

Isolated distal deep vein thrombosis: efficacy and safety of a protocol of treatment. Treatment of Isolated Calf Thrombosis (TICT) Study

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Aim. The optimal treatment of isolated distal deep vein thrombosis (ID-DVT) is still controversial. A complete anticoagulation as soon as the diagnosis is made is recommended by some authors. Alternatively, other authors suggest to perform serial ultrasonography assessments to detect the possible extension of DVT towards proximal veins. Only in this case the treatment should be initiated. Furthermore, the optimal duration of treatment is far from established. The Treatment of Isolated Calf Thrombosis (TICT) study was set up to assess the efficacy and safety of a particular treatment regimen of ID-DVT based on low molecular weight heparins (LMWH).

Methods. The drug treatment consisted of a twice-daily subcutaneous administration of a full dose of weight-adjusted LMWH for one week, followed by a half dose of LMWH administered once-daily for another three weeks. At the end of the four-week period of treatment, a colour-coded Doppler ultrasonography (CCDU) assessment was scheduled and after three months a follow-up visit was performed. If a patient was unable to attend the visit, he was contacted by a phone-call to assess if any adverse events occurred. The study enrolled 192 outpatients with ID-DVT confirmed by CCDU. Twenty-one out of 192 patients (10.9%) were excluded for violation of protocol. Thus 171 (39.9% men, mean age of 60.45 years) were eligible and were included in the study. Sixty-one patients (36.6%) presented an unprovoked ID-DVT.

Results. Events during the period of treatment (4 weeks). Ten out of 171 patients (5.8%) had complications: five patients showed an extension proximal to the knee (2.9%) all with an unprovoked ID-DVT; two showed an extension of thrombus within the distal veins. Three patients (1.7%)

suffered from minor bleeding; there was no major bleeding. Further events during three months of observation occurred. Five patients had thrombus recurrences: four patients showed a proximal DVT (3 with a previous unprovoked ID-DVT, 1 with a previous ID-DVT secondary to a traumatic leg fracture, with persistent difficulty of deambulation); one, with a previous secondary thrombosis, showed a ID-DVT.

Conclusion. In our study only 2.9% of patients with ID-DVT showed a progression of thrombosis to proximal deep veins; the majority of thrombus progression, during the treatment period, was observed in patients with unprovoked ID-DVT. Our results support the usefulness of a prolonged treatment in unprovoked ID-DVT.

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Venous thromboembolism (VTE) is a common occurrence in the clinical practice both for general practitioners and hospital specialists.

Better diagnostic strategies by means of non-invasive and repeatable examinations, and a better knowledge of this topic are of great relevance.

The most used non-invasive diagnostic tool is ultrasonography (Duplex scan). This method gives a bidimensional image of tissues and vessels below the ultrasonic probe, generated by the ultrasonic beam. The main clue for the diagnosis of thrombosis is represented by the failure of a full collapse of the vein with the standardized method of the compression ultrasound (CUS) performed over the venous vessel with the ultrasonographic probe.¹⁻³

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The sensitivity and specificity of compression ultrasound (CUS) for proximal DVT (limited to the popliteal and femoral veins) are high (97% and 98%, respectively).⁴ With growing experience in venous ultrasound, the examination was extended to segments below the popliteal fossa.

As to distal DVT two meta-analyses considered studies comparing ultrasound examination with venography as the gold standard in symptomatic patients. In one Kearon *et al.*⁵ estimated a sensitivity of 73%, and a specificity of 94% for distal veins.

The introduction of the colour-coded Doppler ultrasonography (CCDU) brought noteworthy advantages in the diagnosis of DVT.

More recently, a meta-analysis⁶ revealed that a CCDU examination is more sensitive for distal veins (75% vs 59%) and slightly less specific (94% vs 98) as compared with CUS only. Schellong affirms that the distal ultrasound, using a well-structured protocol of examination, is a valid four-minute procedure, which can easily be added to the examination of proximal veins.⁷ Concerning the duration of the treatment after a first episode of venous thromboembolism, six months of prophylactic oral anticoagulation led to a lower recurrence rate than did treatment lasting for six weeks.⁸ In the treatment of ID-DVT, Pinede *et al.*⁹ randomized about 200 patients with ID-DVT to receive LMWH followed by oral anticoagulants for 12 weeks or for 6 weeks; the incidence of the thromboembolic events was 3.4% and 2% respectively in both groups. The authors concluded that a treatment of 6 weeks was adequate.

In another study¹⁰ the efficacy of a treatment with LMWH has been evaluated in patients with isolated thrombosis of the muscular veins of the calf. Patients allocated in the treatment group received subcutaneous full dose, weight-adjusted LMWH, whereas patients allocated in the control group received only graduated compression stockings and clinical surveillance.

Patients belonging to the first group showed no progression to the proximal deep venous system, whereas in the control group 25% of patients demonstrated an extension of ID-DVT to the proximal veins.

In one recent study the following strategy for the treatment of distal vein thrombosis has been suggested: 1) 6 weeks with a triggering factor, 3 months with a permanent thrombophilic condi-

tion for collecting vein thrombosis; 2) 10 days with a triggering factor, 6 weeks with a permanent thrombophilic condition for muscular vein thrombosis.¹¹

The Italian Society for the Study of Haemostasis and Thrombosis (SISST) in 2003 recommended anticoagulant treatment for 6 weeks¹² in patients with ID-DVT whereas the American College of Chest Physicians (ACCP) in 2004 recommended a three months duration of treatment.¹³

Therefore, the optimal treatment of ID-DVT is still controversial, because full anticoagulation is recommended by most authors but the duration of therapy is not well established.

In addition there is a significant association between post operative, also asymptomatic, DVT and the occurrence of late post-thrombotic syndrome (PTS).¹⁴ In some studies, the risk of PTS was higher in patients with proximal rather than distal (calf) DVT.¹⁵

Purpose and design of study

The aim of the Treatment of Isolated Calf Thrombosis (TICT) study was to assess the efficacy and safety of a treatment regimen in symptomatic outpatients with ID-DVT a with twice-daily subcutaneous administration of a full dose weight-adjusted of LMWH for one week, followed by a half dose of LMWH administered once-daily for the next three weeks.

Materials and methods

At the end of the four weeks of treatment, a CCDU assessment was scheduled and after three months a follow-up visit was planned. If patients could not attend the visit, a phone contact was scheduled to assess if any adverse events occurred.

The inclusion criteria were: age >18 years; outpatients; symptomatic ID-DVT objectively documented by CCDU without involvement of proximal deep veins; informed consent.

Exclusion criteria were: in-patients; history of documented previous DVT in the symptomatic leg; pregnancy; contraindication to LMWH treatment (*e.g.* ongoing bleeding, uncorrected major coagulopathy); severe liver or renal failure; thrombocytopenia <50 000/dL.

Primary efficacy end-points of the study were

to document the progression of ID-DVT to the proximal veins, symptomatic PE, or death.

Primary safety end-points were major bleeding indicated as clinically overt hemorrhages associated with a drop in hemoglobin of at least 2 g/L or with the need of transfusion of 2 or more units of packed cells; disabling retroperitoneal, or intracranial hemorrhages.

Secondary and safety end-points of the study were the extension of ID-DVT to adjacent venous compartment, always limited to the calf without extension to proximal deep veins; incidence of bleeding. The data for all patients were recorded in a computerized register.

The study was carried out between January 2003 and July 2005. All patients underwent a physical examination and CCDU on the day of referral; during the study period 192 outpatients with ID-DVT confirmed by means of CCDU were enrolled. Out of these patients, 21 (10%) were excluded for violation of protocol (4 patients had anticoagulation therapy with coumadin, 8 prolonged heparin therapy over 4 weeks, 2 with initial thrombosis in tibio-fibular trunk and 1 with thrombosis on superficial vein including popliteal vein, 3 excluded because of the absence of a check-in after three months or because of the absence of essential data, 1 enrolled after July 2005, 2 were inpatients). Two patients were included although their therapy was prolonged seven and ten days beyond the protocol.

Statistical analysis

STATA (STATA corp. L.P.TEXAS) and MINITAB Inc. were used for the statistical analysis.

Multiple logistic regression to assess the relationship between the outcome (complications) and age, gender, and unprovoked ID-DVT (as covariates). The results of these analyses were expressed as odds ratios (OR) and 95% confidence intervals (CI). The Fischer test is considered statistically significant with value of $P < 0.05$.

Results

One hundred and seventy-one patients were included in our study, 68 males and 103 females, mean age of 60.45 years \pm 15.7 2 SD (range 90-21). One hundred and twenty-six patients (73.6%) pre-

sented only thrombosis of the muscular veins. Sixty-one patients (36.6%) had an unprovoked ID-DVT.

Events during the period of treatment (4 weeks)

Ten patients out of 171 patients (5.8%) had complications. Five patients showed a progression of thrombosis into the proximal veins (2.9%); the progression of DVT was always associated with an unprovoked ID-DVT.

Two patients showed a ID-DVT progression confined to the distal veins: one in a previous unprovoked ID-DVT, one in a previous secondary ID-DVT. Three patients (1.7%) suffered from minor bleeding; there was no major bleeding (0%).

Further events during three months of observation

Five patients developed a recurrence: four patients showed a proximal DVT (three with a previous unprovoked ID-DVT, one with a previous ID-DVT secondary to a traumatic leg fracture, with persistent difficulty of deambulation; the latter developed leukemia); the fifth showed a ID-DVT. One patient with progression during the first month and two patients with progression after three months developed a cancer (two intestinal cancer and one leukemia).

Statistical analysis

The statistical analysis showed a statistically significant association between unprovoked ID-DVT and ID-DVT and complications in the first month (Odds ratio 8.15, CI 1.67-39.15), also the Fischer test for complication DVT and unprovoked ID-DVT is significant ($P < 0.005$).

No differences were observed in progressions between muscular (5) and tibial-peroneal (2) thrombosis.

Discussion

Most studies on VTE and its prevention have used sensitive diagnostic tests to detect DVT.

There is a bulk of evidence that the majority of the thrombi diagnosed by non-invasive sensitive diagnostic tests are confined to the calf, clinically silent, and do not progress or develop embolic complications. This was probably due to the spon-

taneous lysis of the thrombus (in 50% of cases), or to a spontaneous limitation of disease (25% of cases).

However, approximately 10% to 20% of calf thrombi extend to proximal veins.¹⁶⁻¹⁸

The proportion of ID-DVT in all DVT differs between the studies. In an unselected population of 499 patients with DVT, 58 (12%) had thrombosis confined to the calf veins;¹⁹ in another study on out- and in-patients examined for suspected DVT, the ID-DVT represented 47%.¹¹ Recent studies reported that the risk of PE in patients with ID-DVT is similar to the risk of PE in patients with proximal DVT (24.6%).²⁰

The extensive use of CCDU technique highlighted the problem of ID-DVT. Indeed, many aspects on treatment of VTE are still debated. It means that 80% to 90% of patients with distal DVT perhaps do not need anticoagulation. The question is how to identify the remaining 10% to 20%.²¹

An approach has been to omit the search of the distal DVT and wait for those progressing to the proximal district. Depending on the incidence of proximal DVT in the referral cohort, this means that 65% to 85% of cases undergo a second ultrasound examination. Because the test has a range of positivity between 0.7% and 1.3%,^{2, 9} this approach is not cost-effective.^{7, 21}

This study showed a very low incidence of thrombotic complications. In fact only 2.9% of patients in the first month and 2.3% in the next 3 months developed DVT. A similar rate of recurrent thrombosis was detected by Pinede.⁹ Moreover, in the study carried out by Pinede the results concerned a sample treated for six weeks. All patients with thrombosis in the tibio-fibular trunk at the diagnosis were excluded. The inclusion of those patients would have yielded a significant increase of the progressions during the first month.

Instead, in the present study, the thrombotic progression to the proximal veins, during the treatment period, was observed in patients with unprovoked ID-DVT and the statistical analysis showed a highly significant association between unprovoked ID-DVT and complications in the first month.

No differences were observed in progressions between muscular (5) and tibial-peroneal (2) thrombosis at the first month of treatment. This finding suggests that the adoption of a different

treatment between muscular and tibial thrombosis is not justifiable.

During the three-month follow-up, we found only one proximal DVT in a patient who had a traumatic fracture of the tibia with persistent poor mobilisation.

Conclusions

A lot of studies showed a strong association between proximal DVT and cancer. In accordance with this data, we observed that patients with recurrent DVT in the first month and in the three-month follow-up, developed cancer.

Although a larger sample of patients is needed in order to define correctly the problem of the treatment of ID-DVT, our results suggest that a prolonged treatment may be indicated (well beyond four weeks) in unprovoked ID-DVT.

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