joint, thereby regaining lost function. Whether an ACLR can prevent development of posttraumatic osteoarthritis is currently unclear.[41,46] The incidence of ACLR is estimated at 36.9 per 100,000 in the United States,[21] with similar numbers reported from Scandinavian countries.[14,23,25,35,36,38]

The number of surgeries performed in an outpatient setting has increased over the past decade in Norway, accounting for 69% of ACLRs conducted in 2012.[38] Outpatient surgery depends on efficient control of postoperative pain.[11] This is both to ensure an early discharge from the hospital and to prevent an increased risk of adverse events such as impaired wound healing, infection, chronic pain, and cardiopulmonary complications.[6-8,32,34] Multimodal and procedure-specific pain regimens have evolved, consisting of different analgesics and analgesic techniques, to ensure sufficient perioperative pain control.[13,33] These regimens commonly include the administration of nonsteroidal anti-inflammatory drugs (NSAIDs).

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Hamstrings tendon (HT) and bone–patellar tendon–bone (BPTB) autografts are the most frequently used grafts in Norway.[38,40] A crucial point in ACLR is the biological process involved in the healing of a graft in a bone tunnel in the tibia and femur. Experimental studies have shown that NSAIDs impair tendon healing,[12] tendon-to-bone healing,[13] and bone healing.[28,41] Diaphyseal fracture healing was impaired by NSAIDs in some human studies.[4,9,19] However, the potential adverse effects of NSAIDs on healing of human metaphyseal fractures and the tendon-to-bone interface are still not elucidated.[15,16,19,47] The clinical evidence on tendon-to-bone healing is limited.[5] However, at least 1 clinical study has suggested a deleterious effect of NSAIDs on ACL laxity.[37]

Therefore, this study aimed to assess the effect of NSAIDs on the risk of revision and patient-reported quality of life (QOL) in individuals undergoing primary ACLR.

METHODS

This cohort study was based on prospectively collected data from the national Norwegian Knee Ligament Registry (NKLR). Studies have confirmed a high coverage rate of primary ACLR in the NKLR.[2,48] Registry surgeons report the patient-, injury-, and surgery-specific data postoperatively on a paper form. Since 2007, the report has included data about NSAID administration (yes/no; if administered, which agent and recommended duration of use).[39] The timing of NSAID administration in relation to surgery was not reported. Comprehensive details regarding the NKLR were described previously.[22,23,25]

All Norwegian citizens have a unique 11-digit national identification number that enables the NKLR to link the primary ACLR to any later knee surgical events. The NKLR includes follow-ups at 2, 5, and 10 years postoperatively using the Knee Injury and Osteoarthritis Outcome Score (KOOS).[43] Frobell et al[18] proposed the KOOS to be used as a tool to track "clinical failure" and suggested a KOOS-QOL subscale score <44 as a cutoff. Published studies based on data from the NKLR reveal an association between inadequate knee function, as measured by the KOOS, and a prospective ACLR graft failure.[24,29] On the basis of these findings, we defined a KOOS-QOL score <44 at 2-year follow-up as equivalent to graft failure.

This study included patients older than 15 years who had undergone primary isolated ACLR using HT or BPTB autografts in the period from January 1, 2008 to December 31, 2013 (Figure 1). Patients who underwent ACLR in 2007 were not included because of unreliable data on NSAID administration for these individuals. Patients with insufficient data regarding administration of NSAIDs and those with associated knee ligament injuries requiring surgical treatment were excluded from this study. In addition, patients who had undergone revision as a result of an infection were excluded from the study because of the unknown causal link between NSAIDs and infection and wound healing.[10]

To assess the risk of inferior knee function, patients with insufficient data regarding KOOS scores at 2 years of follow-up or those who had already undergone revision within 2 years of primary ACLR were excluded from the KOOS analysis. The primary endpoint in our study was

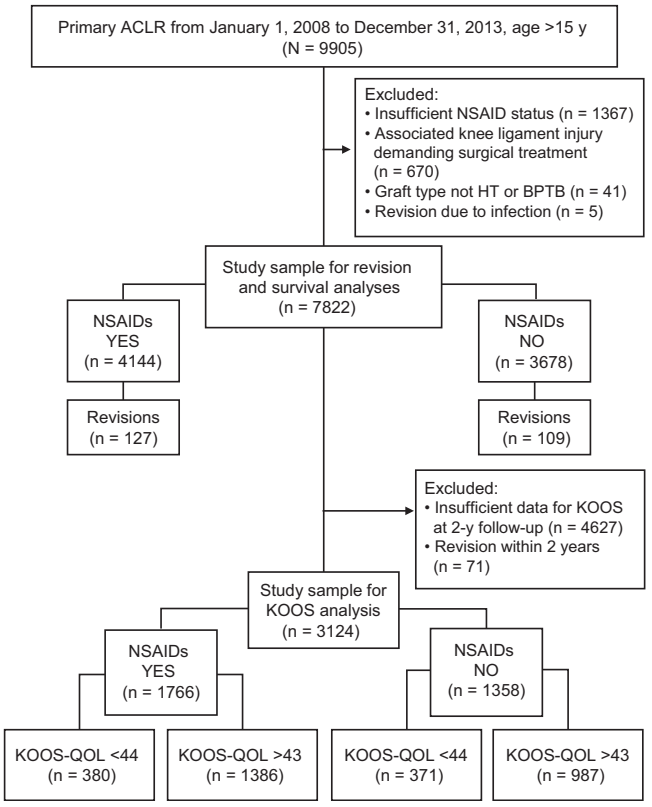

Figure 1. Study flowchart. ACLR, anterior cruciate ligament reconstruction; BPTB, bone–patellar tendon–bone; FU, follow-up; HT, hamstrings tendon; KOOS, Knee Injury and Osteoarthritis Outcome Score; NSAID, nonsteroidal anti-inflammatory drug; QOL, quality of life.

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TABLE 1
Baseline Data for Assessment of Graft Survival and Risk of Revision[a]

Variable	NSAID Given		*P* Value[b]
	No (n = 3678)	Yes (n = 4144)	
Age at surgery, y	29.0 ± 10.2	28.9 ± 10.1	.582
Age group, y, n (%)			.504
>15-19	801 (21.8)	940 (22.7)	
20-29	1314 (35.7)	1436 (34.7)	
>29	1563 (42.5)	1768 (42.7)	
Male patients, %	58	58	.569
Height, cm	175 ± 9.1	175 ± 8.7	.056
Weight, kg	76 ± 14.5	77 ± 14.1	.075
Body mass index, kg/m^2	25.0 ± 3.8	25.1 ± 3.6	.378
Outpatient surgery, %	47.5	77.4	**<.001**
Previous surgery in index knee, %	19.5	17.5	**.024**
Acute meniscal injury, %	24.6	21.5	**.001**
ICRS grade 3-4, %	8.5	6.1	**<.001**
Follow-up, y	2.6 ± 1.6	2.9 ± 1.6	**<.001**
Less than 2 years of follow-up, % yes	39.3	31.6	**<.001**
Time injury to surgery, y	1.9 ± 3.6	1.6 ± 3.2	**<.001**
Bone–patellar tendon–bone graft, %	17.7	27.1	**<.001**
Revision ACLR, %	3.0	3.1	.794
Revision ACLR within 2 y of surgery, %	1.8	2.0	.676

[a]Data are reported as mean ± SD unless otherwise indicated. ACLR, anterior cruciate ligament reconstruction; ICRS, International Cartilage Repair Society; NSAID, nonsteroidal anti-inflammatory drug.
[b]Continuous variables were analyzed using the *t* test, and categorical variables were analyzed using the chi-square test. Bolded *P* values indicate a statistically significant between-group difference ($P < .05$).

TABLE 2
Baseline Data for Assessment of Inferior Knee Function After ACLR (KOOS-QOL Score <44 at 2-Year Follow-up)[a]

Variable	NSAID Given		*P* Value[b]
	No (n = 1358)	Yes (n = 1766)	
Age at surgery, y	30.4 ± 10.8	29.4 ± 10.2	.982
Age group, y, n (%)			.171
>15-19	280 (20.6)	402 (22.8)	
20-29	415 (30.6)	558 (31.6)	
>29	663 (48.8)	806 (45.6)	
Male patients, %	52.9	53.9	.565
Height, cm (n = 358)	173.7 ± 9.6	174.9 ± 8.3	.197
Weight, kg (n = 359)	74.8 ± 11.9	74.8 ± 9.6	.988
Body mass index, kg/m^2 (n = 358)	24.8 ± 3.8	24.4 ± 2.9	.288
Outpatient surgery, %	40.6	73.9	**<.001**
Previous surgery in index knee, %	22	18.2	**.009**
Acute meniscal injury, %	7.1	7.6	.582
ICRS grade 3-4, %	9.1	6.3	**.004**
Follow-up, y	3.7 ± 1.1	3.8 ± 1.1	**.002**
Time from injury to surgery, y	2.1 ± 4.1	1.6 ± 3.1	**<.001**
Revision ACLR, %	1.8	1.6	.673
BPTB graft, n (%)	173 (12.7)	518 (29.3)	**<.001**
Preoperative KOOS score			
QOL	34.4 ± 17.8	35.6 ± 19.0	.113
Sports and recreation function	41.9 ± 26.6	44.2 ± 27.4	**.028**
Pain	73.5 ± 18.5	74.8 ± 18.1	.054
Symptoms	72.3 ± 18.3	73.5 ± 17.8	.103
Activities of daily living	82.1 ± 18.7	83.5 ± 17.7	.056

[a]Data are reported as mean ± SD unless otherwise indicated. ACLR, anterior cruciate ligament reconstruction; BPTB, bone–patellar tendon–bone; ICRS, International Cartilage Repair Society; KOOS, Knee Injury and Osteoarthritis Outcome Score; NSAID, nonsteroidal anti-inflammatory drug; QOL, quality of life.
[b]Continuous variables were analyzed using the *t* test, and categorical variables were analyzed using the chi-square test. Bolded *P* values indicate a statistically significant between-group difference ($P < .05$).

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revision of the ACLR, and the secondary endpoint was a KOOS-QOL score <44 at the 2-year follow-up.

Previous studies have shown that younger age is a risk factor for revision,[3,27,31,45] and we thus split the population into 3 groups based on age at the time of surgery (>15-19, 20-29, and >29 years). We conducted separate analyses for age groups, sex, and type of graft to assess graft survival, risk of revision, and risk of inferior knee function after administration of NSAIDs to patients undergoing primary ACLR.

Statistical Analysis

Statistical analyses were performed using SPSS software (version 22 for Mac).[28] All tests were 2-sided, with a statistical significance level set to .05. Although the statistical significance refers to the probability of a finding being due to chance, the clinical significance indicates the smallest value of effect being harmful or beneficial to patients.[30] The chi-square test was used for categorical variables and the *t* test was used for continuous variables to compare baseline data by NSAID use for both study samples (Tables 1 and 2).

A chi-square, linear-by-linear association test was used to assess any change in the annual rate of NSAID administration during the study period. Graft survival curves were calculated by the Kaplan-Meier method and distributional differences were compared by the log-rank test. Cox regression analyses were performed to assess relative differences in risk for revision (hazard ratios [HRs]).

Potential confounders were evaluated and included in the multivariate analysis if $P < .2$. In the survival analyses, observation times of unrevised grafts were censored at the date of death or emigration or at the end of study on December 31, 2013.

To assess the risk of inferior results according to the KOOS-QOL subscale (KOOS-QOL < 44), logistic regression analysis was used. Potential confounders were evaluated and included in the multivariate analysis if $P < .2$.

To assess any differences at baseline, a paired *t* test was used to compare the groups that were or were not administered NSAIDs. The same test was used to compare data from baseline and 2-year follow-up within each group. In addition, we used the independent *t* test to compare the mean KOOS results at 2-year follow-up.

RESULTS

Baseline data for the graft revision study sample showed small differences for the amount of outpatient surgery, previous surgery to the index knee, acute meniscal injuries, cartilage injuries (International Cartilage Repair Society [ICRS] grade 3-4), type of graft, mean time from injury to surgery, and time to follow-up (Table 1).

Baseline data for the study subsample used to assess the risk of a KOOS-QOL score <44 at 2-year follow-up (n = 3124) showed differences for the fraction of outpatient surgery performed, previous surgery to the index knee, cartilage injury (ICRS grade 3-4), mean time from injury to surgery, type of graft used, and preoperative KOOS sports and recreation function subscale score (Table 2).

TABLE 3
Type of Nonsteroidal Anti-Inflammatory Drug Administered (n = 4062)

Nonsteroidal Anti-Inflammatory Drug	No. of Patients (%)
Diclofenac	3793 (91.5)
Ketorolac	127 (3.1)
Celecoxib	98 (2.4)
Other	44 (1.0)

Of 7822 patients who underwent ACLR, 4144 (53%) were administered NSAIDs. The mean follow-up was 2.8 years (range, 0-5.9 years). There were 236 ACLR revisions during the study period; of these, 127 (54%) were among patients who had received NSAIDs postoperatively, and 150 revisions (64%) were performed within 2 years after the primary ACLR. The mean (±SD) time to revision was 2.8 ± 1.6 years.

The most commonly administered NSAID was diclofenac, which was given to 91.5% of patients (Table 3). The recommended duration of NSAIDs use was included in the NKLR form in 2012. The mean duration reported for 1181 patients was 6.7 days (range, 1-14 days). The annual administration of NSAIDs to patients during the study period declined ($P < .001$) from 62% in 2008 to 45% in 2013.

Of the patients in the youngest population, 6.3% underwent ACLR revision during the study period. In the groups aged 20-29 years and >29 years, 3.1% and 1.3% underwent ACLR revision, respectively; 3.4% of female patients and 2.7% of male patients were revised during the study period.

The Kaplan-Meier survival curves did not reveal any difference in overall graft survival between the groups who were or were not administered NSAIDs (Figure 2). Adjustment for potential confounders in Cox regression analyses demonstrated the same result (HR, 1.0; 95% CI, 0.8-1.3) (Table 4). Furthermore, we observed similar findings within subgroups defined by sex or age and for patients reconstructed with HT grafts.

However, administration of NSAIDs showed a beneficial significant effect on risk of revision in patients reconstructed with BPTB grafts (HR, 0.3; 95% CI, 0.1-0.8) (Figure 3, Table 5).

Both patients who were or were not administered NSAIDs achieved statistically significant improvement ($P < .001$) in KOOS scores comparing the preoperative scores with the results at 2-year follow-up. At 2-year follow-up, patients administered NSAIDs demonstrated statistically significant higher mean scores for all subscales. There were no significant differences in the distribution of inferior KOOS-QOL scores for age groups ($P = .187$) or sex ($P = .672$) at the 2-year follow-up.

Patients administered NSAIDs showed a reduced risk of a KOOS-QOL score <44 at 2-year follow-up (OR, 0.8; 95% CI, 0.6-0.9) (Table 6). In a separate analysis for age, NSAIDs did not affect the risk of inferior knee function for patients aged >15 to 19 years or 20 to 29 years (Table 7). For patients

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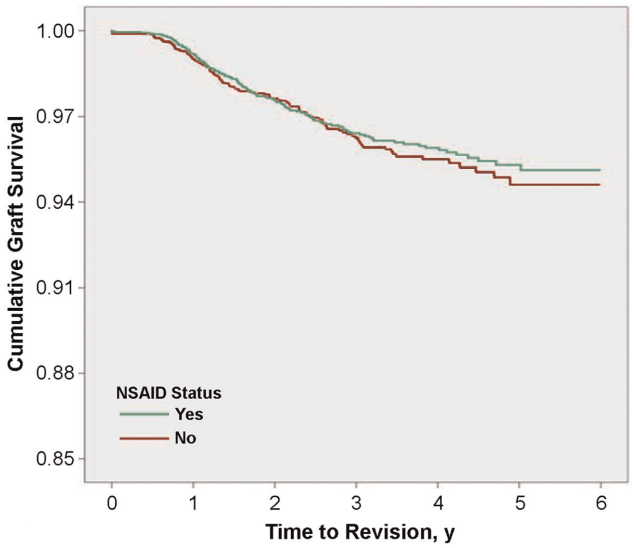

Figure 2. Kaplan-Meier survival curves for NSAID status (P = .568, log-rank test; n = 7822). NSAID, nonsteroidal anti-inflammatory drug.

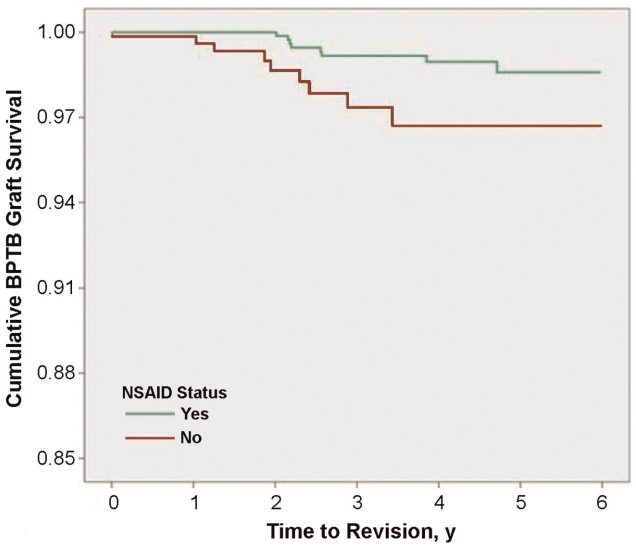

Figure 3. Survival curves for bone–patellar tendon–bone (BPTB) graft demonstrating superior survival for patients administered NSAIDs (P = .001; n = 1778). NSAID, nonsteroidal anti-inflammatory drug.

TABLE 4
Adjusted Cox Regression Analysis of Risk of ACLR Revision[a]

Factor	No. of Patients	Hazard Ratio (95% CI)	P Value[b]
NSAID given			
No	3520	1	
Yes	3973	1.0 (0.8-1.3)	.972
Sex			
Female	3132	1	
Male	4361	0.9 (0.7-1.2)	.675
Age group, y			
>15-19	1680	4.1 (2.8-5.9)	**.001**
20-29	2647	2.4 (1.5-3.1)	**.001**
>29	3166	1	

[a]ACLR, anterior cruciate ligament reconstruction; NSAID, nonsteroidal anti-inflammatory drug.
[b]Bolded P values indicate statistical significance ($P < .05$).

TABLE 5
Subgroup Analyses for Risk for ACLR Revision, Using Cox Regression Analysis[a]

Factor	NSAID Given	No. of Patients	Hazard Ratio (95% CI)	P Value[b]
Graft type				
BPTB	No	625	1	
	Yes	1076	0.3 (0.1-0.8)	**.016**
HT	No	2895	1	
	Yes	2897	1.1 (0.8-1.4)	.53
Sex				
Female	No	1458	1	
	Yes	1674	1.4 (0.9-2.0)	.113
Male	No	2062	1	
	Yes	2299	0.7 (0.5-1.1)	.117
Age group, y				
>15-19	No	773	1	
	Yes	907	0.9 (0.6-1.4)	.740
20-29	No	1266	1	
	Yes	1381	1.3 (0.8-2.0)	.276
>29	No	1481	1	
	Yes	1685	0.6 (0.3-1.1)	.111

[a]Analysis adjusted for sex, age, type of graft, time from injury to surgery, and prior surgery in the index knee. ACLR, anterior cruciate ligament reconstruction; BPTB, bone–patellar tendon–bone; HT, hamstrings tendon; NSAID, nonsteroidal anti-inflammatory drug.
[b]Bolded P values indicate statistical significance ($P < .05$).

aged >29 years, the risk of inferior results was reduced among those who were administered NSAIDs (OR, 0.7; 95% CI, 0.5-0.9). NSAID administration revealed a nonsignificant reduction in the risk of a KOOS-QOL score <44 for both BPTB (OR, 0.7; 95% CI, 0.4-1.1) and HT (OR, 0.8; 95% CI, 0.6-1.0) groups. Administration of NSAIDs did not affect the risk of inferior knee function for female patients; however, there was a small but significant reduced risk for male patients administered NSAIDs (OR, 0.7; 95% CI, 0.5-0.9).

DISCUSSION

Patients undergoing ACLR who were administered NSAIDs did not demonstrate lower graft survival, increased risk of revision, or increased risk of inferior patient-reported knee function.

Baseline data demonstrated some differences between the groups. A possible explanation could be that patient-specific

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TABLE 6
Adjusted Logistic Regression Analysis to Assess Risk of Inferior Knee Function After ACLR (KOOS-QOL Score <44 at 2-Year Follow-up)[a]

Factor	No. of Patients	Odds Ratio (95% CI)	*P* Value[b]
NSAID given			
No	1108	1	
Yes	1483	0.8 (0.6-0.9)	**.009**
Sex			
Female	1223	1	
Male	1368	1.1 (0.9-1.3)	.48
Age group, y			
>15-19	571	2.1 (1.5-2.7)	**<.001**
20-29	827	1.9 (1.4-2.3)	**<.001**
>29	1193	1	

[a]Adjusted for sex, age group, International Cartilage Repair Society grade, prior surgery to the index knee, time to surgery, and preoperative results on the KOOS subscales (pain, symptoms, activities of daily living, sports and recreation function, and QOL). ACLR, anterior cruciate ligament reconstruction; KOOS, Knee Injury and Osteoarthritis Outcome Score; NSAID, nonsteroidal anti-inflammatory drug; QOL, quality of life.
[b]Bolded *P* values indicate statistical significance ($P < .05$).

TABLE 7
Subgroup Analyses for Risk for Inferior Knee Function After ACLR (KOOS-QOL Score <44 at 2-Year Follow-up), Using Adjusted Logistic Regression Analysis[a]

Factor	NSAID Given	No. of Patients	Odds Ratio (95% CI)	*P* Value[b]
Graft type				
BPTB	No	142	1	
	Yes	464	0.7 (0.4-1.1)	.135
HT	No	966	1	
	Yes	1019	0.8 (0.6-1.0)	.077
Sex				
Female	No	523	1	
	Yes	700	0.8 (0.6-1.0)	.103
Male	No	585	1	
	Yes	783	0.7 (0.6-0.9)	**.033**
Age group, y				
>15-19	No	224	1	
	Yes	347	0.8 (0.5-1.2)	.316
20-29	No	358	1	
	Yes	469	0.8 (0.6-1.1)	.223
>29	No	526	1	
	Yes	667	0.7 (0.5-0.9)	**.042**

[a]Adjusted for sex, age group, International Cartilage Repair Society grade, prior surgery to the index knee, time to surgery, and preoperative results on the KOOS subscales (pain, symptoms, activities of daily living, sports and recreation function, and QOL). ACLR, anterior cruciate ligament reconstruction; BPTB, bone–patellar tendon–bone; HT, hamstrings tendon; KOOS, Knee Injury and Osteoarthritis Outcome Score; NSAID, nonsteroidal anti-inflammatory drug; QOL, quality of life.
[b]Bolded *P* values indicate statistical significance ($P < .05$).

criteria (eg, an outpatient setting, the use of BPTB grafts, and previous surgery) increased the likelihood for the surgeon to administer NSAIDs. On the other hand, acute meniscal injuries or more extensive chondral injuries may have guided the surgeon to be more restrictive in his or her recommendations.

The use of NSAIDs in modern multimodal pain therapy after surgery is well established, partly on the basis of results of previous studies that were later retracted because they were based on corrupted data.[26,44] In addition, NSAIDs are commonly prescribed intentionally to avoid the common and discomforting adverse effects of opioids. Despite the many advantages of NSAIDs, the potential impairing effect of these drugs on musculoskeletal healing remains unsolved. Our study sheds light on this topic, first by demonstrating no increased risk of revision after the primary ACLR in patients administered NSAIDs postoperatively. Second, the analysis for our second endpoint (KOOS-QOL <44 at 2 years follow-up) demonstrated a significantly reduced risk of inferior results among patients older than 29 years who received NSAIDs postoperatively. The explanation of our results is uncertain. The duration of administration was limited, and we have no reason to believe that the dosage was beyond the recommendations. The beneficial pain-relieving effect of NSAIDs could contribute to early and increased quality of postoperative rehabilitation, providing better outcomes for patients. To our knowledge, most experimental studies to date have focused on the first inflammatory and proliferative phase of healing, in which NSAIDs could have a negative effect in reducing inflammatory cell signaling. This could be a possible explanation for the results of a retrospective study by Mehta et al,[37] which demonstrated increased laxity of ACLRs at 6 weeks postoperatively in patients administered ketorolac. However, NSAIDs could have a more positive effect on healing in the later maturation and remodeling phase because they can contribute to increased protein synthesis.[1]

Experimental studies have demonstrated impaired healing of supraspinatus reattachment in rats after NSAID treatment,[12] patellar tendon reattachment in rats,[17] and the Achilles tendon in the tibial bone tunnel in rats.[16] Our study does not demonstrate any clinically significant adverse effects of NSAIDs on ACLR healing.

The goal of ligament reconstruction surgery is to ensure a sufficient attachment of the graft to the adjacent bone to regain joint stability. Whereas the HT graft depends on tendon-to-bone tunnel healing, the BPTB graft relies on bone-to-bone tunnel healing. These grafts are similar, in that both repair mechanisms depend on bony ingrowth in the tunnel and fibrovascular scar tissue formation to anchor the graft to the insertion site. Tendon-to-bone healing is considered to be a more fragile process than bone-to-bone healing, because the differences in morphological properties of bone and ligament/tendons are immense.[42]

A previous study by Persson et al[40] revealed an increased risk for revision in ACLRs using HT compared with BPTB autografts. With the biological mechanisms involved in anchoring a graft to the respective bone, one could assume that this result is partly attributable to a more extensive

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NSAID-induced impairment of tendon-to-bone healing than of bone-to-bone healing. Our study does not provide evidence that this difference could be attributable to the effects of NSAIDs.

Our large study sample makes it possible to unveil factors that may influence the rate of revision despite few revisions during the study period. The data collected are based on the contribution of numerous surgeons and hospitals, reporting patient data for a variety of ages, activity levels, and surgical techniques. Thus, the results are applicable to the general population.

This study has some limitations. Surgeons guide the choice of graft and the administration of NSAIDs. In addition, the level of experience or annual number of procedures is not reported for each surgeon. Furthermore, a multivariate regression analysis can adjust for known confounders, but some confounders may not be known. There were insufficient data on NSAID status for 1376 patients. Of 4144 patients, the type of NSAID and duration was reported for 4062 and 1181 patients, respectively. Together with the uncertainty regarding surgeon-reported administration of NSAIDs, this could possibly affect our findings. The data in this study partly rely on the surgeons reporting to the NKLR, which includes data on the administration of NSAIDs. Prior studies have verified a high rate of reliable data being reported after the primary ACLR. The rate and reliability of the data reported after revisions of ACLR are not confirmed in similar studies.

Our study does not reveal an increased risk of revision, or inferior KOOS-QOL score at 2-year follow-up, in patients who undergo ACLR and are administered NSAIDs. We emphasize caution when administering NSAIDs by keeping their duration of use and dosage as short and low as possible to ensure sufficient pain relief while limiting patients' exposure to any known or unknown adverse effects.

Some of the adverse effects of NSAIDs on tissue healing demonstrated in experimental studies have thus far been challenging to reproduce and demonstrate in clinical studies. The results from our study should be confirmed by other ACL registries, but our study indicates that short-term use of NSAIDs after ACLR is safe.

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