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BRIEF REPORT

Effect of anticoagulant treatment on pain in distal deep vein thrombosis: an ancillary analysis from the cactus trial

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Essentials

- Management of patients with calf deep vein thrombosis remains controversial.
- We conducted a post-hoc analysis of a placebo controlled LMWH randomized clinical trial.
- Pain was assessed using visual analogue scale at inclusion, one and six weeks.
- There was no difference in pain control between the two arms.

Summary. *Background:* The optimal management of distal deep vein thrombosis (DVT) is highly debated. The only available placebo-controlled trial suggested the absence of clear benefit of anticoagulation. Many physicians feel that, beyond preventing thromboembolic complications, anticoagulation with low-molecular-weight heparin (LMWH) has the potential to improve pain control. *Objectives:* To analyze whether LMWHs decrease pain in patients with distal deep vein thrombosis. *Patients and methods:* Two-hundred and fifty-two patients included in a multicenter, placebo-controlled, randomized clinical trial of LMWH in patients with acute distal DVT and who were asked to rate their pain at inclusion and at each medical visit, using a visual analogue pain scale (VAS). *Results:* One hundred and thirty patients were randomized in the therapeutic nadroparin arm and 122 patients were randomized in the placebo arm. Mean VAS values were 4.6 (standard deviation [SD] 2.5) at inclusion, 2.1 (SD 2.0) at 1 week and 0.4 (SD 1.2) at 6 weeks. We calculated the individual variation in VAS between inclusion and 1 week in patients in whom VAS was available at the two study time-points. There was no difference in the mean VAS reduction between patients treated with therapeutic nadroparin (n = 106) and with placebo (n = 109): −2.6 (SD 2.4) vs. −2.3 (SD 2.0) after 1 week and −4.4 (SD 2.8) vs. −4.0 (SD 2.4) after 6 weeks, respectively. The use of compression stockings was associated with a reduction in pain. *Conclusion:* These data suggests that LMWH use does not improve pain control as compared with placebo in patients with acute distal DVT.

Keywords: distal deep vein thrombosis; low-molecular-weight heparin; pain; visual analogue pain scale.

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Introduction

Isolated calf deep vein thrombosis (DVT) (i.e. infra-popliteal DVT without extension to proximal veins or pulmonary embolism [PE]), also known as distal DVT, is frequent and represents up to 50% of all lower-limb DVT [1]. Optimal management of distal DVT remains controversial [2–8]. In the recently published CACTUS trial, full-dose anticoagulation with low-molecular-weight heparin (LMWH) was not superior to placebo in reducing the risk of proximal extension or thromboembolic events

after distal DVT, but was associated with a significantly higher risk of bleeding [9].

However, another reason put forward by advocates of anticoagulation, and in particular LMWH, is that LMWHs might reduce pain thanks to their anti-inflammatory properties [9,10]. As clinical data to support this hypothesis are lacking, we sought to analyze the effect of LMWH on pain in patients with distal DVT included in the CACTUS placebo-controlled randomized clinical trial [9].

Methods

Patients

The methods of the CACTUS trial have been extensively described elsewhere [9]. Briefly, we conducted an international (Canada, France and Switzerland), multicenter, placebo-controlled, randomized clinical trial of LMWH to prevent thromboembolic complications in patients with distal DVT. Outpatients with an acute symptomatic, objectively confirmed, distal DVT were eligible for the study. The diagnosis of DVT was established by compression ultrasonography (CUS). The criterion for calf DVT was the presence of an incompressible venous segment in deep calf veins (posterior tibial, peroneal or anterior tibial) or muscular veins (gastrocnemius or soleus). Exclusion criteria included: less than 18 years of age, pregnancy, previous documented venous thromboembolism (VTE), calf DVT associated with a proximal DVT or a clinically suspected PE, active malignancy, another indication for long-term anticoagulation, thrombocytopenia (platelet count below 100 g L^{-1}), impaired renal function (serum creatinine above 180 μmol L^{-1} or a creatinine clearance below 30 mL min^{-1}), known hypersensitivity to heparin, active bleeding or a condition associated with a high risk of bleeding (gastric ulcer or cerebral malignant disease), or a body weight above 115 kg or below 40 kg. Patients were also excluded if they had already received therapeutic doses of anticoagulants for more than 2 days or had an ongoing requirement for thromboprophylaxis, or were using daily non-steroidal anti-inflammatory drugs (NSAIDs) (aspirin accepted if ≤160 mg per daily). We did not collect information on the use of acetaminophen. The study was approved by the ethics committees of all participating centers and registered on ClinicalTrials.gov (NCT00421538).

Patients were randomly assigned in a 1 : 1 ratio to receive nadroparin 171 UI kg^{-1} daily or an identically packaged placebo injection (sterilized NaCl 0.9%), administered subcutaneously for 42 days. All participants in the study were masked to group assignment. All patients were also prescribed calf-length 20–30-mmHg elastic compression stockings.

The primary outcome was the composite of extension of calf DVT to proximal veins, contralateral proximal DVT or a symptomatic PE (fatal or not) at 6 weeks. All suspected outcomes were reviewed by a central adjudication committee whose members were unaware of group assignment. Patients were seen for a follow-up visit and serial ultrasound in clinic at Day 5 (±2) and at Day 42 (±5). A follow-up phone call was also performed at Day 90 (±5).

At inclusion and at each follow-up visit, patients were asked to rate the pain associated with distal DVT, using a visual analogue pain scale (VAS). The compliance with compression stockings was evaluated at each study visit. We determined the mean and standard deviation for the VAS at each study time-point and estimated the variation between VAS scores at inclusion and follow-up. We compared the individual variation in pain scores according to the randomization arm, using a Student's *t*-test. We tested whether the location of the calf DVT (muscular vein involvement vs. isolated troncular DVT) was associated with pain severity, and whether there was an association between the use of compression stockings and pain severity. Analyses were performed using SPSS software (version 24.0; IBM Corporation, Armonk, NY, USA).

Results and discussion

One hundred and thirty patients were randomized in the therapeutic nadroparin arm and 122 patients were randomized in the placebo arm. Because of missing values, VAS was available for 225 patients at inclusion, 230 at 1 week and 216 at 6 weeks, and the variation in VAS between inclusion and 1 week could be computed in 215. Mean VAS values were 4.6 (standard deviation [SD] 2.5) at inclusion, 2.1 (SD 2.0) at 1 week and 0.4 (SD 1.2) at 6 weeks. There was no imbalance in the VAS values according to the randomization arm. We calculated the individual variation in VAS between inclusion and 1 week in patients in whom VAS was available at the two study time-points. After 1 week of treatment, there was a mean reduction in VAS of −2.6 (SD 2.4) points in patients treated with therapeutic nadroparin (n = 106) vs. −2.3 (SD 2.0) among patients receiving placebo (n = 109) (difference, 0.3 [95% CI, −0.3 to 0.9]). After 6 weeks, the VAS reduction was −4.4 (SD 2.8) and −4.0 (SD 2.4) points in the nadroparin and the placebo arm, respectively (difference, 0.4 [95% CI, −0.3 to 1.1]).

We also analyzed if pain severity and reduction in pain level on treatment were different between patients with muscular vein involvement vs. patients with a DVT limited to tibial posterior or peroneal veins. Similar initial pain severity and responses to treatment were observed (Table 1). Only a few patients reported the use of NSAIDs, nine (three in the placebo arm and six in the nadroparin arm) at 1 week and five (one in the placebo arm and four in the nadroparin arm) at 6 weeks. We did not collect information on the use of acetaminophen.

Finally, we analyzed the impact of graduated elastic compression (elastic calf-length stockings with pressure of 20–30 mmHg) on pain reported by patients on the VAS

Table 1 Variation of pain as assessed by the VAS over 6 weeks, according to the location of the index distal DVT

Location	Initial VAS	VAS variation at 1 week on placebo	VAS variation at 1 week on LMWH	VAS variation at 6 weeks on placebo	VAS variation at 6 weeks on LMWH
Muscular ± troncular (n = 159)	4.8 (SD 2.5)	−2.4 (SD 2.0)	−2.7 (SD 2.4)	−4.1 (SD 2.3)	−4.8 (SD 2.5)
Troncular only (n = 66)	4.3 (SD 2.6)	−2.0 (SD 1.9)	−2.4 (SD 1.9)	−3.8 (SD 2.7)	−3.7 (SD 3.2)

VAS, visual analogic pain scale; DVT, deep vein thrombosis; LMWH, low-molecular-weight heparin; SD, standard deviation.

scale. Pain reduction was greater among the 186 patients who reported wearing their elastic stockings regularly during the first week of treatment than among the 29 patients who did not: −2.6 (±2.2) points vs. −1.3 (±1.9) points, respectively (difference, 1.3 [95% CI, 0.5–2.2]). Limitations of our analysis include the fact that this was a *post-hoc* analysis. Pain was not part of the main study outcomes and this information was missing in approximately 10% of patients. Also, our sample size was somewhat limited because of early discontinuation of the CACTUS trial.

In summary, our data suggest that the use of LMWH is not superior to placebo for pain control in patients with distal DVT. This was true for both patients with muscular vein involvement and patients in whom DVT was located in the troncular veins (peroneal and posterior tibial veins). On the other hand, our data suggest that regular use of graduated elastic stockings is associated with faster pain control.

Despite the negative results of the CACTUS trial regarding the balance between the thromboembolic and bleeding complications associated with LMWH when compared to placebo in patients with acute calf DVT [9], the use of anticoagulant treatment for distal DVT is widespread and is often performed with LMWH. One of the reasons put forward to favor LMWH use is the assumption that the anti-inflammatory effects of LMWH will result in faster and more efficient pain control [10,11]. However, we did not observe a significant difference in the variation of pain level among patients on placebo or LMWH included in the CACTUS trial. There was no difference in the use of NSAIDs between arms.

The last American College of Chest Physicians guidelines suggest that low-risk patients with symptomatic calf DVT, such as patients without a previous DVT or active malignancy, could safely be managed with serial ultrasound testing and no anticoagulant therapy [12]. In addition, our data suggest that pain control should not be a reason to prefer LMWH over ultrasound surveillance for the management of patients with distal DVT. Another common belief is that muscular vein thromboses are often more painful than troncular distal or proximal DVT. We did not observe a difference in pain severity according to thrombus location.

The use of compression stockings in patients with DVT serves several purposes. One of the main indications has been to prevent the post-thrombotic syndrome (PTS). However, distal location of DVT has been associated with a lower risk of PTS than proximal DVT [13,14]. Moreover, the benefit of compression stockings for PTS prevention has been challenged by a large randomized controlled trial [15]. Although this has never been properly studied, compression stockings have long been thought to improve pain control in patients with acute DVT [16]. A secondary analysis of the SOX trial did not find a beneficial effect on pain control in patients with proximal DVT [17], but this issue remains highly debated [18,19]. Our data suggest that patients with a distal DVT might benefit from compression at the acute phase. Admittedly, the benefit was modest (approximately 1-point additional reduction in pain level in regular users vs. non-regular users at 1 week) and our sample size was limited. Moreover, reasons for using or not using the compression were not documented.

In conclusion, the CACTUS trial showed no clear benefit of anticoagulation over placebo in patients with distal DVT in terms of thromboembolic complications vs. bleeding. This ancillary analysis of the CACTUS trial shows that in addition, LMWH use does not improve pain control as compared with placebo in patients with acute distal DVT. More studies are needed to better define the optimal management of distal DVT.

Addendum

M. Righini, G. Le Gal, I. Quéré, J.-P. Galanaud and M. Carrier designed research, performed research, collected data, analyzed data and wrote the paper. G. Le Gal, I. Quéré, H. Robert-Ebadi, M. Blondon, F. Glauser, P. Frappé, J.-P. Galanaud and S. Kahn performed research, collected data and analyzed data. M. Righini, G. Le Gal, I. Quéré, J.-P. Galanaud, H. Robert-Ebadi, P. Frappé, M. Carrier and S. Kahn designed research, performed research, collected data, analyzed data and wrote the paper.

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Disclosure of Conflict of Interests

G. Le Gal has been a co-investigator on clinical trials for Portola Pharmaceuticals, Boehringer-Ingelheim, Bristol-Myers Squibb, LEO Pharma, Daiichi Sankyo and Bayer, and has received honoraria from Bayer, Pfizer, LEO Pharma, Sanofi and bioMérieux, outside the submitted work. The other authors state that they have no conflict of interests.

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