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Journal Title: International angiology : a journal of the International Union of Angiology

Volume: 23 Issue: 3 Month/Year: 2004 Pages: 206-12

Article Author: Partsch H; Kaulich M; Mayer W

Article Title: Immediate mobilisation in acute vein thrombosis reduces post

Imprint:

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Immediate mobilisation in acute vein thrombosis reduces post-thrombotic syndrome

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Aim. To investigate the effect of compression and immediate ambulation in the acute stage of deep vein thrombosis (DVT) on the development of postthrombotic syndrome (PTS).

Methods. Design: follow-up study of patients who previously have been enrolled in a randomized controlled trial. Setting: outpatient department of a municipal hospital. Subjects and interventions: a follow-up was performed 2 years after 53 patients with acute proximal DVT had been enrolled into a randomized controlled trial, comparing bed rest and no compression (n=17), Unna boot bandages plus walking (n=18) and compression stockings plus walking (n=18). Telephone interviews could be conducted with 11 patients, 37 patients could be reevaluated by independent observers (11 from the bed-rest group, 13 from the bandage group and 13 from the stocking group).

Compression stockings up to the time of the follow-up were worn by 8/11 (73%) of the bed-rest patients and by 13/26 (50%) of the mobile patients. Main outcome measures included clinical and venous duplex investigation, pain assessment using Visual Analogue Scale and Lowenberg test, leg circumference, clinical "PTS-score" combining 5 subjective symptoms with 6 objective signs (Villalta-Prandoni scale).

Results. Duplex investigation of the deep veins and pain assessment by visual analogue scale showed no significant differences between the groups. Nine out of 11 patients after bed rest, but only 16/26 in the mobile groups showed a larger calf circumference on the diseased leg (n.s.). Judged by the Villalta-Prandoni scale a significantly better outcome could be found in the mobile group (mean score 5.1) than in the bed-rest group (mean score 8.2), (p=0.01) (*Mild PTS*: score 5-14, *severe PTS*: score ≥15). Eighteen out of 26 mobile patients, but only 2/11 bed-rest patients had a score ≤5 (*no PTS*).

Conclusion. Immediate mobilisation with compression in the acute stage of DVT reduces the incidence and the severity of PTS.

Key words: Venous thrombosis - Postphlebitic syndrome, prevention and control - Bandages - Compression stockings.

Increasing evidence demonstrates that walking with good compression under low molecular weight heparin provides a more favourable outcome in the acute phase of deep vein thrombosis (DVT) than bed rest. There is a faster reduction of pain and swelling if patients are mobilized immediately and the rate of thrombus progression is reduced. The frequency of new pulmonary emboli is not significantly increased in comparison with bed rest.

Hull et al. have shown that the quality of initial anticoagulant response to heparin in the first 24 hours has a deciding influence on the recurrence rate in the next 3 months. Failure to achieve a therapeutic activated partial thromboplastin time (aPTT) within 24 hours was associated with a 23.3% frequency of venous thromboembolism versus 4.6% for those whose aPTT exceeded the therapeutic threshold after 24 hours (p=0.02). Thrombus progression in the first hours and recurrence of venous thromboembolism probably do not only depend on the quality of anticoagulation but also on blood flow velocity in the acute phase of DVT. Phlebographic controls after DVT have demonstrated thrombus extension with bed rest in contrast to early mobilisation.

Two randomized controlled trials have clearly shown that consequent wearing of medical compression stockings for 2 to 6 years after proximal DVT is able to significantly reduce the frequency and severity of postthrombotic syndrome (PTS). However, in both studies compression therapy was started only after 10-14 days following initial heparin treatment. Until now no data have been available from the literature showing a potential benefit concerning the prevention of PTS by walk-
ing and compression in the acute phase of DVT immediately upon the diagnosis is made.

Therefore, we performed a follow-up of the patients from our previous study in which the outcome of bed rest versus walking exercises using compression bandages or stockings was compared in the acute phase of proximal DVT.

Materials and methods

In the previous study 53 mobile patients admitted to the hospital because of acute proximal DVT were enrolled. They received subcutaneous injections of dalteparin with a dosage of 200 IU per kilogram body weight every 24 hours and were randomized into 3 groups: bed rest for 9 days without compression (n=17), thigh length compression stockings (Sigvaris 503®), (n=18), or firm inelastic compression bandages with Unna boot on the lower leg and a firm adhesive bandage (Panelast®) on the thigh (n=18). After 9 days all patients were encouraged to walk with compression class II stockings, calf length or thigh length depending on the swelling of the thigh, which were renewed every 6 months. Oral anticoagulation was continued for at least 6 months.

The follow-up investigations took place 2 years later (28.9±4.9 months).

Telephone contact

From 11 patients information could be obtained by phone calls with the patients, with relatives or with the family physician. Three had died (one 78-year-old male with a newly detected carcinoma of the pancreas 4 months after discharge, one 79-year-old male and one 81-year-old female, both 2 years after DVT). One 78-year-old lady with previous attacks of bilateral thrombotic events developed ulcers on both legs, 7 were reported to be well without specific problems. Five patients could not be contacted.

Follow-up investigations

When they were invited all patients were instructed about the aim of the investigation. Thirty-seven patients could be reinvestigated: 11 from the bed-rest group, 13 from the compression stocking group and 13 from the group treated initially by compression bandages. For further analysis the results of the 2 mobile groups treated with stockings and bandages were put together.

History

History was taken, concentrating especially on the compliance of oral anticoagulation and wearing of compression stockings, and on the occurrence of new episodes of venous thromboembolism during the follow-up period.

Pain assessment

Pain assessment was performed by 2 methods, which were also used in the primary study: spontaneous pain was measured using a visual analogue scale. As a kind of "objective" test a modified Lowenberg test was applied: A blood pressure cuff is gradually inflated on both calves and the patient is asked to indicate when this procedure is getting painful. The "Lowenberg difference" between the 2 legs, which is normally around zero, gives an objective parameter for painful tenderness in one calf.

As an attempt to quantify the severity of post-thrombotic syndrome a clinical scoring system consisting of a combination of subjective and objective parameters was used as described and validated by Villalta et al. (Table 1).
stage of DVT using the clinical classes of the CEAP classification.10

As in the previous study the circumstances of ankles and calves were measured. Compression sonography of the deep veins by duplex was carried out using the same criteria as in the first investigation.1 The colleagues who performed the follow-up investigation were not aware about the allocation to the 3 treatment modalities of the previous study. The location of the most proximal pathological venous segment was marked on the skin and the distance to the inguinal fold was measured in order to assess a progression or regression of the primary thrombus extension. Refluxes were assessed in the sitting position using Valsalva's manoeuvre and compression of the calf. A reflux duration of longer than 0.5 seconds was considered to be pathological.

Statistics

Medians with minimal and maximal values or interquartile ranges are given. Non-parametric tests were used for the quantitative outcome parameters: the u-test (Mann Whitney) and the Kruskal Wallis test respectively, to compare the results of 2 or 3 treatment groups. The χ² test was used to compare proportions.11

Results

Table II shows the main characteristics and further management of the 37 DVT patients who could be reinvestigated. Clinical events and development of skin changes during the follow-up period are summarized in Table III. In the 6 patients who suffered from new DVT or phlebitis no progression of the clinical CEAP classes was observed. Ulcer scars (C5) in 3 patients were already present when DVT occurred 2 years previously. There was no new active ulceration (C6) in the group of reinvestigated patients.

Leg swelling is characterized by the difference of the largest calf circumference between the DVT leg and the contralateral leg (Table IV). In the acute stage of DVT leg edema could be dramatically reduced by compression therapy in contrast to bed rest. After 2 years there was no significant difference between the 3 groups after 2 years. At this stage the swelling of the leg will depend also on the level of compliance of the patient wearing the compression stockings. Therefore the difference of the calves after 2 years was analysed depending on the duration of stocking wear. As can be seen in Figure 1 those patients of the original mobile groups treated by Unna boots or stockings who wore their stockings longer than 1 year and up to the time of the follow-up investigation showed, on average, less swelling than those who stopped compression more than 1 year ago. In the bed-rest group only 3/11 patients did not wear compression stockings at follow-up. The remaining 8 patients had more edema in spite of wearing stockings. Only 2/11 (18%) patients initially treated by bed rest had no edema versus 10/26

| TABLE II — Basic characteristics and management during the follow-up period (median, minimum—maximum) |
|-----------------|-----------------|-----------------|-----------------|
| Acute stage of DVT | Bed rest | Stocking | Bandage |
| N               | 11         | 13          | 13            |
| Edema           | 4/7        | 5/8         | 6/8           |
| Age (years)     | 47         | 61          | 62            |
|                        | (22-73)    | (25-84)     | (33-79)       |
| Thrombus extension thigh: pelvis | 9.2        | 8.5          | 9.4           |
| Previous ipsilateral DVT | 3          | 4           | 3             |
| Follow-up (months) | 29         | 26          | 27.5          |
|                        | (25-9)     | (21-42)     | (21-38)       |
| Oral anticoagulation (months) | 12         | 7           | 6             |
|                        | (6-29.5)   | (6-25)      | (6-29)        |
| Stocking wear (months) | 27         | 12          | 21            |
|                        | (3-30)     | (3-32)      | (4-30)        |
| Stocking wear >1 year | 8/11       | 7/13        | 6/13          |
| Call length stocking only | 8/11       | 7/13        | 13/13         |
Table IV.—Differences of the largest circumference at calf level between leg with DVT and contralateral leg (cm.), median, interquartile range.

<table>
<thead>
<tr>
<th></th>
<th>Bed rest</th>
<th>Stocking</th>
<th>Bandage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference of calf circumference at acute DVT (day 6)</td>
<td>2.5</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>On day 9:</td>
<td>(1.75-4.5)</td>
<td>(0.5-2.25)</td>
<td>1 p&lt;0.01*</td>
</tr>
<tr>
<td></td>
<td>1.5</td>
<td>(0.5-1.75)</td>
<td>1 p&lt;0.05*</td>
</tr>
<tr>
<td>After 2 years</td>
<td>1.5</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>(0.5-1.75)</td>
<td>(0.5-1.75)</td>
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</tr>
</tbody>
</table>

(38%) in the group that was treated by compression and ambulation \( (\chi^2 \text{ test: not significant}) \).

The pain level assessed by visual analogue scale and by the Lowenberg difference respectively is summarised in Table V. Although after 2 years lower pain levels are found in the groups initially treated by compression and walking the difference compared with initial bed rest is not significant.

Figure 2 shows the Villata-Prandoni scores \(^1\) in the groups that had been kept mobile in contrast to those of the bed-rest group. The median value (interquartile range) in the mobile group is significantly lower (5 [3 to 6.5]) than in the bed-rest group (8 [6.5 to 11], \( p<0.01 \)). Score values less than 5 indicating "no postthrombotic syndrome" are present in 12/26 (46%) patients of the mobile groups but only in 2/11 (18%) patients after bed rest (\( \chi^2 \) test: n.s.).

The results of the duplex investigation of the deep veins are summarized in Figure 3. No remnants of thrombi could be detected in 58.3% of the mobile group and in 54.5% of the bed-rest group (n.s.). Most of these segments showed refluxes. Morphological changes in the femoral vein were still observed in 41.7% and in 45.5% respectively with an extension compared to the initial finding in 8.3% and in 9.1%. One third of the patients in both groups showed still partial obstructions and wall changes.

There was no significant correlation between recanalisation and obstruction on one side and the amount of swelling and pain on the other side.

Discussion

Most of the eventual cases of PTS declare themselves within the first 2 years after acute DVT.\(^{12,13}\)

Recurrent events of DVT are among the most pertinent risk factors for the development of pain, swelling and skin changes defining the clinical term of a postthrombotic syndrome.\(^{12,14}\) Clinically silent recurrences seem to have a lower risk.\(^{15}\)

In our follow-up study 37 patients were investigated 2 years after proximal DVT, from whom 11 had a thrombus extension into the pelvis. The average age was 47.62 years in the acute stage, 10 patients had suffered already from previous thrombotic episodes.\(^{1}\)

During the 2 years of the follow-up period 3 of
Figure 2.—PTS-scores 9 in the mobile group are statistically significantly lower than in the bed-rest group. Individual and median values are given (p<0.01). A score of less than 5, meaning "no postthrombotic syndrome", was found in 12/26 (46%) of the mobile patients, but only in 2/11 (18%) of the patients treated with bed rest.

The reinvestigated 37 patients had ipsilateral DVT and 5 had superficial phlebitis, but no occurrence of skin changes (CEAP C4) was observed.

Oral anticoagulation was maintained for at least 6 months in all cases with an average duration between 9.1 and 16.6 months. The mean duration of compression stocking wear was between 15.5 and 28.5 months.

The overall outcome concerning late sequelae is comparable with data in the literature, showing that even with optimal therapy approximately 1/3 of DVT patients will acquire PTS.\(^5\) However, it has to be stressed that pathological signs according to a CEAP class 4 and class 5 lesion could also be found on the contralateral leg.

Analyzing the outcome parameters according to the treatment modalities in the acute stage of DVT in association with the physical activity seems to be relevant. This study indicates that the development of postthrombotic sequelae after symptomatic proximal DVT depends, among several other factors, on the physical activity of the patient in the acute stage.

Up to now the superior effect of low molecular weight heparin compared with unfractionated heparin in most trials has been attributed to the pharmacological advantages of LMWH.

Only recently has it been pointed out that subtherapeutic ranges for aPTT in patients receiving unfractionated heparin may additionally account for the inferior results achieved by this drug.\(^18\)

However, the fact that subcutaneous injections of LMWH do not require bed rest, in contrast to intravenous UF heparin-infusions, has not been considered up to now, although previous studies have shown that early mobilization is associated with a lesser degree of thrombus progression.\(^8\)

Checking thrombus regression on day 21 after acute DVT by phlebography Bredinin et al. were able to demonstrate that unfractionated heparin given for 5-7 days intravenously showed less thrombus regression and a higher rate of recurrence in the first 90 days than LMWH administered subcutaneously.\(^19\) In another trial in which intravenous heparin infusions were continued for 12 to 16 days, repeated venography revealed even worse results.\(^20\) When in this study LMWH was given intravenously the changes in the Marder score were significantly worse than after subcu-

Figure 3.—Duplex investigations after 2 years show no significant difference between the initial mobile and bed-rest groups concerning recanalization, progression and regression of the primary extension of DVT.
taneous administration of the same substance. It may be assumed that 12–16 days of bed rest with intravenous infusions may have promoted thrombus progression which could explain this result.

In our previous trial comparing bed rest with walking exercises and compression in proximal DVT, duplex reinvestigation at 9 days showed a lesser degree of thrombus progression in the walking patients compared with bed rest. Meissner et al. have demonstrated that venous segments not developing reflux had a shorter median lysis time (65 to 130 days) than those with reflux (214 to 474 days). Patients with a lysis in the first 4 months have a better prognosis not to develop refluxes. Physical activity and compression probably influence this outcome. As is shown in the present study, 2 years later the majority of the thrombi are recanalised, both in the initially mobile and the bed-rest group, and refluxes at some point of the deep venous axis may be found in practically all cases.

For the individual patient pain and swelling are more important than the outcome of objective testing that often does not correlate with the severity of subjective symptoms.

Although in this follow-up pain and swelling are less pronounced in the initially mobile group, with no statistical significance can be demonstrated due to the low number of patients. However, taking into account subjective and objective symptoms and signs by using the validated Villalta-Prandoni scale, the outcome after 2 years was significantly better in the initially mobile patients than in the bed-rest group. Slightly modified versions of this scale have also been used by Brandjes et al. and by Prandoni. A total score of less than 5, meaning "no postthrombotic syndrome", was found in 12 out of 26 (46%) of the mobile patients, but in 2 out of 11 (18%) patients treated with bed rest.

As we know from 2 large trials the rate and severity of a postthrombotic syndrome some years after proximal DVT can be halved by subsequent wearing of compression stockings. In both studies compression stockings were prescribed only 10–14 days after the onset of DVT so that no information on their potential effect in the acute phase may be gained.

In the present follow-up those patients from the mobile group who still wore their stockings showed less swelling on average than those who did not continue to use stockings for longer than 1 year (Figure 1). Six out of 26 patients (23%) even had a lower calf circumference compared to the contralateral leg. This is in contrast to the bed-rest group, which presented with leg swelling in nearly all cases, even in those who still wore their stockings.

Prevention of postthrombotic syndrome after DVT has a tremendous impact on the quality of life of the patient and on the socio-economic consequences. However, this issue is widely underappreciated. Two Canadian surveys of DVT patients and physicians revealed an amazing discrepancy between patients' and doctors' opinions regarding the use of compression stockings. While patients after DVT were willing to comply with compression stockings, most of them finding stockings helpful, only 26% of the doctors recommended compression as soon as the diagnosis of DVT was made.

PTS is strongly related to recurrent episodes of DVT. Adequate and prolonged oral anticoagulation to prevent ipsilateral recurrences may therefore also be considered. However, the effectiveness of this approach is endorsed only by a few studies. Compression stockings alone were not able to prevent new episodes of DVT but were able to significantly reduce the frequency and the severity of PTS.

Conclusions

We conclude from our data that in the acute stage of DVT preventive measures of stasis by compression and walking may be of similar importance to an instantly effective anticoagulation in the first 24 hours, which is nowadays easier and safer to achieve using LMWH than unfractionated heparin. In mobile patients, walking exercises with good compression starting immediately upon the diagnosis of DVT do not increase the risk of pulmonary embolism, but they decrease the rate and severity of postthrombotic syndrome.

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