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Research Article

Pharmacological Thromboprophylaxis Effectiveness in Low-Risk Patients Undergoing Arthroscopic Anterior Cruciate Ligament Reconstruction: A Randomized Clinical Trial

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Abstract

Background: There is a paucity of evidence and controversies regarding prophylaxis strategies in low-risk patients undergoing knee arthroscopy. This study aims to evaluate the effectiveness and safety of aspirin and low-molecular-weight heparin (LMWH) in an arthroscopic anterior cruciate ligament (ACL) reconstruction for low-risk patients.
Methods: We performed a preoperational evaluation a week before surgery for any sign of pulmonary embolism (PE) and deep vein thrombosis (DVT). For this purpose, we used single limited compression Doppler ultrasonography (CUS) of the lower extremities. Rehabilitation started before the time of the surgery to improve the range of motion (ROM) and quadriceps muscle function. A team of 3 orthopedists performed the procedures. The same surgical technique and graft were used with spinal anesthesia, and operation time was recorded.
Results: The mean age of participants was 31.4 ± 5.6 years, with 93 individuals (67%) being men and 23% women. No cases of DVT or PE were observed. Three cases in the LMWH group and one case in the aspirin group experienced minor surgical site bleeding. One case of hemarthrosis with normal ultrasonography occurred in the LMWH group. Regarding safety and effectiveness, there was no statistically significant difference between the parallel arms.
Conclusion: The use of LMWH or aspirin after simple arthroscopic ACL reconstruction in low-risk patients showed no difference in effectiveness. Hence, the routine use of thromboprophylaxis in this setting is questionable although adverse events are rare.

Keywords: Knee; Venous Thrombosis; Arthroscopy; Low-Molecular-Weight Heparin; Aspirin; Randomized Controlled Trial

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Background

The annual incidence of anterior cruciate ligament (ACL) injuries ranges from 10 to 50 per 100000 persons. There are 250000 ACL reconstructions per annum in the United States (US), making it one of the most common orthopedic surgeries. Athletes and young adults constitute a significant portion of ACL injury cases because of the higher intensity of their activities. Along with its benefits, performing knee arthroscopy procedures brings about some complications, either through surgical (3.68%), medical (0.77%), or anesthetic interventions (0.23%) (1-4).

Orthopedic surgery places patients in a pathophysiological state in Virchow's triad, making venous thromboembolism (VTE) more favorable. Immobilization and tourniquet use cause stasis, surgical manipulation causes endothelial injury, and trauma increases thromboplastin. More than half of the hospitalized patients are at risk of VTE, and without any prevention, the VTE rate can reach 5%. Up to 40% of hospitalized cases will be complicated by deep vein thrombosis (DVT) (5-7).

While the use of pharmacological prophylaxis, such as low-molecular-weight-heparin (LMWH) and aspirin, is recommended in major orthopedic surgeries, it is not suggested for all patients undergoing knee arthroscopy (5). There is a 0.2% risk for pulmonary embolism (PE) and a 2% risk for asymptomatic DVT after ACL reconstruction (8). Guidelines are not implemented correctly in practice, especially in developing countries where 78% of patients who do not require prophylaxis receive inappropriate thromboprophylaxis (6).

Adequate studies have investigated the risk of developing PE and DVT after major orthopedic surgery (total knee/hip arthroplasty, hip/leg fracture) and possible preventive interventions. Results showed that pharmacological and mechanical prophylaxis had more advantages than complications, especially in high-risk groups with a history of previous VTE. In addition, some studies have not found a significant difference between aspirin and enoxaparin (9). Still, there is a paucity of evidence and controversies regarding prophylaxis strategies in low-risk patients undergoing knee arthroscopy (5, 10, 11). Despite no evidence of thromboprophylaxis effectiveness in minor orthopedic surgeries, many surgeons use pharmacological options to prevent VTE based on their individual experiences (6, 12, 13).

The purpose of this study was to evaluate the effectiveness and safety of aspirin and LMWH in ACL reconstruction of low-risk patients in comparison with no treatment.

Methods

Study Setting and Patients: We conducted a single-center, assessor-blind, simple randomized clinical trial (RCT) from March 2019 until May 2020. Patients aged between 18 to 45 years, with ACL rupture diagnosed by magnetic resonance imaging (MRI), were enrolled in the study. From March 2019 until May 2020, 471 cases were assessed for inclusion. Out of these, 137 (27%) subjects were included and then randomized. Forty-six subjects were assigned to each of the LMWH, aspirin, and no-treatment arms of the study. All patients agreed to participate, and no violation of prescribed drugs was reported. Moreover, no patients reported the use of additional pharmacological agents during the study. Table 1 shows participants' characteristics and duration of the procedure, which were reasonably balanced among the study's three arms.

One participant was lost on follow-up due to personal reasons and did not mention any symptoms during the phone call 14 days after the procedure. We excluded patients with other ligament injuries in addition to ACL, patients with concomitant damage to the same sidelong osseous tissue, and patients who needed other procedures that could interfere with rehabilitation after surgery. To select low-risk patients, individuals using oral contraceptives, smokers, those with a history of DVT, current use of pharmacologic thromboprophylaxis, history of cancer, active infection, anemia, history of an allergic reaction to aspirin or LMWH, coagulopathic disorders, a body mass index (BMI) higher than 30 kg/m^2, and patients younger than 18 years and older than 45 years were excluded. One hundred thirty-eight eligible patients were assigned to three parallel arms of the study with 46 participants in each, using random allocation software 2.0.

We performed a preoperational evaluation a week before surgery for any sign of PE and DVT. For this purpose, we used single limited compression Doppler ultrasonography (CUS) of the lower extremities. Rehabilitation started before the time of the surgery to improve the range of motion (ROM) and quadriceps muscle function. A team of 3 orthopedists performed the procedures. The same surgical technique and graft were used with spinal anesthesia, and operation time was recorded.

The Institutional Ethics Committee approved the study, and informed consent was provided for all participants. Confidentiality of patients' information was considered. The study is registered at the Iranian Register of Clinical Trials (IRCT) (Ethic Committee reference number: IR.SBMU.MSP.REC.1398.791).

Intervention: We had three study arms to compare the effectiveness and safety of interventions. For the first arm of the study, 80 milligrams (mg) of aspirin, twice daily, starting from the first day of operation for 14 days, was prescribed. The study's second arm was prescribed a daily 40 mg subcutaneous injection of LMWH for 14 days. A physician trained the patient to self-inject the medication. The third arm was selected as a control group with no treatment. All individuals underwent a rehabilitation protocol to improve ankle pump, quadriceps muscle, and hamstring muscle function. For post-operation pain management, 500 mg acetaminophen three times per day was prescribed.

Outcome and Endpoints: The primary efficacy endpoint was DVT and PE up to 28 days post-operation. All participants were evaluated weekly post-operation for any sign or symptom of DVT or PE, and if indicated, computed tomography (CT) angiography was requested. A radiologist performed CUS four weeks after the procedure to search for DVT signs and filling defects in the lower extremities. During follow-up sessions, an orthopedist assessed knee effusion and hemarthrosis (14). The primary safety outcome was bleeding and hemarthrosis. Patients were asked if they felt the loss of consciousness, dyspnea, heart palpitation, back pain, gastrointestinal (GI) bleeding, epistaxis, knee swelling, bleeding, or discharge at the surgical site, and any change in the size of extremities.

Statistical Analysis: Continuous results were stated as the mean ± standard deviation (SD). The categorical data were shown as number and percentage. The Kolmogorov-Smirnov test confirmed the normal distribution of age, BMI, and surgery duration. A chi-square test was performed for the comparison of qualitative variables. Analysis of variance (ANOVA) test was used to compare quantitative results between the three arms of the study. The significance level (α) for all tests was considered as 0.05. Analyses were performed with SPSS software (version 24.0, IBM Corporation, Armonk, NY, USA).

Results

Among 137 patients, 46 participants were in the control group, 45 participants received aspirin treatment, and 46 participants were in the LMWH treatment group. There were 93 (67%) male and 44 (33%) female patients. The mean age was 31.4 ± 5.6 years and the mean BMI was 24.0 ± 3.3 kg/m^2 (Table 1).

The baseline characteristics of patients and surgery duration are presented in table 1, which showed no significant differences among the groups. There was no loss of consciousness, dyspnea, heart palpitation, back pain, GI bleeding, or epistaxis in participants. Two patients complained of knee swelling, one of whom had a stroke score of +1, as shown in table 2. One patient in the aspirin arm and three in the LMWH arm experienced minor surgical site bleeding days after surgery, which was self-limited.

As shown in table 2, no statistically significant difference in patient-reported symptoms was observed among the three arms during follow-up. The results of examinations on two follow-up visits and ultrasonography evaluation for DVT in the lower extremities were also similar between groups. No patients showed signs of DVT, PE, or any signs of adverse events or bleeding.

Table 1. Baseline characteristics of the participants on each arm

Number of participants	No treatment (n = 46)	Aspirin (n = 45)	LMWH (n = 46)	Total (n = 137)	P-value
Age (year)	30.5 ± 4.4	31.7 ± 6.3	32.0 ± 6.1	31.4 ± 5.6	0.446
Sex (men)	26 (56.0)	27 (60.0)	30 (65.0)	93 (67.8)	0.602
BMI (kg/m^2)	23.9 ± 3.1	24.3 ± 3.5	23.9 ± 3.3	24.0 ± 3.3	0.770
Duration of procedure (minute)	71.5 ± 20.5	69.0 ± 19.4	74.8 ± 18.7	71.8 ± 19.6	0.363

Data are presented as mean ± standard deviation (SD) or number and percentage
BMI: Body mass index; LMWH: Low-molecular-weight heparin

Table 2. Study outcomes on each study arm

Number of participants	No treatment (n = 46)	Aspirin (n = 45)	LMWH (n = 46)	Total (n = 137)	P-value
Loss of consciousness	0 (0)	0 (0)	0 (0)	0 (0)	-
Dyspnea	0 (0)	0 (0)	0 (0)	0 (0)	-
Heart palpitation	0 (0)	0 (0)	0 (0)	0 (0)	-
Back pain	0 (0)	0 (0)	0 (0)	0 (0)	-
Symptoms of gastrointestinal bleeding	0 (0)	0 (0)	0 (0)	0 (0)	-
Epistaxis	0 (0)	0 (0)	0 (0)	0 (0)	-
Knee swelling	0 (0)	0 (0)	2 (4)	2 (2)	0.128
Surgical site bleeding	0 (0)	1 (2)	3 (6)	4 (3)	0.160
Surgical site infection	0 (0)	0 (0)	0 (0)	0 (0)	-
Weekly stroke examination (11)					0.544
Zero	42 (92)	42 (94)	40 (87)	124 (91)	
Trace	4 (8)	3 (6)	6 (13)	13 (9)	
+1	0 (0)	0 (0)	0 (0)	0 (0)	
Ultrasonography examination of lower extremities at postoperative day 28	No abnormality	No abnormality	No abnormality	No abnormality	-

Data are presented as number and percentage
LMWH: Low-molecular-weight heparin

Discussion

ACL surgery is among the most prevalent orthopedic procedures, and a significant proportion of patients undergoing them are at low risk for VTE. Despite the dominant view against the routine use of thromboprophylaxis in arthroscopic ACL reconstruction, many orthopedists still implement their personal preferences to use pharmacological options.

In this study, we observed no evidence of VTE as the primary endpoint of effectiveness; hence, the use of LMWH or aspirin is not recommended after simple ACL reconstruction in low-risk patients.

Results showed that daily LMWH subcutaneous injection after arthroscopic ACL reconstruction had no major complications in the low-risk population, which is barely distinguishable from previously published reviews (15-17). Only three patients (6%) showed minor bleeding in our study, making LMWH a safe but effective option. Zhu et al. conducted a systematic review to evaluate the risks and benefits of LMWH in patients undergoing arthroscopic ACL reconstructions. Their study found no difference in major VTE [relative risk (RR = 1.00)], all VTE (RR = 0.31-1.29), and major bleeding events (RR = 0.98) when comparing postoperative LMWH with non-LMWH strategies. However, there was a 64% increase in all bleeding events (15). In many orthopedic procedures, the use of LMWH is considered safe and effective to prevent VTE. Hence, educating orthopedic surgeons is recommended to avoid complications and cost-imposition when LMWH is not indicated.

This is the second RCT evaluating the effectiveness of aspirin after arthroscopic knee surgery. The aspirin arm of the study also did not show any effectiveness and safety, confirming previous studies. Kaye et al.'s study in low-risk populations after arthroscopic surgery found no VTE cases, similar to our results. Except for one minor bleeding case, we did not find any complications. Kaye et al.'s study showed minor complications in the aspirin group (9% knee swelling, 3% joint line tenderness) (18).

Various methods and timing are used to detect DVT and PE in studies. We evaluated DVT by CUS of the lower extremities on post-operative week 4 and assessed PE through patients' history and examination during weekly visits. Most studies used patient-reported symptoms to assess PE, but various tools were used for DVT examination. Ultrasonography and venography are different modalities with different results when used as DVT screening tools. Using venography will boost the DVT rate compared with CUS, and almost all of this rise is due to the detection of asymptomatic DVT cases. Asymptomatic DVT may not be clinically irrelevant, and it is controversial to decide when to start the treatment in this setting (8, 17). Although magnetic resonance venography (MRV) is considered a gold standard for detecting DVT, ultrasound is an accurate diagnostic test with a diagnostic odds ratio (OR) of 39, even in asymptomatic post-operative patients (19).

Several limitations could have influenced the results. This study evaluated low-risk patients elected for arthroscopic ACL reconstruction, while risk assessment for pharmacologic thromboprophylaxis is not well established; accordingly, different guidelines in different regions of the world are plausible. Physicians should consider patients' risk for VTE and bleeding, cost, and patient preferences when implementing studies. Our study population was over-selected, and individuals in the three arms of the trial had an extremely low risk for thrombosis, first because of restricted exclusion criteria and second, due to a higher incidence of ACL injuries in young ages. Therefore, it is recommended that further studies evaluate the effectiveness of thromboprophylaxis in intermediate and high-risk patients.

Additionally, other arthroscopic procedures of the knee can be included in the next studies. We preferred to use CUS to study DVT incidence; further studies with the use of venography alongside CUS are recommended so that asymptomatic DVT and its clinical significance could be more acknowledged. This RCT was single-center, and there is a possible risk of bias; hence, multi-center studies are also recommended. The rationale for starting pharmacologic agents to prevent VTE among orthopedic surgeons is also a new research topic.

Conclusion

The use of LMWH or aspirin after simple arthroscopic ACL reconstruction in low-risk patients has no significant effectiveness. Hence, routine use of thromboprophylaxis in this setting is questionable although adverse events are rare. The evidence from this study supports individual risk assessment rather than the regular use of thromboprophylaxis with LMWH and aspirin.

Conflict of Interest

The authors declare no conflict of interest in this study.

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