Venous thrombosis following lower-leg cast immobilization and knee arthroscopy: From a population-based approach to individualized therapy

Németh, B.

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No indication for thromboprophylactic therapy following knee arthroscopy or lower-leg casting

Adapted from:

1. B. Németh et al. Thromb Haemost. 2016 Oct 28;116(5):1001

2. B. Németh et al. Injury. 2017 Dec;48(12):2887-2888

In this chapter we respond to two trials which studied the efficacy of thromboprophylaxis following 1. Knee arthroscopy and 2. Lower-leg cast immobilization. For both trials, we question the validity of the results and we point out our concerns with regards to the study outcome.

THE ERIKA TRIAL:
still limited evidence on the efficacy of thromboprophylaxis after knee arthroscopy

Németh B, van Adrichem RA, Cannegieter SC.
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Dear editor,
We read with great interest the recent article by Camporese and colleagues "Efficacy of Rivaroxaban for thromboprophylaxis after Knee Arthroscopy (ERIKA). A phase II, multicentre, double-blind, placebo-controlled randomised study".[1] This study considers a highly relevant clinical problem, i.e. whether or not to prescribe thromboprophylaxis in patients undergoing knee arthroscopy (KA). The authors conclude that a seven day course of 10-mg rivaroxaban reduced both symptomatic and asymptomatic venous thrombosis (VT) (absolute risk difference -5.3% [95%CI -11.4 to -0.8], number needed to treat (NNT)=19). In addition, it is stated that this treatment may be safely employed in this patient group.

These statements raised some concern from our perspective and we would like to point out the following: First, the study found an overall symptomatic VT risk of 3.0% within 3-months following KA (0.8% versus 5.3% in the rivaroxaban and placebo controlled group respectively). All but one symptomatic events were diagnosed at day seven, just before ultrasonography. This risk is much higher than (recent) published numbers derived from very large observational studies. For example, a study from Portsmouth, USA, reported a cumulative incidence of 0.53% for symptomatic VT after 16.558 anterior cruciate ligament reconstructions,[2] while other studies showed an incidence of 0.3% within 4 weeks (12.595 patients),[3] and 0.4% within 35 days (4833 patients).[4] This strong discrepancy made us question the method that was used to classify events as symptomatic. The investigators actively asked patients about signs and symptoms of VT before ultrasonography, which was performed by a trained nurse blinded to treatment arm. One positive sign or symptom combined with a thrombus found during ultrasonography resulted in the classification of a symptomatic event. This method most likely does not represent the pattern of signs and symptoms that is present when patients seek medical advice during follow-up themselves, i.e. the truly symptomatic events. The severity of these symptomatic events is therefore questionable and it is not known how many of these events would have spontaneously dissolved or progressed to real symptomatic cases. Also, it is not stated how many patients without thrombus formation had signs or symptoms of VT just before ultrasonography (information that would clarify the frequency of the symptoms).

Second, the authors conclude that rivaroxaban can be safely administered for

thromboprophylaxis after KA. This statement cannot be made based on the low sample size of this study. In addition, the study was not powered to determine the balance between treatment benefits (reducing thrombosis) and risks (induce bleeding). As a result of these two points, the presented NNT of 19 is not informative: 1. the primary efficacy outcome includes asymptomatic events as well, which also contribute to the NNT. What knowledge do we gain if we treat x number of patients to prevent x number of asymptomatic events?, and 2. without a number needed to harm it is difficult to decide on the net benefit of treatment.

To conclude, we believe that the results from this study are valuable as they demonstrate a possible benefit of rivaroxaban on prevention of asymptomatic events. Nevertheless, the clinical consequences of this study are limited for practice as any conclusion on its efficacy or safety in patients undergoing KA is precluded due to the low number of patients in the study. We agree with the authors that a larger randomised trial is needed to verify these findings and to confirm efficacy of rivaroxaban or other anticoagulants for the prevention of symptomatic VT after KA.

Conflict of interest disclosure: The authors of this letter collaborate on a randomized controlled trial on the efficacy and safety of thromboprophylaxis after knee arthroscopy.

CAST IMMOBILIZATION OF THE LOWER-LEG:
no indication for thromboprophylactic therapy

Németh B & Cannegieter SC.
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Dear editor,
We read the manuscript entitled "Nadroparin or fondaparinux versus no thromboprophylaxis in patients immobilised in a below-knee plaster cast (PROTECT): A randomised controlled trial" with great interest.[5]

In this recently published randomized controlled trial, adults with an ankle or foot fracture, who required below-knee cast immobilization for a minimum of four weeks, were randomly assigned to receive no therapy (control group) or to one of the intervention groups: daily subcutaneous self-injection of either nadroparin (2850 IE anti-Xa = 0.3 ml) or fondaparinux (2.5 mg = 0.5 ml) (1:1:1). The primary outcome was the occurrence of deep vein thrombosis (DVT) verified by duplex sonography and/or symptomatic pulmonary embolism verified by CT angiography.[5]

The authors conclude that thromboprophylaxis with nadroparin or fondaparinux significantly reduces the risk of a thromboembolic event and therefore they propose to routinely prescribe thromboprophylaxis in patients with an ankle or foot fracture who are conservatively treated in below-knee cast immobilisation.

The trial concerns an important field of research. However, in our opinion, the study findings are not a sufficient basis for the authors' conclusion, for several reasons. First, the primary outcome was mainly asymptomatic DVT which occurred in 14 patients (11/94 in the control group, 2/92 in the nadroparin group and 1/92 in the fondaparinux group). In total, only two patients developed a symptomatic event, i.e. pulmonary embolism (control group). This finding indeed suggests a protective effect of thromboprophylaxis for the prevention of asymptomatic events. However, the authors cannot simply extrapolate these findings to symptomatic venous thromboembolism (VTE), because of the limited sample size. In the PROTECT trial, a risk reduction for symptomatic VTE of 2.1% was found (i.e. risk in pooled treatment group 0/184 (0%) minus risk in control group 2/94 (2.1%)). From these numbers, we can calculate that the risk for a type I error (p-value) is 12%. Moreover, the probability of a type I error increases up to 50% if we do not pool both treatment arms (2-sided Fisher's exact p).

Second, screening for asymptomatic VTE does not reflect clinical practice and up till now, the clinical relevancy of asymptomatic DVT is questionable. In 2014, Chan and colleagues performed a large systematic review of high quality VTE prevention trials (mainly in orthopaedic surgery patients), in which they concluded there was very poor agreement between the efficacy of thromboprophylaxis on asymptomatic DVT versus symptomatic VTE. Therefore the authors stated that "asymptomatic DVT is not a reliable surrogate for symptomatic events".[6]

Third, of all 467 randomized patients, only 278 patients (60%) were included in the intention-to-treat analysis. A large proportion of excluded patients, did not undergo duplex sonography (59 patients) and therefore no information on the primary outcome was available in this group. This drop-out could have led to significant bias, for example, an under- or overestimation of the incidence of both asymptomatic and symptomatic VTE. We could speculate that those patients who did not undergo duplex sonography probably did not develop a symptomatic event, otherwise they would have been subjected to duplex sonography. Alternatively, some of these patients may have been hospitalized due to a pulmonary embolism, which would result in an underestimation of the incidence. These issues question the validity of the results, in particular those concerning symptomatic VTE because of the limited numbers.

The PROTECT conclusion contradicts with that of the POT-CAST trial which was recently published by our research group.[7] In the POT-CAST trial, 1519 patients treated with a lower-leg cast (both surgically and conservatively) for a minimum of 1 week, were randomized to receive either a prophylactic dose of low-molecular-weight-heparin for the complete duration of cast immobilization (treatment group) or no treatment (control group). Patients were followed for 3-months and only symptomatic VTE was considered as an outcome event. In the treatment group 10/719 (1.4%, 95%CI 0.7 to 2.5) patients developed symptomatic VTE versus 13/716 (1.8%, 95%CI 1.0 to 3.1) in the control group (risk difference -0.4%, 95%CI -1.8 to 1.0). No difference in major bleeding was observed. From this large, sufficiently powered trial we concluded that thromboprophylaxis was not effective to prevent symptomatic VTE in patients treated with lower-leg cast immobilization.[7] The PROTECT conclusion is not very helpful in advancing the field as physicians are now confronted with two contradictory messages. Considering the fact that the POT-CAST trial was 5 times larger, had wide inclusion criteria a 98% complete follow-up, treatment compliance of 87% and that it took only clinically relevant events into account, we urge physicians to discard the conclusion of the PROTECT trial and not to routinely treat all lower-leg cast patients with thromboprophylactic therapy, hence exposing their patients to its risk and burden.

However, we agree with the authors that VTE still is a substantial problem that occurs in about 1.5% of these patients. As the current strategy does not appear to work, a more feasible and efficient approach would be to target high-risk patients with higher dosage or longer duration of anticoagulation.[8] Further research should focus on these high risk patients in order to optimize thromboprophylactic therapy following lower-leg cast immobilization.

REFERENCE LIST

1. Camporese G, Bernardi E, Noventa F, Bosco M, Monteleone G, Santoro L, et al. Efficacy of Rivaroxaban for thromboprophylaxis after Knee Arthroscopy (ERIKA). A phase II, multicentre, double-blind, placebo-controlled randomised study. Thrombosis and haemostasis. 2016;116(2):349-55.
2. Gaskill T, Pullen M, Bryant B, Sicignano N, Evans AM, DeMaio M. The Prevalence of Symptomatic Deep Venous Thrombosis and Pulmonary Embolism After Anterior Cruciate Ligament Reconstruction. The American journal of sports medicine. 2015;43(11):2714-9.
3. Krych AJ, Sousa PL, Morgan JA, Levy BA, Stuart MJ, Dahm DL. Incidence and Risk Factor Analysis of Symptomatic Venous Thromboembolism After Knee Arthroscopy. Arthroscopy. 2015.
4. Mauck KF, Froehling DA, Daniels PR, Dahm DL, Ashrani AA, Crusan DJ, et al. Incidence of venous thromboembolism after elective knee arthroscopic surgery: a historical cohort study. Journal of thrombosis and haemostasis 2013;11(7):1279-86.
5. Bruntink MM, Groutars YM, Schipper IB, Breederveld RS, Tuinebreijer WE, Derksen RJ, et al. Nadroparin or fondaparinux versus no thromboprophylaxis in patients immobilised in a below-knee plaster cast (PROTECT): A randomised controlled trial. Injury. 2017;48(4):936-40.
6. Chan NC, Stehouwer AC, Hirsh J, Ginsberg JS, Alazzoni A, Coppens M, et al. Lack of consistency in the relationship between asymptomatic DVT detected by venography and symptomatic VTE in thromboprophylaxis trials. Thrombosis and haemostasis. 2015;114(5):1049-57.
7. van Adrichem RA, Németh B, Algra A, le Cessie S, Rosendaal FR, Schipper IB, et al. Thromboprophylaxis after Knee Arthroscopy and Lower-Leg Casting. The New England journal of medicine. 2017;376(6):515-25.
8. Németh B, van Adrichem RA, van Hylckama Vlieg A, Bucciarelli P, Martinelli I, Baglin T, et al. Venous Thrombosis Risk after Cast Immobilization of the Lower Extremity: Derivation and Validation of a Clinical Prediction Score, L-TRiP(cast), in Three Population-Based Case-Control Studies. PLoS medicine. 2015;12(11):e1001899; discussion e.