REVIEW ARTICLE

Thromboprophylaxis with nadroparin in the orthopaedic setting, a brief appraisal of the recent literature

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Abstract:

Low-molecular-weight heparins represent well-established agents for thromboprophylaxis in the orthopaedic and traumatological setting. The availability of different compounds requires the doctor to make a careful choice especially in the dose and duration of treatment, which represent two key factors for a successful therapy. In addition to the clinical benefit for the patient, an appropriate therapeutic choice allows the physician not to incur in medico-legal implications. In the present paper, we briefly review recent data from new trials in which nadroparin was used in patients after knee arthroscopy and lower leg plaster cast, and discuss the mode of use of the drug and the potential medico-legal implications.

Keywords: Low-molecular-weight heparins; nadroparin; orthopaedics and traumatology; legal medicine.

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1. Introduction

Venous Thromboembolism (VTE) is a well-recognized complication in the orthopaedic and traumatological setting, with potentially fatal consequences as pulmonary embolism (PE). One of the most widely used VTE prophylaxis strategies is represented by the treatment with Low-Molecular-Weight Heparins (LMWHs) consistent with the recommendations of the major guidelines.[1] While prophylaxis with LMWHs must always be considered in the major orthopaedics setting, its routinely use is still debated in the minor orthopaedics setting. Current evidences suggest that not all patients should be routinely treated but only those with high individual risks, such as patients with history of cancer or previous VTE, patients who require hospitalization or those having two or more risk factors including older age, obesity, smoking, hormone use or chronic venous insufficiency.[2] To note, some variability exists in the use of different LMWHs in terms of dose and treatment duration, according to the data of clinical trials. In particular, nadroparin (nadroparin calcium) is effective in preventing deep vein thrombosis (DVT) and pulmonary embolism after major general or orthopedic surgery, in bedridden medical patients and in ambulatory cancer patients receiving chemotherapy.[3-5] Also, nadroparin is effective in the treatment of acute DVT.[3,6] The recent publication of new trials in which nadroparin was used in in patients after knee arthroscopy lower leg plaster cast led us to make some considerations on the mode of use of the drug and the potential medico-legal implications.

2. Recent trials

Recently, two pragmatic clinical trials, entitled *Prevention of Thrombosis after Knee Arthroscopy* (POT-KAST) and *Prevention of Thrombosis after Lower Leg Plaster Cast* (POT-CAST), have been published in *The New England Journal of Medicine* on February 9, 2017.[7] The results of these trials showed that the routinely thromboprophylaxis with LMWHs (nadroparin or dalteparin) is not more effective than no anticoagulant therapy in reducing symptomatic VTE after knee arthroscopy and lower-leg plaster cast. Although the Authors have already brilliantly discussed the factors elucidating these results – e.g. the open design, the sample size calculation, the risk of patients, and the evaluation of only asymptomatic VTE – some considerations related to the treatment regimen with nadroparin, in

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terms of dosage and duration, deserve an in-depth analysis. The Authors highlight that "the nadroparin dose of 2,850 IU may have been too low, despite the fact that this is the standard dose for thromboprophylaxis", and that in the POT-KAST trial all VTE events occurred after the end of treatment (8 days), while in the POT-CAST 9 out of 23 VTE events (39%) occurred after the cast was removed and the treatment was stopped.[7]

A further, recent trial entitled *Nadroparin or fondaparinux versus no thromboprophylaxis in patients immobilised in a below-knee plaster cast (PROTECT): A randomized controlled trial*, published few weeks after the POT-KAST and POT-CAST studies, compared nadroparin as a thromboprophylactic treatment with a control group that did not receive any form of thromboprophylaxis evaluating the incidence of DVT diagnosed with venous duplex sonography.[8] Nadroparin was used at the same dose of the two previous studies, for the duration of the immobilization. The PROTECT trial highlighted that thromboprophylaxis with nadroparin significantly reduced the risk of a thromboembolic event in patients with a fracture of the ankle or foot who were conservatively treated with a below-knee cast (2.2% vs 11.7%; p = 0.011).[8]

3. Discussion

Previous randomized controlled studies and metanalysis have clearly shown a benefit of VTE prophylaxis with LMWHs for patients after knee arthroscopy and lower leg plaster cast, revealing that the incidence of DVT with nadroparin prophylaxis was significantly lower than that in the control group.[9,10]

Table 1 summarizes the main results. Chapelle et al. evaluated 14 randomized trials including a total of 4,726 non-major orthopaedic patients with transient reduced mobility, comparing prophylactic LMWH with no prophylaxis, and use objective methods to confirm asymptomatic or symptomatic thromboembolic events.[9] The non-major orthopaedic setting was defined as leg immobilization for fracture or soft-tissue injury of the lower limb or knee arthroscopy. Study results highlighted an overall major VTE incidence of 2.9% (95% CI, 2.2% to 3.7%) in patients not receiving prophylaxis. A significant 68% reduction in the risk of VTE was observed in favour of LMWH compared with no prophylaxis (RR, 0.32; 95% CI, 0.20 to 0.51, P <0.0001).

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Table 1.

Meta-analysis	Chapelle C et al.[9]	Sun Y et al.[10]
Methods	Meta-analysis conducted using data from all available randomized trials comparing LMWH with placebo or no prophylactic treatment in patients with leg immobilization for fracture or soft-tissue injury of the lower limb or in patients undergoing knee arthroscopy. The primary endpoint was the incidence VTE, including asymptomatic proximal deep-vein thrombosis, symptomatic VTEs, and VTE-related death.	Systematic review and meta-analysis of the literature to assess the efficacy of prophylaxis to prevent DVT after knee arthroscopic surgery. Only randomized controlled trials (RCTs) or prospective studies were considered. Studies were excluded if they were not original prospective studies concerning DVT detected by imaging after knee arthroscopic surgery. Pooled proportions of postoperative DVT and proximal DVT were calculated.
Patients and studies included	4,726 patients from 14 studies were included.	3,998 patients from 13 studies were included.
Results	Significant 68% reduction in the risk of major VTEs was observed with LMWH prophylaxis (relative risk [RR], 0.32; 95% CI, 0.20 to 0.51; P < .001). The treatment effect was not modified by the clinical setting, that is, distal lower limb injury (7 studies; 1,711 patients; RR, 0.42; 95% CI, 0.20 to 0.86) or knee arthroscopy (6 studies; 2,428 patients; RR, 0.27; 95% CI, 0.15 to 0.49).	In RCTs, the pooled risk ratio of DVT was 0.180 (range, 0.065 to 0.499), in favour of the treatment with LMWH. An absolute risk reduction of 1.2% (from 1.5% to 0.3%) for the development of proximal DVT was observed.

Also considering only symptomatic events, without prophylaxis, the rate of VTE was estimated to be 2.3% (95% CI, 1.6% to 3.0%), with a significant 63% risk reduction with LMWH prophylaxis (RR, 0.37; 95% CI, 0.19 to 0.71; P = 0.003). No concerns on the safety profile of LMWH raised from the study, since the rate of major bleeding was 0.5% (95% CI, 0.2% to 0.9%) in the control group, with a

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nonsignificant increase in the LMWH group (RR, 1.35; 95% CI, 0.53 to 3.47; P =0.53). Similar results were obtained in the rate of any bleeding, 3.1% in control group with a nonsignificant increase in the in the LMWH group.[9] Sun et al. performed a systematic review and meta-analysis of randomized controlled trials or prospective studies to assess the efficacy of LMWH prophylaxis to prevent DVT after knee arthroscopic surgery, including a total of 13 studies and 3,998 patients.[10] Overall, patients receiving LMWH to prevent DVT had an average incidence of DVT of 1.8%, while a rate of 6.8% was observed in the control group. Compared with patients not receiving prophylaxis, patients treated with LMWH showed a significant 82% reduction in the risk of developing DVT (RR 0.18; 95% CI, 0.065 to 0.499).[10]

Considering specifically nadroparin, it was previously investigated in several randomized controlled trials (RCTs) in the orthopaedic setting, generally adopting a weight-adjusted dosage,[3] remarkably higher than the one used in the POT-KAST and POT-CAST trials (2,850 IU). The nadroparin weight-adjusted dosage is also recalled by the Italian Inter-Society Consensus Statement on Antithrombotic Prophylaxis in Orthopaedics and Traumatology (OTODI, SIAARTI, SIMG, SIOT, SISET).[2] According to RCTs, nadroparin has been registered in several countries worldwide for the indication "prophylaxis of deep venous thrombosis in orthopaedic surgery" with the posology summarized in Table 2.[11] The treatment for post-operative VTE should be tailored to the single patient for at least 10 days, in all cases prophylaxis should continue for the entire period at risk and until the patient is actively ambulant.[11] This dosing regimen was initially studied by Leyvraz et al. in an open randomised multicentre trial, controlled vs. unfractionated heparin, including 349 patients undergoing total hip replacement.[12] The total incidence of DVT was 16% in patients receiving unfractionated heparin and 12.6% in patients receiving nadroparin (p=0.45), while the incidence of proximal DVT was 13.1% and 2.9%, respectively (p<0.001).[12] Such weight-adjusted regimen of nadroparin was evaluated also in a relatively recent prospective study including a large number (1,800) of consecutive patients undergoing knee arthroscopy.[13] During a two-week follow-up, a low rate (0.38%) of DVT was observed, and all events were distal.[13]

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Table 2.

Body Weight	38 IU/kg: 12 hours before and after surgery, and then once daily to the 3rd postoperative day	57 IU/kg from the 4th postoperative day onwards
	Volume injected (anti-factor Xa IU)	Volume injected (anti-factor Xa IU)
< 50 kg	0.2 ml (1,900)	0.3 ml (2,850)
50 – 69 kg	0.3 ml (2,850)	0.4 ml (3,800)
≥ 70 kg	0.4 ml (3,800)	0.6 ml (5,700)

This dosing regimen should be considered as the standard dose for thromboprophylaxis in the clinical practice in the orthopaedic setting. It differs from the regimen adopted in the POT-KAST and POT-CAST trials, and may potentially offer a higher antithrombotic effectiveness. In addition to the dose, another relevant factor is represented by the duration of treatment, which is longer compared to the POT-KAST trial (at least 10 days vs 8 days). Moreover, the label of the product highlights a crucial factor: the assessment of period at risk for each patient, that, in the orthopaedic setting, may last for quite a long time.

3.1 Medical-legal issues

The possibility of adjusting the dose of the LMWH to the single patient, especially to its body weight, also helps to overcome medical-legal issues. These may result from a hypodosage or overdose that may occur when using standard doses for prophylaxis in obese or underweight patients or in patients with renal failure. In these cases, the summary of product characteristics (SPC) of the LMWHs recommended as a standard dose requires the patient's parametric clinical monitoring by the physician, with imaginable discomforts also to the doctor. In these cases, the off-label use of dosages different than those recommended for thromboprophylaxis by

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the SPC of the medicine employed would expose the doctor to an important medical-legal risk, and the patient to potential efficacy and safety risks. The off-label use occurs under the doctor's responsibility, and any possible adverse event would represent an objective element of medical fault, especially if such use is not supported even by scientific research or if other, more appropriate drugs are available. Therefore, in the prophylaxis of VTE, the use of medicines that can be tailored to the patient's characteristics, in accordance with the SPC recommendations, place both the physician and the patient in a safe condition. In fact, the responsibility for a dose-related adverse event lies with the manufacturer and the health authority who approved the use. For what concerns the duration of the treatment, not to follow the duration prescribed by the SPC or by the guide-lines exposes the physician to medical faults claims in case adverse events occur.

4. Conclusions

LMWHs are a well-established option for VTE prophylaxis in the orthopaedic setting. The availability of different compounds requires the doctor to make a careful choice especially in the dose and duration of treatment, which represent two key factors for a successful therapy. In addition to the clinical benefit for the patient, an appropriate therapeutic choice allows the physician not to incur in medico-legal implications.

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References

1. Guyatt GH, Akl EA, Crowther M, Gutterman DD, Schuünemann HJ; American College of Chest Physicians Antithrombotic Therapy and Prevention of Thrombosis Panel. Executive summary: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141(2 Suppl):7S-47S.

2. Randelli F, Romanini E, Biggi F, Danelli G, Della Rocca G, Laurora NR, Imberti D, Palareti G, Prisco D. II Italian intersociety consensus statement on antithrombotic prophylaxis in orthopaedics and traumatology: arthroscopy, traumatology, leg immobilization, minor orthopaedic procedures and spine surgery. J Orthop Traumatol. 2013;14(1):1-13.

3. Davis R, Faulds D. Nadroparin calcium. A review of its pharmacology and clinical use in the prevention and treatment of thromboembolic disorders. Drugs Aging. 1997;10(4):299-322.

4. Ageno W, Bosch J, Cucherat M, Eikelboom JW. Nadroparin for the prevention of venous thromboembolism in nonsurgical patients: a systematic review and meta-analysis. J Thromb Thrombolysis. 2016;42(1):90-8.

5 Agnelli G, Gussoni G, Bianchini C, Verso M, Mandalà M, Cavanna L, Barni S, Labianca R, Buzzi F, Scambia G, Passalacqua R, Ricci S, Gasparini G, Lorusso V, Bonizzoni E, Tonato M; PROTECHT Investigators. Nadroparin for the prevention of thromboembolic events in ambulatory patients with metastatic or locally advanced solid cancer receiving chemotherapy: a randomised, placebo-controlled, double-blind study. Lancet Oncol. 2009;10(10):943-9.

6. Charbonnier BA, Fiessinger JN, Banga JD, Wenzel E, d'Azemar P, Sagnard L. Comparison of a once daily with a twice daily subcutaneous low molecular weight heparin regimen in the treatment of deep vein thrombosis. FRAXODI group. Thromb Haemost. 1998;79(5):897-901.

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7. van Adrichem RA, Nemeth B, Algra A, le Cessie S, Rosendaal FR, Schipper IB, Nelissen RGHH, Cannegieter SC; POT-KAST and POT-CAST Group. Thromboprophylaxis after Knee Arthroscopy and Lower-Leg Casting. N Engl J Med 2017;376(6):515-25.

8. Bruntink MM, Groutars YME, Schipper IB, Breederveld RS, Tuinebreijer WE, Derksen RJ; PROTECT studygroup. 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.

9. Chapelle C, Rosencher N, Jacques Zufferey P, Mismetti P, Cucherat M, Laporte S; Meta-Embol Group. Prevention of venous thromboembolic events with low-molecular-weight heparin in the non-major orthopaedic setting: meta-analysis of randomized controlled trials. Arthroscopy. 2014;30(8):987-96.

10. Sun Y, Chen D, Xu Z, Shi D, Dai J, Qin J, Qin J, Jiang Q. Deep venous thrombosis after knee arthroscopy: a systematic review and meta-analysis. Arthroscopy. 2014;30(3):406-12.

11. Nadroparin (Seleparina) Summary of Product Characteristics.

12. Leyvraz PF, Bachmann F, Hoek J, Buller HR, Postel M, Samama M, Vandenbroek MD. Prevention ofdeep vein thrombosis after hip replacement: randomised comparison between unfractionated heparin and low molecular weight heparin. BMJ. 1991;303:543-8.

13. Pascale W, Mineo G, Pascale V. Prevention of venous thromboembolism after knee arthroscopy: six-year experience with the low molecular weight nadroparin calcium. Minerva Ortop Traumatol. 2007;58(5):347-52.

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